CHAPTER 4

Molluscan Shellfish Allergy

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Contents

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Abstract

Food allergies affect ~3.5–4.0% of the worldwide population. Immediate-type food allergies are mediated by the production of IgE antibodies to specific proteins that occur naturally in allergenic foods. Symptoms are individually variable ranging from mild rashes and hives to life-threatening anaphylactic shock. Seafood allergies are among the most common types of food allergies on a worldwide basis. Allergies to fish and crustacean shellfish are very common. Molluscan shellfish allergies are well known but do not appear to occur as frequently. Molluscan shellfish allergies have been documented to all classes of mollusks including gastropods (e.g., limpet, abalone), bivalves (e.g., clams, oysters, mussels), and cephalopods (e.g., squid, octopus). Tropomyosin, a major muscle protein, is the only well-recognized allergen in molluscan shellfish. The allergens in oyster (Cra g 1), abalone (Hal m 1), and squid (Tod p 1) have been identified as tropomyosin. Cross-reactivity to tropomyosin from other molluscan shellfish species has been observed with sera from patients allergic to oysters, suggesting that individuals with allergies to molluscan shellfish should avoid eating all species of molluscan shellfish. Cross-reactions with the related tropomyosin allergens in crustacean shellfish may also occur but this is less clearly defined. Occupational allergies have also been described in workers exposed to molluscan shellfish products by the respiratory and/or cutaneous routes.

With food allergies, one man's food may truly be another man's poison. Individuals with food allergies react adversely to the ingestion of foods and food ingredients that most consumers can safely ingest (Taylor and Hefle, 2001). The allergens that provoke adverse reactions in susceptible individuals are naturally occurring proteins in the specific foods (Bush and Hefle, 1996). Molluscan shellfish, like virtually all foods that contain protein, can provoke allergic reactions in some individuals.

Key Words: Shellfish, Mollusc, Allergy, Allergen, IgE, Tropomyosin

I. MOLLUSCAN SHELLFISH CLASSIFICATION AND IMPORTANCE AS FOOD

Seafoods can include fish and shellfish. Shellfish belong to two major phyla — Mollusca and Anthropoda. The Anthropoda phylum contains the Crustacea class of shellfish that includes shrimp, prawns, lobster, crab, crayfish, and barnacles (Table 4.1). The Mollusca phylum is divided into eight classes including three classes that are of importance for human food — Gastropoda, Bivalvia, and Cephalopoda as displayed in Table 4.1 (Hickman *et al.*, 2004). The major gastropod species in the food supply include abalones, conches, limpets, freshwater and marine snails, and whelks (Brusca and Brusca, 1990; Hefle *et al.*, 2007). Gastropoda contains more than 70,000 species but many are not eaten as food (Hickman *et al.*, 2004). Clams, cockles, scallops, mussels, and oysters are the major edible bivalves (Brusca and Brusca, 1990; Hefle *et al.*, 2007). Squid, cuttlefish, and

TABLE 4.1 Shellfish species

Crustacean shellfish
Shrimps
Prawns
Crabs
Lobsters
Crayfish
Barnacles
Molluscan shellfish
Gastropods
Abalones
Limpets
Terrestrial (land) snails
Marine snails
Whelks
Conches
Bivalves
Clams
Oysters
Mussels
Scallops
Cockles
Cephalopods
Squids
Octopuses
Cuttlefishes

octopus are primary cephalopods in commerce (Brusca and Brusca, 1990; Hefle and Bush, 2001). Collectively, mollusks comprise a large, diverse group with more than 100,000 species living in saltwater, in freshwater, and on land.

Molluscan shellfish play an important role in human nutrition and the world economy (Wild and Lehrer, 2005). Table 4.2 provides data on the worldwide production/catch of various molluscan shellfish species for 2005. The most widely available species are oyster, squid, clam, mussel, and scallop. Aquaculture has become an important contributor to the production of molluscan shellfish with the exception of the cephalopods. However, the popularity and frequency of consumption of various molluscan shellfish varies widely across various countries and cultures. Accurate information on comparative consumption patterns for molluscan shellfish in various countries does not exist. Molluscan shellfish are consumed as freshly cooked or even raw seafood items particularly in coastal communities. But mollusks also are consumed as processed foods in a variety of forms.

II. PREVALENCE OF MOLLUSCAN SHELLFISH ALLERGIES

The importance of molluscan shellfish allergy is increasingly recognized. The European Union recently added molluscan shellfish to the list of most commonly allergenic foods in Europe (EFSA, 2006). Although not known

TABLE 4.2 Worldwide production and catch of molluscan shellfish — 2005

	Capture (in tons)	Aquaculture (in tons)	Total
Freshwater mollusks	415,105	145,462	560,567
Abalones, winkles, conches	120,400	333,947	454,347
Oysters	166,145	4,615,400	4,781,545
Mussels	143,182	1,795,779	1,938,961
Scallops	711,342	1,224,843	1,936,185
Clams, cockles, arkshells	705,649	4,175,907	4,881,556
Squids, cuttlefishes, octopuses	3,892,145	16	3,892,161
Misc. marine mollusks	1,049,731	1,107,395	2,157,126
Total			20,602,448

Data from Food & Agriculture Organization of the United Nations.

with certainty, the prevalence of molluscan shellfish allergy is likely to parallel consumption patterns being more frequent in locales where consumption is frequent.

The overall prevalence of food allergies is unknown on a worldwide basis. However, in the United States, the overall prevalence of food allergies has been estimated at 3.5–4.0% or 10–12 million Americans (Sicherer *et al.*, 1999, 2004). The prevalence and severity of food allergies appear to be increasing in several developed countries for reasons that are not entirely clear (Taylor and Hefle, 2001). Food allergies occur more frequently in infants and young children than among adults (Taylor and Hefle, 2001). The prevalence of food allergies among infants younger than the age of 3 can be as high as 8% (Sampson, 1990). In infants, the most common allergenic foods are milk, eggs, and peanuts (Sampson and McCaskill, 1985). Most food allergies developed in infancy are outgrown during infancy or early childhood (Bock, 1982; Hill and Hosking, 1992). Allergies to certain foods such as milk, eggs, and soybeans are much more likely to be outgrown than allergies to other foods such as peanuts (Bock, 1982; Bock and Atkins, 1989). Among adults, the most common allergenic foods are crustacean shellfish (shrimp, crab, lobster), peanuts, and tree nuts such as almonds, walnuts, and cashews (Sicherer *et al.*, 1999, 2004).

The prevalence of allergies to specific foods is unknown for the most part. Good estimates exist of the prevalence of milk allergy in infancy (Host and Halken, 1990) and peanut and tree nut allergy throughout the life span (Sicherer *et al.*, 1999). However, the prevalence of allergies to seafoods including molluscan shellfish is not precisely known.

The most accurate estimates of prevalence would be derived from clinical challenge studies conducted on a representative sample of the general population. However, the only studies of mollusk allergy in the general population have been questionnaire-based surveys (Rance *et al.*, 2005; Sicherer *et al.*, 2004). Self-reporting through surveys may yield an overestimate of the prevalence of a particular food allergy (Altman and Chiaramonte, 1997). Certainly, the existence of allergy to molluscan shellfish was not corroborated by clinical diagnostic approaches in the individual patients involved in these surveys. However, these surveys do provide intriguing information on the prevalence of molluscan shellfish allergy.

Sicherer *et al.* (2004) conducted a nationwide random telephone survey of the prevalence of seafood allergies in the United States and a standardized questionnaire. Responses were categorized on the basis of convincing symptoms and self-reported physician confirmation of the allergy. The survey involved 14,948 individuals with 67 reporting reactions to molluscan shellfish including scallops, clams, oysters, and mussels. The self-reported prevalence in this study population was 0.4%.

Rance *et al.* (2005) conducted a questionnaire-based survey of food allergy in 2716 school children in France. Four cases of molluscan shellfish allergy were reported to mussels, snails, and oysters among this group. Thus, the self-reported prevalence of molluscan shellfish allergy in this population of children was 0.15%.

These two surveys are in reasonably good agreement regarding prevalence estimates for molluscan shellfish allergy. That is especially true since all the ages were included in the surveyed population of Sicherer *et al.* (2004) while only children were involved in the French survey (Rance *et al.*, 2005). Hypothetically, sensitization to molluscan shellfish might develop later in life than for other foods because of the infrequent consumption pattern.

In 1999, the Codex Alimentarius Commission adopted a list of the most commonly allergenic foods and food groups (CAC, 1999). This list includes milk, eggs, fish, crustacean shellfish, peanuts, tree nuts, soybeans, and wheat (CAC, 1999; FAO, 1995). These eight foods or food groups are thought to account for more than 90% of all IgE-mediated food allergies on a worldwide basis (Bousquet *et al.*, 1998). Subsequently, various countries or regions have considered the Codex guidance and developed their own lists of the most commonly allergenic foods. While the United States list these eight foods or food groups, the list in the European Union additionally includes sesame seeds, celery, mustard, lupine, and molluscan shellfish. The Canadian list additionally includes sesame seeds and refers to shellfish which presumably encompasses both crustacean and molluscan shellfish. At this time, only the European Union and Canada recognize molluscan shellfish as among the commonly allergenic foods.

Beyond the commonly allergenic foods or food groups, any food that contains protein has the potential to elicit an allergic reaction among susceptible individuals (Taylor and Hefle, 2001). Hefle *et al.* (1996) identified more than 160 other foods beyond the 8 foods or food groups recognized by Codex that had been documented as causing food allergies on a less frequent basis. Molluscan shellfish are considered to be among a group of allergenic foods, just below the well-recognized, eight most commonly allergenic foods or food groups. In fact, individuals with shellfish allergies, usually manifested primarily by adverse reactions to crustacean shellfish, are often told to avoid all types of shellfish including molluscan shellfish. Thus, molluscan shellfish may be avoided to a similar extent as if this group of foods was more commonly allergenic. Molluscan shellfish are among a group of foods including sesame seeds, poppy seeds, cottonseed, and other legumes beyond peanuts and soybeans, that are worthy of mention because, although they less frequently cause allergies, they have been associated with severe reactions (Taylor and Hefle, 2001).

Do molluscan shellfish belong on a list of most commonly allergenic foods? When the original Codex list of the eight most commonly allergenic foods was originally proposed in 1995 (FAO, 1995), prevalence data were indeed scant so that the expert panel had to make their recommendation on the basis of limited information. Subsequently, the correctness of this list was endorsed by Bousquet *et al.* (1998) based upon better, though still incomplete, information on comparative prevalence and evidence of severe reactions. Bousquet *et al.* (1998) especially noted the dearth of data relating to the prevalence of shellfish allergies, both crustaceans and mollusks. However, if the true prevalence of molluscan shellfish allergies does fall within the range of 0.15–0.40% as suggested by the surveys of Sicherer *et al.* (2004) and Rance *et al.* (2005), then the prevalence of molluscan shellfish allergies may be in the same range as more well-accepted commonly allergenic foods such as fish (Sicherer *et al.*, 2004) and tree nuts (Sicherer *et al.*, 1999).

The comparative prevalence of molluscan shellfish allergies within groups of patients from allergy clinics can offer some clues. Clearly, these populations are skewed toward individuals who seek medical assistance for their allergies. Thus, the prevalence in these populations is going to be considerably higher than for the general population. However, the prevalence of molluscan shellfish allergy within such predisposed groups can be compared to the prevalence of allergies to more well-accepted commonly allergenic foods to see if they are comparable. Unfortunately, although numerous studies of this type have been reported in the medical literature, many studies involve infants and young children who may not yet have been exposed to molluscan shellfish and other studies do not distinguish molluscan from crustacean shellfish.

Castillo *et al.* (1996) studied 142 food-sensitized patients from Gran Cranaria, Spain. Of these individuals, 120 reported clinical symptoms following ingestion of one or more foods. While shrimp was the most common allergenic food, squid was the second most common allergenic food with 33 cases. Additionally, 12 cases were reported to oyster, 10 to clam, and 10 to mussels.

In another Spanish study, Crespo *et al.* (1995) evaluated 355 children on the basis of clinical history, skin prick tests (SPTs), and specific serum IgE to mollusks. Allergies to molluscan shellfish were noted in 10 of these children or 2.8%. However, mollusks caused 1.6% of 608 allergic reactions among this group of children.

In a survey of patients with food allergies appearing at 17 clinics in 15 cities in the Baltic region of Europe, 6.2% of participants indicated allergies to clam, 3.2% to oyster, and 1.4% to snail (Erikson *et al.*, 2004). These percentages are even more noteworthy in light of the fact that the survey indicated that fewer than 50% of these clinic patients had even eaten clams, oysters, or snails.

Among a total of 305 pediatric patients in Japan who were diagnosed as having IgE-mediated food allergies, 12 cases of allergy to molluscan shellfish (3.9%) were identified (Ebisawa *et al.*, 2003). Seven of these cases were to cuttlefish and five cases involved octopus. Clearly, while these foods may be consumed by young children in Japan, such dietary habits would not be so common in many other countries. By contrast, 93.4% of these Japanese children were diagnosed with egg allergy and another 58.0% with milk allergy (Ebisawa *et al.*, 2003).

The number of studies estimating the comparative prevalence of molluscan shellfish allergy is limited. The frequency of consumption of molluscan shellfish might be higher in some of the locales where such studies have been performed. Clearly, more comparative clinical data would be helpful. However, the molluscan shellfish certainly seem to be a comparatively common allergenic food in some locales and among some populations.

III. IgE-MEDIATED REACTIONS IN MOLLUSCAN SHELLFISH ALLERGY

Individualistic adverse reactions to foods can occur through several different types of mechanisms (Taylor and Hefle, 2001). True allergic reactions can include both IgE-mediated immediate hypersensitivity reactions and cell-mediated delayed hypersensitivity reactions (Taylor and Hefle, 2001). However, only IgE-mediated reactions have been documented to occur with ingestion of molluscan shellfish in sensitive individuals.

While all humans have IgE antibodies that are involved in defense against parasitic infections, only humans who are predisposed to the development of allergies will produce IgE antibodies upon exposure to certain protein allergens present in their environment including their diet. Only a few of the many proteins found in foods are capable of stimulating the production of specific IgE antibodies in susceptible individuals (Taylor, 2002). With molluscan shellfish, only one, or perhaps a few, of the numerous proteins is known to provoke the production of IgE antibodies that specifically recognize one or more species of molluscan shellfish.

The first step in the development of an IgE-mediated food allergy is sensitization. In this phase, exposure to the allergen stimulates production of specific IgE antibodies. Exposure is certainly a critical aspect of sensitization but exposure does not usually result in allergic sensitization. Instead, exposure to dietary proteins usually results in oral tolerance, a normal immunologic response that is not associated with adverse reactions (Strobel, 1997). Even among individuals predisposed to development of IgE-mediated allergies, exposure to most dietary proteins will induce oral tolerance. The reasons why some allergic individuals mount an IgE-mediated response to one particular antigen while other similar individuals produce a similar response to an antigen from a completely different source remains unclear. Although sensitization can occur on the first known exposure to the allergen, this is not always the case. Thus, an individual may develop a food allergy at any age. Sensitization to molluscan shellfish, and especially some species of molluscan shellfish, is unusual probably because exposure is uncommon or infrequent even among susceptible individuals.

Once sensitized, individuals will react adversely upon subsequent exposure to the particular allergen, the so-called elicitation phase of the allergic response. After the allergen-specific IgE antibodies are formed, they attach to mast cells in the tissues and basophils in the blood. Mast cells and basophils possess granules that contain physiologically active chemicals that mediate the allergic response (Church *et al.*, 1998). During the elicitation phase, exposure of the sensitized individual to the allergen results in the allergen cross-linking two IgE antibodies on the surface of the mast cell or basophil membrane. The cross-linking stimulates the release of mediators from the mast cells and basophils into the tissues and blood. Histamine is one of the primary mediators of IgE-mediated allergic reactions (Simons, 1998). However, many other mediators have been identified including various leukotrienes and prostaglandins (Taylor and Hefle, 2001).

Many different symptoms can occur during IgE-mediated food allergies including cutaneous, gastrointestinal, respiratory, and sometimes cardiovascular symptoms (Table 4.3). Reactions can sometimes be fairly mild, but severe and life-threatening reactions involving symptoms such as laryngeal edema, asthma, and anaphylactic shock can occur on occasion.

TABLE 4.3 Symptoms of IgE-mediated allergic reactions

Gastrointestinal:	Nausea Vomiting Diarrhea Abdominal cramping
Cutaneous:	Pruritis Dermatitis Urticaria Angioedema
Respiratory:	Conjunctivitis Rhinitis Asthma Laryngeal edema
Systemic:	Anaphylactic shock Hypotension

Individuals with allergies to the same food can experience quite different symptoms depending upon their degree of sensitization, the dose of exposure to the offending food, and the sensitivity of receptors in their various tissues to the specific mediators. The nature and severity of the symptoms experienced by a food-allergic individual may vary from one episode to another also depending on the dose of the offending food that has been inadvertently ingested, the degree of sensitization at the time of the episode, and probably other factors (Taylor and Hefle, 2001). Fatal reactions, attributed to food-allergic reactions, have been well documented (Bock *et al.*, 2001, 2007; Sampson *et al.*, 1992; Yunginger *et al.*, 1988). Fatal reactions usually involve the inadvertent ingestion of the offending food by individuals who know that they were allergic to that food. Although asthma is not a particularly common manifestation of food allergy, the individuals at greatest risk of life-threatening reactions are those with food-induced asthma (Sampson *et al.*, 1992). In IgE-mediated food allergies, symptoms begin to emerge in most cases within a few minutes after ingestion of the offending food. Hence, these responses are known as immediate hypersensitivity reactions.

IV. DIAGNOSIS AND TREATMENT OF MOLLUSCAN SHELLFISH ALLERGY

The diagnosis of IgE-mediated food allergies cannot be based solely on the symptomatic profile of the patient (Metcalfe, 1984). The dietary history of the patient should be carefully taken in an attempt to establish a convincing association between intake of the molluscan shellfish and elicitation of an adverse reaction. With immediate hypersensitivity reactions to molluscan shellfish that may be eaten only occasionally, the history can often be very important and revealing in the diagnostic workup. In cases where a convincing history is not obtained, the optimal method for documenting the existence of a specific food-associated adverse reaction is the double-blind, placebo-controlled food challenge (DBPCFC) (Bock *et al.*, 1988). Neither the history nor the DBPCFC can reveal the mechanism of the adverse reaction. Therefore, once the adverse reaction is well documented, the proof of an IgE mechanism should be sought. SPTs using molluscan shellfish extracts (Bock *et al.*, 1977) and radioallergosorbent tests (RASTs), where binding of IgE antibodies from serum of the patient to molluscan shellfish proteins bound to a solid phase is measured *in vitro* (Adolphson *et al.*, 1986), are the two most common procedures used to establish an IgE mechanism. With seafood allergies, mixtures of shellfish, including both crustacean and molluscan, are sometimes used especially with the SPT. The use of such mixed antigens is expeditious but does not allow any association of the allergic reaction with a specific type of shellfish. The use of mixed antigens also often leads to advice to avoid all seafoods or all shellfish. A more specific diagnosis can be made if the extracts contain only a certain species of shellfish or a more narrowly defined group (clams, shrimp, etc.).

Bousquet *et al.* (1998) established criteria for the placement of foods or groups of foods on the list of commonly allergenic foods. The criteria included compelling evidence of the association of the food with allergic reactions ideally involving positive DBPCFCs, evidence of severe and life-threatening reactions, and evidence of an IgE mechanism through positive SPTs or RASTs. For molluscan shellfish, these criteria are not met because the medical literature contains very little, if any, evidence of positive DBPCFCs for molluscan shellfish. However, DBPCFCs are contraindicated in cases of very severe food allergies (Bock *et al.*, 1988).

Allergic reactions to foods, including molluscan shellfish, can be treated with certain drugs (Furukawa, 1988; Simons, 1998). Antihistamines will counteract the effects of histamine (Simons, 1998), but do not counteract the effects of the other mediators released from mast cells and basophils during an allergic reaction. Epinephrine or adrenaline is considered as the life-saving drug for individuals at risk of severe anaphylactic reactions to foods (Sampson *et al.*, 1992). Epinephrine is available as a self-injectable drug. Consumers with a history of severe anaphylactic reactions to molluscan shellfish or other foods should carry epinephrine at all times.

The only prophylactic approach to prevent allergic reactions to foods is a specific avoidance diet (Taylor *et al.*, 1986, 1999). With molluscan shellfish allergies, individuals are advised to avoid the ingestion of one or more species of molluscan shellfish. Often, patients with shellfish allergies are advised to avoid all molluscan shellfish species or all shellfish (both molluscan and crustacean) or even all seafood. While some evidence exists for cross-reactions, the need for avoidance diets restricting all shellfish or all seafood is not clear in most cases. With better diagnosis, more specific advice could be given on the most appropriate avoidance diets. Since cross-reactions between finfish and molluscan shellfish have not been identified, avoidance of all seafood is probably especially unnecessary. Physician will need to conduct a lengthier diagnosis including possibly several DBPCFCs to provide sound advice on which specific shellfish must be avoided. Often, the expeditious approach of counseling patients to avoid all shellfish is chosen.

A. Severity of allergic reactions of molluscan shellfish

Severe, life-threatening anaphylactic reactions can occur among a subset of individuals with IgE-mediated food allergies; fatalities have been recorded (Bock *et al.*, 2001, 2007; Sampson *et al.*, 1992; Yunginger *et al.*, 1988). In the United States, the majority of fatal food-allergic reactions result from the inadvertent ingestion of peanuts and tree nuts (Bock *et al.*, 2007). However, severe, life-threatening reactions have been described for many allergenic foods on a less frequent basis. Individuals with food-induced asthma seem to be at particularly high risk for development of severe and life-threatening reactions (Sampson *et al.*, 1992).

Fatal allergic reactions from the ingestion of molluscan shellfish are rarely reported. Two deaths have been ascribed to snail allergy (Pumphrey, 2004; Wu and Williams, 2004). Several other severe anaphylactic shock reactions have also been linked to snails (Banzet *et al.*, 1992; Guilloux *et al.*, 1998; Moneret-Vautrin *et al.*, 2002). In a report from the Allergy Vigilance Network of 107 fatal or near-fatal reactions occurring mainly in France in 2002, Moneret-Vautrin *et al.* (2004) did not distinguish between molluscan and crustacean shellfish but did note that 5 of the cases were attributed to snails which amounted to 4.7% of all reactions. Limpet, another gastropod species, has also been linked to several severe anaphylactic episodes, although no fatal reactions have been recorded (Maeda *et al.*, 1991; Morikawa *et al.*, 1990). Oyster is the only other molluscan species that has been clearly implicated in a case of anaphylactic shock (Gonzalez Galan *et al.*, 2002). Several of the molluscan species have been associated with the provocation of bronchospasm or asthma which can be life threatening is some cases. Most such reactions have been attributed to snail (Ardito *et al.*, 1990; Banzet *et al.*, 1992; Pajno *et al.*, 1994; Tomas *et al.*, 1997) and limpet (Azofra and Lombardero, 2003; Carrillo *et al.*, 1991, 1994; Castillo *et al.*, 1994).

B. Natural history of molluscan shellfish allergy

Generally, the prevalence of food allergies is greater among infants and young children than adults (Sampson, 1990). As noted previously, some of the food allergies that commonly affect infants and young children, especially egg and milk allergies, are frequently outgrown. The age distribution of allergies to molluscan shellfish seems to differ from milk, eggs, and some other allergenic foods and affects older children and adults more frequently than infants and young children (EFSA, 2006). This observation has not been documented by clinical studies. However, the later introduction of mollusks into the human diet seems to coincide with this trend. No information exists on the likelihood that molluscan shellfish allergy will be outgrown once manifested.

C. Minimal eliciting (threshold) dose for mollusks

The threshold dose for the offending food for elicitation of allergic reactions in sensitized individuals is quite low, perhaps as low as 1 mg or less (Taylor *et al.*, 2002). No information exists on the threshold dose for molluscan shellfish but total avoidance including caution with respect to cross contamination particularly in foodservice facilities is probably wise.

D. Allergic reactions to specific types of molluscan shellfish

The existence of allergic reactions to molluscan shellfish is a well-accepted clinical fact. However, an examination of the medical literature actually reveals only a modest level of evidence of allergic reactions to molluscan shellfish especially as compared to the eight most commonly allergenic foods or food groups. Shellfish allergies are very frequently mentioned in the medical literature, but these reactions are often related to crustacean shellfish with no mention of molluscan shellfish allergies. Although many people with crustacean shellfish allergy also avoid molluscan shellfish, the existence of molluscan shellfish allergies among these individuals is unknown. Molluscan shellfish allergy is probably best described as an underreported clinical entity, and the underreporting causes considerable uncertainty about the clinical importance of molluscan shellfish allergy.

Molluscan shellfish allergy has been described in the medical literature to virtually all of the commonly ingested types of molluscan shellfish. The following sections will summarize published reports of allergic reactions to the major categories of edible molluscan shellfish — gastropods, bivalves, and cephalopods.

E. Allergies to gastropods

Among the gastropods, snail allergy is certainly the most frequently described cause of allergic reactions. IgE-mediated snail allergy has been described in several European countries where snails are a popular food including Italy (Amaroso *et al.*, 1988; Ardito *et al.*, 1990; Grembiale *et al.*, 1996; Longo *et al.*, 2000; Meglio *et al.*, 2002; Pajno *et al.*, 1994, 2002; Peroni *et al.*, 2000), France (Banzet *et al.*, 1992; Guilloux *et al.*, 1998; Moneret-Vautrin and Kanny, 1995; Moneret-Vautrin *et al.*, 2002, 2004; Petrus *et al.*, 1997; Vuitton *et al.*, 1998), Portugal (Palma Carlos *et al.*, 1985; Tomas *et al.*, 1997), Spain (De la Cuesta *et al.*, 1989), and the Netherlands (van Ree *et al.*, 1996a). Snails can provoke a range of allergic reactions including severe reactions such as asthma and laryngeal edema on occasion. As noted earlier, fatal reactions have also been ascribed to snail allergy (Pumphrey, 2004; Wu and Williams, 2004). Snail allergy appears to occur more frequently among individuals with allergies to dust mites or other mites (Amaroso *et al.*, 1988; De la Cuesta *et al.*, 1989; DeMaat-Bleeker *et al.*, 1995; Pajno *et al.*, 2002; Peroni *et al.*, 2000; Tomas *et al.*, 1997; Van Ree *et al.*, 1996a). In fact, the possibility exists that individuals with snail allergy were first sensitized to mites and then experience cross-reactions on ingestion of snails.

Most of the allergic reactions to snails are described for terrestrial snail, usually *Helix* sp. Such snails are frequently eaten in some cultures as escargot and other delicacies. However, marine snails of several types, including whelks and turban shells, are also likely to be a source of allergic reactions, although rarely reported. Several cases of turban shell allergy are reported from Japan where this mollusk is eaten (Ishikawa *et al.*, 1998c; Juji *et al.*, 1990). One of these cases was a single case of exercise-induced anaphylaxis in a young female (Juji *et al.*, 1990). Stewart and Ewan (1996) noted a case of anaphylactic shock in the United Kingdom associated with ingestion of whelk. Several dozen patients who were sensitized to the common whelk, *Buccinum undatum*, were identified in Korea (Lee and Park, 2004), although no evidence is provided of either allergic histories to ingestion of whelk or the results of clinical oral challenge studies to confirm the provocation of adverse reactions.

Allergic reactions to the gastropod, limpet, are also well described. All reported cases to date are from Spain, Japan, or Singapore which may parallel frequency of consumption of this particular mollusk. Allergic reactions to limpet appear to be quite severe in many of the reported cases. The first cases of limpet allergy were two cases in Spain of asthma provoked by ingestion of limpet as described by De la Cuesta *et al.* (1989). Later, two cases of severe, systemic anaphylaxis to ingestion of limpet were reported from the Canary Islands (Carrillo *et al.*, 1991). These cases were both quite severe and involved hypotension, asthma, and loss of consciousness in addition to other symptoms. Evidence of an IgE-mediated reaction was obtained. Later, Carrillo *et al.* (1994) described six cases of allergic reactions to limpet. Two of the described cases were severe, although these may be the same two patients described in the report from several years earlier. All six of these limpet-allergic individuals experienced asthmatic reactions to ingestion of limpet. Castillo *et al.* (1994) identified five patients experiencing anaphylaxis with severe asthma upon ingestion of limpet. Joral *et al.* (1997) identified an additional two cases of anaphylaxis to limpet from Spain. Five more limpet-allergic patients from Spain were described by Azofra and Lombardero (2003); all five patients experienced asthma which was quite severe in three of the five subjects. Morikawa *et al.* (1990) reported four patients with allergic reactions to grand keyhole limpet in Japan including three subjects who experienced asthmatic reactions, one of which was quite severe. Maeda *et al.* (1991) described three Japanese patients with severe anaphylactic reactions to both limpet and abalone. A single case of exercise-induced anaphylaxis to lapas, a type of limpet, was also reported in Japan (Juji *et al.*, 1990). From Singapore, Thong *et al.* (2005) reported 11 patients with anaphylaxis to limpet and abalone. Evidence of cross-reactions between dust mite allergy and limpet was presented in several of these cases (Azofra and Lombardero, 2003; Castillo *et al.*, 1994).

Abalone allergy is also known but is reported even less frequently than snail and limpet allergy. However, Lopata *et al.* (1997) described a rather large group of 38 individuals with histories of adverse reactions to abalone in South Africa. About two-third of these individuals reported immediate reactions while one-third experienced the onset of symptoms 2–7 h after ingestion of abalone. The symptoms described in these cases included respiratory or cutaneous symptoms in 75% of the patients and 25% with gastrointestinal symptoms. Evidence of IgE-mediated reactions was not obtained for all of these individuals so an allergic mechanism may not have been responsible in all cases. However, evidence of an IgE-mediated mechanism was obtained for some of these patients with 45% having an elevated RAST to abalone and 14 of 24 patients having a positive SPT to abalone. Some evidence existed for cross-reactions to snails, crayfish, mussels, oysters, and squid. In South Africa, a survey of 105 fish-allergic individuals indicated that 35.2% of them believed they were allergic to abalone (Zinn *et al.*, 1997). However, the suspicions of these patients were not confirmed by diagnostic assessments. A single patient with an allergic reactions to abalone was identified in Japan along with four additional limpet-allergic patients who showed some evidence of cross-reactivity to abalone (Morikawa *et al.*, 1990). A further 11 patients with allergic reactions to abalone or grand keyhole limpet were also identified in Japan (Maeda *et al.*, 1991). Dohi *et al.* (1991) described a case of exercise-induced anaphylaxis associated with ingestion of abalone.

F. Allergies to bivalves

Although bivalves are likely the most frequently ingested class of molluscan shellfish, the existence of allergic reactions to bivalves is rather poorly documented in the medical literature. IgE-mediated allergic reactions to oyster, clam, scallop, mussel, and cockle have been reported as described below.

Oyster allergy has only been reported on a few occasions in the medical literature. Moneret-Vautrin *et al.* (2002) briefly described three patients with anaphylaxis to oyster from the French Allergy Vigilance Network. The prevalence of oyster allergy in France was estimated at 0.4% (Rance *et al.*, 2005), but this was based upon a questionnaire survey of 2716 school children without any diagnostic follow-up. Also, one case equals an estimated prevalence of 0.4%, so a larger survey is needed to obtain a better estimate. A dozen cases of clinical hypersensitivity to oyster were identified in Spain with evidence of IgE-mediated mechanisms (Castillo *et al.*, 1994, 1996). In a study of 105 subjects with suspected fish allergy from South Africa, 25 individuals reported allergy to oyster but no diagnostic procedures were conducted to confirm the survey results (Zinn *et al.*, 1997). In a very large survey of 17,280 adults conducted as part of the multicenter European Community Respiratory Health Survey, 2.3% of respondents cited allergy to oyster but no confirmatory diagnostic evaluations were performed (Woods *et al.*, 2001). One case of anaphylactic shock has been ascribed to oyster (Gonzalez Galan *et al.*, 2002), so reactions to this bivalve can apparently be severe on occasion. A single case of exercise-induced anaphylaxis linked to oyster ingestion has also been described (Maulitz *et al.*, 1979).

Evidence of clam allergy is not as profound. The first reports of clam allergy involved a total of six subjects identified in 1916 (Cooke and Vander Veer, 1916; Strickler and Goldberg, 1916). In a survey of 1139 patients with a history of food hypersensitivity in Denmark, Estonia, Lithuania, and Russia, 6.2% indicated that they were allergic to clams, although no diagnostic confirmation was performed (Erikson *et al.*, 2004). Skin testing of 625 Japanese adult asthmatic individuals showed that 6.9% were sensitized to clam but the diagnosis was not supported by histories of these individuals on ingestion of clam or results of challenge trials (Arai *et al.*, 1998). Moneret-Vautrin *et al.* (2002) briefly identified a single case of clam allergy from the French Allergy Vigilance Network. The most definitive cases of clam allergy were documented by Parker *et al.* (1990) and Jimenez *et al.* (2005) but only involve a total of three patients. Parker *et al.* (1990) identified two clam-allergic patients in Canada; one of these patients had gastrointestinal symptoms confirmed by DBPCFC while the other one gave a history of laryngeal edema and was not challenged. Jimenez *et al.* (2005) described the case of an adult woman who experienced pruritis and facial angioedema on three occasions after ingestion of razor clam. Ten individuals with clam allergy were identified from the Canary Islands of Spain (Castillo *et al.*, 1994, 1996). A unique case of clam allergy involves a young girl who experienced tongue edema and pruritis after ingestion of clam, mustard, egg, and pork 2 years after receiving an intestinal transplant (Chehade *et al.*, 2004). This girl had not experienced any food allergies prior to the transplant.

Published cases of allergy to scallops are difficult to locate. Nakamura *et al.* (2005) indicate that scallop allergy is common in Japan but provides no citations to any case reports. In another study from Japan of 99 shrimp-allergic patients, 46 subjects reported eating scallops and 9 of them reported allergic reactions (Tomikawa *et al.*, 2006) but no other evidence is provided of scallop allergy. A single case of a serious systemic reaction to the ingestion of scallop in an adult male was reported by the French Allergy Vigilance Network (2006a). In South Africa, a survey of 105 individuals with suspected fish allergy revealed that 2 individuals suspected an allergy to scallops (Zinn *et al.*, 1997). However, these suspicions were not confirmed by diagnostic evaluations.

Mussel allergy is more frequently reported than either scallop or clam allergy. The prevalence of mussel allergy among school children in France was estimated at 0.8% (Rance *et al.*, 2005), but this estimate was based upon a questionnaire survey with no diagnostic follow-up. In South Africa, a survey of 105 individuals with suspected fish allergy revealed that 33.3% suspected an allergy to black mussels (Zinn *et al.*, 1997). However, these suspicions were not confirmed by diagnostic evaluations. These prevalence estimates are rather weak because of the lack of diagnostic confirmation. However, mussel allergy has been well documented in several reports in the medical literature. Ten patients with mussel allergy were identified in Spain including many who had respiratory symptoms (Castillo *et al.*, 1994, 1996). Eleven cases of allergy to mussels presenting primarily as urticaria and angioedema have also been confirmed in Italy (Nettis *et al.*, 2001). Severe allergic reactions have also been attributed to mussels. Mussels have been implicated in three cases of anaphylaxis requiring emergency treatment in Italy (Novembre *et al.*, 1998; Pastorello *et al.*, 2001). Cianferoni *et al.* (2001) reported one case of anaphylaxis to mussels requiring emergency treatment, but it is unclear if that case is also reported in the earlier publication from this group (Novembre *et al.*, 1998). Thus, the evidence for the existence of mussel allergy is reasonably strong. Additional patients are known to be sensitized to mussels by the presence of mussel-specific IgE in their blood serum or positive SPTs. Moneret-Vautrin and Petithory (1987) indicated that 2.3% of 256 patients at an allergy referral center were sensitized to mussels but the symptoms of the patients to mussel ingestion were not described. Andre *et al.* (1995) identified six patients who were sensitized to mussels but provided no information regarding whether these individuals suffered adverse reactions upon ingestion of mussels. In a large study of 13,300 people from Berlin Germany, only 0.1% were determined to be sensitized to mussels (Zuberbier *et al.*, 2004); no further evidence of allergy to mussels was provided.

Allergic reactions to cockles probably occur but are not particularly well described in the clinical literature. Cockles are described as the cause of single cases of food allergy reported to the French Allergy Vigilance Network (French Allergy Vigilance Network, 2006b; Moneret-Vautrin *et al.*, 2002).

G. Allergies to cephalopods

Allergic reactions to squid are rather well documented. Carrillo *et al.* (1992) describe seven patients with histories of reactions from the ingestion of squid or the inhalation of vapors from cooking of squid. All of these patients experienced asthmatic reactions. Positive SPTs and RASTs were obtained. Six of the seven patients had a history of coexisting shrimp allergy. The cross-reaction with shrimp was confirmed by SPT and RAST in these six individuals. No cross-reactivity could be confirmed between squid and oyster and the patients' histories provided no suggestion of cross-reactivity with other molluscan shellfish. In a study of 48 seafood-allergic patients in the Canary Islands of Spain, 24 individuals were identified as allergic to squid including 18 individuals who were also allergic to crustacean shellfish (Castillo *et al.*, 1994). Later, a group of 33 squid-allergic individuals were described from the Canary Islands that likely includes the 24 patients identified earlier (Castillo *et al.*, 1996). Squid allergy has also been described in Japan (Miyazawa *et al.*, 1996; Tanaka *et al.*, 2000; Tomikawa *et al.*, 2006). Four patients with immediate hypersensitivity to ingestion of Pacific squid (*Todarodes pacificus*) were documented as part of a study primarily aimed at identification of the major squid allergen. Tanaka *et al.* (2000) studied 23 patients with seafood allergies and determined that 18 of them were sensitized to squid. However, none of the patients were confirmed as squid-allergic by either history or challenge trials. In a study of 99 patients with shrimp allergy, 63 individuals had attempted squid ingestion and 11 subjects were identified as squid-allergic (Tomikawa *et al.*, 2006). Faeste *et al.* (2003) described an individual from Norway who was weakly sensitized to squid and more strongly sensitized to crustacean shellfish but provided no other evidence of squid allergy. A case of severe anaphylaxis to squid was reported to the French Allergy Vigilance Network from the isle of Reunion (Morisset and Parisot, 2003). In a case from France, a mite-sensitized child experienced angioneurotic edema after ingestion of squid and had a positive labial challenge test (Petrus *et al.*, 1999). A total of 656 children in Thailand were surveyed by parental questionnaires to identify 41 children with possible food allergies (Santadusit *et al.*, 2005). Diagnostic evaluation confirmed that seafoods were the most common cause of food allergy among a group of 29 children between 3 and 6 years of age; squid or crab was identified as the causative seafood product by challenge trial in three of these children (Santadusit *et al.*, 2005). In South Africa, a survey of 105 individuals with suspected fish allergy revealed that 12 of the 105 subjects suspected an allergy to squid (Zinn *et al.*, 1997), but these suspicions were not confirmed by diagnostic evaluations. A survey of 659 Portuguese adults revealed 3 individuals reporting allergy to squid and octopus but further confirmation of these self-reported allergies was not sought (Falcao *et al.*, 2004). Several cases of exercise-induced anaphylaxis associated with squid ingestion have been described — all in Japan (Dohi *et al.*, 1991; Miyake *et al.*, 1988a,b; Tanaka, 1994).

Allergic reactions to octopus are more rarely reported. Castillo *et al.* (1994) indicate that some of the 24 squid-allergic patients were also allergic to octopus but the exact number is unclear. Similarly, Carrillo *et al.* (1992) determined that their seven squid-allergic patients were highly cross-reactive to octopus extracts in *in vitro* IgE-binding experiments but no other evidence of octopus allergy is provided. A single case of IgE-mediated urticaria resulting from octopus was described in Japan (Arai *et al.*, 1998). Subsequently, three additional cases of octopus allergy were briefly described in a study focused primarily on the elucidation of the octopus allergen (Ishikawa *et al.*, 2001). Tanaka *et al.* (2000) indicated that 19 of 23 seafood-allergic subjects were sensitized to octopus but did not confirm the octopus allergy by either history or challenge trials. In a study of 99 shrimp-allergic patients in Japan, 62 subjects had tried octopus and 11 of them reported symptoms from eating octopus (Tomikawa *et al.*, 2006). Five cases of allergy to octopus were diagnosed in a series of pediatric food allergy cases from Japan (Ebisawa *et al.*, 2003). A recent case report from Spain describes an adult female who had octopus allergy but could tolerate ingestion of squid, cuttlefish, shrimp, crab, and lobster (San Miguel-Moncin *et al.*, 2007). A survey of 659 Portuguese adults revealed 3 individuals reporting allergy to squid and octopus but further confirmation of these self-reported allergies was not sought (Falcao *et al.*, 2004).

Only nine allergic reactions to cuttlefish have been described (Caffarelli *et al.*, 1996; Ebisawa *et al.*, 2003; Shibasaki *et al.*, 1989). One patient was a 10-year-old female who experienced a severe reaction to ingestion of cuttlefish that was manifested by urticaria, angioedema, asthma, abdominal pain, laryngeal edema, and hypotension (Shibasaki *et al.*, 1989). SPT and RAST were positive. This patient reportedly tolerated octopus, clam, oyster, abalone, mussel, and scallop but reacted to crab and shrimp. Caffarelli *et al.* (1996) describe a 14-year-old female who had cuttlefish-dependent, exercise-induced anaphylaxis. Ebisawa *et al.* (2003) reported 7 cases of allergy to cuttlefish among a series of 305 pediatric cases of food allergy but provided no specifics on the circumstances or symptoms of these patients.

H. Food-dependent, exercise-induced molluscan shellfish allergy

With food allergies, some individuals react only when they eat the particular food in conjunction with exercise. Several such cases have been described for molluscan shellfish. In one of the earliest reports of exercise-induced food anaphylaxis, the provocateurs were oysters and shrimp for an adult male in conjunction with long-distance running (Maulitz *et al.*, 1979). A 17-year-old female experienced urticaria, dyspnea, syncope, and hypotension while riding a bicycle after eating *Lapas* shellfish, a type of limpet (Juji *et al.*, 1990). This same patient later experienced a similar reaction from running after eating *Turbo cornutus*, a marine snail.

This reaction was confirmed using an exercise challenge. Evidence of a cross-reaction with keyhole limpet was also provided. A 14-year-old male experienced asthma and severe anaphylaxis on several occasions after running or swimming following the ingestion of snails (Longo *et al.*, 2000). No exercise challenge was reported to confirm this history. A positive RAST to snail, crab, and dust mite was reported. Caffarelli *et al.* (1996) described the case of a 14 year-old female who experienced dyspnea, hoarseness, facial and neck swelling, and diffuse urticaria after eating cuttlefish and playing volleyball; an exercise challenge confirmed the reaction. In a questionnaire survey of school children in Japan, one student was identified with squid-associated exercise-induced anaphylaxis after playing soccer (Tanaka, 1994), although exercise challenge was not conducted to confirm the reaction. In an investigation of 11 cases of food-associated exercise-induced anaphylaxis, Dohi *et al.* (1991) described two mite-sensitized young women who reported histories of exercise-induced reactions associated with ingestion of molluscan shellfish. The first patient had episodes associated with crab and shrimp as well as squid. The squid reaction occurred after playing tennis. The second patient had reactions to abalone after either bicycling or running. Miyake *et al.* (1988a) reported three cases of food-dependent, exercise-induced anaphylaxis in male children. One of these cases involved ingestion of either squid or shrimp associated with playing volleyball and was described more fully in another report (Miyake *et al.*, 1988b).

I. Occupational allergies to molluscan shellfish

Occupational allergies can also occur in the food industry. In these cases, individuals experience reactions from the inhalation or skin contact with the offending food. They may or may not be able to eat the offending food safely. Occupational contact with various seafoods, either by skin contact or inhalation, is a rather well-known cause of occupational allergies (Jeebhay *et al.*, 2001). Molluscan shellfish have been less commonly implicated in these occupational allergies than other seafoods such as crustacean shellfish and fish. Several cases have been described of occupational allergies to molluscan shellfish. These reactions can be provoked by either the shells or the meat of the mollusks. The mechanisms involved in these occupational allergies are often not well investigated but can involve IgE-mediated, immediate hypersensitivity reactions or cell-mediated, delayed hypersensitivity reactions.

With respect to the shellfish meat, asthma and contact urticaria were reported in a restaurant worker from the handling of scallops (Goetz and Whisman, 2000). Inhalation of lyophilized clam in a factory producing freeze-dried clam was reported as a cause of occupational asthma (Desjardins *et al.*, 1995). Occupational asthma has also been linked to abalone (Clarke, 1979), mussels (Nava *et al.*, 1983), and clam liver extract in a laboratory research scientist (Karlin, 1979). Cases of contact dermatitis have been described from cuttlefish in a restaurant worker (Burches *et al.*, 1992), squid, oysters, mussels, and scallops among several different restaurant workers (Freeman and Rosen, 1991), oysters in oyster shuckers (Yamura and Kurose, 1966), fisherman from handling of cuttlefish (Olszanski and Kotlowski, 1997; Tomaszunas *et al.*, 1988), and mussels in mussel processors (Glass *et al.*, 1998; Zhoutyi and Borzov, 1973). A single case of contact urticaria in a restaurant cook was linked to squid (Valsecchi *et al.*, 1996). In the most significant report of occupational allergy, Tomaszunas *et al.* (1988) identified 66 deep-sea fishermen with occupational allergies, principally asthma, as a result of handling cuttlefish. Occupational asthma from cuttlefish has also been reported among 50 fishermen (Olszanski and Kotlowski, 1997).

The dust from mollusk shells can also provoke occupational allergies. Inhalation of mollusk shell dust in a nacre button factory was associated with hypersensitivity pneumonitis (Orriols *et al.*, 1990, 1997). A similar case was identified in Korea (Kim *et al.*, 1982). Several Japanese investigators have described occupational asthma occurring among workers who culture oysters (Nakashima, 1969; Wada *et al.*, 1967). Exposure to dust from mother-of-pearl in a souvenir maker (Tas, 1972) and to cuttlefish bones in a jewelry polisher (Beltrami *et al.*, 1989) was linked to occupational asthma.

V. MOLLUSCAN SHELLFISH ALLERGENS

The major allergen of molluscan shellfish is tropomyosin, a muscle protein. The term major allergen is used to define proteins that elicit IgE binding in the sera of half or more of patients with allergies to the specific source (Metcalfe *et al.*, 1996). Tropomyosin is a ubiquitous muscle protein in all animals. Tropomyosin is a 34- to 36-kDa protein that is highly water soluble and heat stable as evidenced by the fact that tropomyosin can be isolated from the water used to boil shrimp (Daul *et al.*, 1994). Tropomyosin can actually be found in both muscle and many nonmuscle cells in animals. In muscle cells, tropomyosin is associated with the thin filaments in muscle and plays a role in the contractile activity of muscle cells. In nonmuscle cells, tropomyosin is found in microfilaments but its function is less well understood. Tropomyosins are present in all eukaryotic cells. Different isoforms of tropomyosin are found in different types of muscle cells (skeletal, cardiac, smooth), brain, fibroblasts, and other nonmuscle cells. While these tropomyosins are highly homologous, small differences do exist in their amino acid sequences. These differences may be important in the various functions of tropomyosins in muscle and nonmuscle cells.

Tropomyosin is a well-known allergenic protein. Tropomyosin was first identified as the major allergen from shrimp (Daul *et al.*, 1994; Shanti *et al.*, 1993). Tropomyosin is now recognized as a pan-allergen among invertebrate animal species (Reese *et al.*, 1999). Allergenic tropomyosins have been found in many invertebrate species including crustacean shellfish (shrimp, crab, lobster, etc.), arachnids (house dust mites), insects (e.g., cockroaches), and molluscan shellfish (e.g., squid, octopus, cuttlefish, mussel, scallop, and oyster) (Reese *et al.*, 1999). Table 4.4 contains a list of allergenic tropomyosins from various molluscan shellfish species. As shown in Table 4.4, tropomyosin has been identified as the major allergen of gastropod species including abalone, whelk, and turban shell, bivalve species such as clam, mussel, oyster, and scallop, and cephalopod species including squid, cuttlefish, and octopus. While tropomyosin is also a known allergen of snails, it appears to be a more minor allergen in snails (Asturias *et al.*, 2002).

TABLE 4.4 Tropomyosin allergens from molluscan shellfish species

Species	Allergen	Reference
Snail (*Helix aspersa*)	Hel as 1	Asturias *et al.*, 2002
Abalone (*Haliotis discus*)	Hal d 1	Choi *et al.*, 2003
Abalone (*Haliotis midae*)	Hal m 2	Lopata *et al.*, 1997
Abalone (*Haliotis rufescens*)	Hal r 1	Chu *et al.*, 2000
Common whelk (*Buccinum undatum*)	Buc u 1	Lee and Park, 2004
Turban shell (*Turbo cornutus*)	Tur c 1	Ishikawa *et al.*, 1998c
Fan shell (*Pinna atropurpurea*)	Pin a 1	Leung and Chu, 1998
Razor clam (*Ensis macha*)	Ens m 1	Jimenez *et al.*, 2005
Mussel (*Perna viridis*)	Per v 1	Chu *et al.*, 2000
Oyster (*Crassostrea gigas*)	Cra g 1	Ishikawa *et al.*, 1997; Ishikawa *et al.*, 1998a; Leung and Chu, 2001
Scallop (*Chlamys nobilis*)	Chl n 1	Chu *et al.*, 2000; Lu *et al.*, 2004
Octopus (*Octopus vulgaris*)	Oct v 1	Ishikawa *et al.*, 2001
Squid (*Todarodes pacificus*)	Tod p 1	Miyazawa *et al.*, 1996

The IgE-binding epitopes of tropomyosin have been elucidated in some cases. Evidence exists for the presence of both common and cross-reactive and more species-specific epitopes (EFSA, 2006). As will be discussed later, the diversity in epitopes likely explains the lack of uniform allergic cross-reactivity that is observed clinically. One of the primary IgE-binding epitopes of the oyster allergen, Cra g 1, has been identified as IQLLEEDMERSEER (Ishikawa *et al.*, 1998a, 1999). Another oyster allergen, Cra g 2, contains an identical epitope (Ishikawa *et al.*, 1998b); this may be another isoform of tropomyosin. The tropomyosin epitope in the gastropod species, *T. cornutus*, is different and resides at the carboxyl-terminal region of the protein (Ishikawa *et al.*, 1998a). In fact, the carboxyl-terminal region of tropomyosins is highly conserved across both molluscan and crustacean shellfish species (Chu *et al.*, 2000). The epitope region for Cra g 1 falls within a segment of the tropomyosin molecule that is more highly variable (Chu *et al.*, 2000).

While invertebrate tropomyosins are likely pan-allergens, vertebrate tropomyosins appear to be nonallergenic (Reese *et al.*, 1999). Using bioinformatics approaches to compare the sequences of tropomyosins from various species, Goodman *et al.* (2002) determined that tropomyosins from vertebrate species — rabbit, pig, chicken, and human — share 53–57% amino acid sequence identity to the known shrimp tropomyosin allergen, Met e 1. This comparison likely explains why vertebrate tropomyosins are not allergenic and do not cross-react with IgE antibodies specific to invertebrate tropomyosins.

Fig. 4.1 provides a percent identity matrix for the amino acid sequences of tropomyosins from a range of invertebrate and vertebrate species. As previously noted by Goodman *et al.* (2002), the vertebrate tropomyosins show between 50% and 60% amino acid sequence identity with all invertebrate tropomyosins. However, the amino acid sequence identities are higher for the molluscan tropomyosins ranging from 68% to 88% and even higher within the various classes of molluscan shellfish — 91–100% among cephalopod tropomyosins, 70–100% among tropomyosins from bivalves, and 85–97% among gastropod tropomyosins. The amino acid sequence identities for crustacean versus molluscan tropomyosins range from 56 to 68%, only slightly higher than the comparison to vertebrate tropomyosins. The comparison to mite and cockroach tropomyosins shows 56–66% amino acid sequence identity with molluscan tropomyosins.

Evidence suggests that tropomyosin is not the only molluscan shellfish allergen. Non-tropomyosin allergens have been identified in a number of molluscan shellfish species including the gastropods: snail (Amoroso *et al.*, 1988; Asturias *et al.*, 2002; Guilloux *et al.*, 1998), pen shell (Leung *et al.*, 1996) whelk (Lee and Park, 2004; Leung and Chu, 1998a,b; Leung *et al.*, 1996), fan shell (Leung and Chu, 1998a,b) abalone

			Gastropods			Cephalopods					Bivalves								Crustaceans					Roaches	Mites and ticks		Primates	Primates	Even-toed ungulates	Rabbits and hares
			A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	BB
Gastropods	Haliotis diversicolor	A	100	97	86	81	81	81	80	82	88	80	74	74	74	70	72	72	60	62	62	63	63	61	63	62	52	55	54	46
Gastropods	Haliotis rufescens (California red abalone)	B	97	100	85	78	79	78	78	79	86	78	72	72	71	68	70	70	59	61	60	61	61	60	62	61	51	53	52	45
Gastropods	Helix aspersa (brown garden snail)	C	86	85	100	84	84	84	82	83	88	80	71	70	70	71	72	72	63	63	63	64	64	63	65	64	52	56	55	46
Cephalopods	Ommastrephes bartramii (red flying squid)	D	81	78	84	100	100	99	96	92	88	79	71	71	70	70	71	71	63	63	62	63	63	61	64	64	52	54	53	47
Cephalopods	Sepioteuthis lessoniana (Bigfin reef squid)	E	81	79	84	100	100	98	96	92	88	79	71	71	70	70	71	71	62	63	62	63	63	61	64	64	52	54	53	47
Cephalopods	Sepia esculenta (golden cuttlefish)	F	81	78	84	99	98	100	98	92	88	80	71	71	70	71	71	71	63	64	63	64	63	61	65	64	52	54	54	47
Cephalopods	Todarodes pacificus (Japanese flying squid)	G	80	78	82	96	96	98	100	91	88	79	71	70	69	70	70	70	61	63	62	63	63	61	64	64	52	54	53	47
Cephalopods	Octopus vulgaris (common octopus)	H	82	79	83	92	92	92	91	100	89	80	71	71	70	72	73	72	63	64	63	64	64	62	64	63	54	55	55	48
Bivalves	Crassostrea virginica (eastern oyster)	I	88	86	88	88	88	88	88	89	100	100	84	84	84	78	79	79	66	67	68	67	68	65	66	66	53	55	55	46
Bivalves	Crassostrea gigas (Pacific oyster)	J	80	78	80	79	79	80	79	80	100	100	75	75	76	72	73	73	62	65	65	64	64	62	63	63	53	55	55	47
Bivalves	Mytilus galloprovincialis (Mediterranean mussel)	K	74	72	71	71	71	71	71	71	84	75	100	100	94	70	71	70	56	58	57	57	57	57	56	56	48	51	50	42
Bivalves	Mytilus edulis (edible mussel)	L	74	72	70	71	71	71	70	71	84	75	100	100	94	69	71	70	56	57	56	57	57	57	56	56	48	51	50	42
Bivalves	Perna viridis	M	74	71	70	70	70	70	69	70	84	76	94	94	100	69	70	70	55	57	55	56	56	56	55	55	49	51	50	43
Bivalves	Chlamys nipponensis (Japanese scallop)	N	70	68	71	70	70	71	70	72	78	72	70	69	69	100	95	92	57	58	57	58	57	56	59	58	51	53	52	45
Bivalves	Mizuhopecten yessoensis (Yesso scallop)	O	72	70	72	71	71	71	70	73	79	73	71	71	70	95	100	92	57	58	56	57	57	56	60	59	50	51	51	44
Bivalves	Mimachlamys nobilis	P	72	70	72	71	71	71	70	72	79	73	70	70	70	92	92	100	58	59	57	58	58	56	60	59	50	51	51	44
Crustaceans	Charybdis feriatus (crab)	Q	60	59	63	63	62	63	61	63	66	62	56	56	55	57	57	58	100	97	91	92	92	85	83	80	56	59	59	52
Crustaceans	Homarus americanus (American lobster)	R	62	61	63	63	63	64	63	64	67	65	58	57	57	58	58	59	97	100	94	95	93	82	83	81	55	57	57	51
Crustaceans	Panulirus stimpsoni	S	62	60	63	62	62	63	62	63	68	65	57	56	55	57	56	57	91	94	100	99	98	82	81	80	53	55	55	49
Crustaceans	Homarus americanus (American lobster)	T	63	61	64	63	63	64	63	64	67	64	57	57	56	58	57	58	92	95	99	100	99	82	81	81	54	56	57	50
Crustaceans	Farfantepenaeus aztecus (pen a 1)	U	63	61	64	63	63	63	63	64	68	64	57	57	56	57	57	58	92	93	98	99	100	82	81	80	54	56	56	50
Roaches	Periplaneta americana (American cockroach)	V	61	60	63	61	61	61	61	62	65	62	57	57	56	56	56	56	85	82	82	82	82	100	81	79	52	55	55	48
Mites and ticks	Dermatophagoides pteronyssinus (dust mite)	W	63	62	65	64	64	65	64	64	66	63	56	56	55	59	60	60	83	83	81	81	81	81	100	96	56	58	58	51
Mites and ticks	Lepidoglyphus destructor	X	62	61	64	64	64	64	64	63	66	63	56	56	55	58	59	59	80	81	80	81	80	79	96	100	56	58	57	51
Primates	Homo sapiens (human)	Y	52	51	52	52	52	52	52	54	53	53	48	48	49	51	50	50	56	55	53	54	54	52	56	56	100	86	85	82
Primates	Homo sapiens (human)	Z	55	53	56	54	54	54	54	55	55	55	51	51	51	53	51	51	59	57	55	56	56	55	58	58	86	100	98	73
Even-toed ungulates	Sus scrofa (pig)	AA	54	52	55	53	53	54	53	55	55	55	50	50	50	52	51	51	59	57	55	57	56	55	58	57	85	98	100	72
Rabbits and hares	Oryctolagus cuniculus (rabbit)	BB	46	45	46	47	47	47	47	48	46	47	42	42	43	45	44	44	52	51	49	50	50	48	51	51	82	73	72	100

FIGURE 4.1 Percent identity matrix for tropomyosins from molluscan shellfish, crustacean shellfish, insects and mites, and vertebrate sources. Compiled with the assistance of John C. Wise, Bioinformatics Specialist, University of Nebraska, Food Allergy Research & Resource Program.

(Choi *et al.*, 2003; Maeda *et al.*, 1991; Morikawa *et al.*, 1990), and limpet (Azofra and Lombardero, 2003; Maeda *et al.*, 1991; Morikawa *et al.*, 1990); the bivalves: oyster (Leung and Chu, 1998; Leung *et al.*, 1996), scallop (Leung and Chu, 1998; Leung *et al.*, 1996), and razor clam (Jimenez *et al.*, 2005); and the cephalopods: squid (Leung and Chu, 1998; Leung *et al.*, 1996), octopus (Leung and Chu, 1998; Leung *et al.*, 1996), and cuttlefish (Lin *et al.*, 1993). These non-tropomyosin allergens remain mostly unidentified. However, several of them have been proposed to be hemocyanin (Juji *et al.*, 1990; Koshte *et al.*, 1989; Maeda *et al.*, 1991; Mistrello *et al.*, 1992; Morikawa *et al.*, 1990), myosin heavy chain (Martins *et al.*, 2005), and amylase (Azofra and Lombardero, 2003). The cross-reactivity of these allergens is not as well defined as tropomyosin. As one example, the 49-kDa allergen from abalone, *Haliotis midae*, has been designated as Hal m 1 by the International Union of Immunological Societies (IUIS). Five abalone-allergic subjects displayed IgE binding to Hal m 1 and to a second major allergen of 38 kDa which is probably tropomyosin (Lopata *et al.*, 1997). That allergen is designated as Hal m 2 in Table 4.4, although it has not received a formal designation by IUIS. The clinical significance of these non-tropomyosin allergens remains to be determined for the most part. Evidence exists for cross-reacting allergens in other molluscan shellfish species including Turban shell, whelk, short-neck clam, clam, and mussel (Ishikawa *et al.*, 1999; Leung *et al.*, 1996).

VI. CROSS-REACTIONS

Solid evidence exists to indicate that tropomyosins are pan-allergen among invertebrate species (Reese *et al.*, 1999). However, non-tropomyosin allergens also exist in at least some species of molluscan shellfish. The clinical picture of cross-reactivity is more complex than might be anticipated.

A. Between molluscan shellfish species

Clearly, some individuals with molluscan shellfish allergy are reactive to all species of molluscan shellfish. Cross-reactivity has been established by clinical history, challenge trials (in a few instances), skin prick testing, and IgE-binding studies. Most clinical studies of cross-reactivity have been limited to a few species often within one class of molluscan shellfish. However, the totality of the evidence indicates that individuals with documented reactivity to one molluscan species and evidence of IgE against that species should be counseled to avoid other molluscan shellfish species. This recommendation is especially prudent for the individual classes of molluscan shellfish: gastropods, bivalves, and cephalopods.

The degree of amino acid sequence homology between the tropomyosin allergens of molluscan shellfish species also supports this recommendation as documented in Fig. 4.1. The tropomyosins of several cephalopod species including squid, cuttlefish, and octopus share 91–100% amino acid sequence identity similar to findings of 92–96% previously reported by Motoyama *et al.* (2006). The tropomyosins of several bivalve species including oyster, mussel, clam, and scallop share 70–100% amino acid sequence identity. The tropomyosins of several gastropod species including abalone and snail share 85–97% amino acid sequence identity. Overall, within the entire molluscan shellfish grouping, amino acid sequence identities for tropomyosin range from 68% to 100% (Fig. 4.1). By contrast, the degree of amino acid sequence identity for the tropomyosins is lower between crustacean and molluscan shellfish species at 56–68% and lower yet for various vertebrate species at 47–55% (Fig. 4.1).

However, clinical evidence of cross-reactivity among the various species of molluscan shellfish is not invariably found. Lopata *et al.* (1997) noted significant evidence of cross-reactions among molluscan shellfish species in patients allergic to abalone. However, Carrillo *et al.* (1992) identified no cross-reactivity between squid and octopus (both cephalopods) or other molluscan shellfish species but did find evidence of cross-reactions with shrimp. Similarly, a single patient with cuttlefish allergy (another cephalopod) tolerated octopus and other molluscan shellfish species but reacted to crab and shrimp (Shibasaki *et al.*, 1989). While Van Ree *et al.* (1996a) found no significant differences between the allergens of terrestrial and sea snails, Vuitton *et al.* (1998) noted that only four of seven patients with allergy to terrestrial snails also indicated reactivity to sea snails. Case reports exist of isolated allergy to octopus (Caiado *et al.*, 2007) and snail (San Miguel-Moncin *et al.*, 2007). In both of these cases, evidence indicated that tropomyosin was not the responsible allergen so the non-tropomyosin allergens may assume more importance in such cases. Certainly, if tropomyosin is the major allergen for most of these patients, the clinical cross-reactivity does not match the degree of amino acid sequence identity very well. If the epitopes on tropomyosin are located in variable regions where the amino acid sequence does vary, this could explain the observed clinical cross-reactivity patterns. The differences among various clinical cases may suggest that all patients do not respond to the same epitopes.

In their telephone-based survey of individuals with seafood allergies, Sicherer *et al.* (2004) identified 67 individuals with self-reported allergy to molluscan shellfish. The inquiries were isolated to clam, scallop, oyster, and mussel which all belong in the bivalve class. Of these 67 individuals, 34 (51%) reported reactions to only 1 species, 13 (19%) to 2 species, 5 (8%) to 3 species, and 15 (22%) to all 4 species. Obviously, the interpretation of this observation is limited because diagnostic confirmation of survey responses was not done. Wu and Williams (2004) evaluated 70 patients from Hong Kong, who were sensitized to molluscan shellfish including 28 patients with a history of severe anaphylaxis. Each of these patients underwent SPTs with extracts of five different species of molluscan shellfish (scallop, clam, oyster, abalone, and limpet). Within this group, the probability of a positive skin test was highest for limpet (0.45) followed by abalone (0.32), oyster (0.21), clam (0.16), and scallop (0.13). The probability of cross-reactive SPTs among the bivalves (scallop, clam, and oyster) ranged from 0.33 (oyster and either clam or scallop) to 0.67 (scallop and clam). The probability of cross-reactive SPTs was higher among the gastropods (limpet and abalone) with a 79% likelihood that an abalone-sensitized patient would react to limpet and a 54% likelihood that a limpet-sensitized patient would react to abalone. Curiously, the probability that an individual sensitized to a bivalve species would also be sensitized to limpet or abalone ranged from 0.42 to 0.88, while the probability that an abalone- or limpet-sensitized patient would also be sensitized to one of the bivalve species ranged from 0.18 to 0.25. If tropomyosin is indeed the major allergen for most of these subjects, a higher concordance of results might have been expected. The clinical cross-reactivity among crustacean species is generally higher (Waring *et al.*, 1985; Wu and Williams, 2004).

B. Between molluscan and crustacean shellfish species

Cross-reactivity between molluscan and crustacean shellfish species also occurs rather frequently. Since tropomyosin is the major allergen in both molluscan and crustacean shellfish, the frequency of cross-reactions is not surprising. Allergy to crustacean shellfish is more frequently diagnosed than molluscan shellfish allergy (Hefle *et al.*, 2007). Many of these individuals may be at risk of reactions to molluscan shellfish also. Appropriately, most individuals with either molluscan or crustacean shellfish allergy are advised to avoid all shellfish.

However, cross-reactivity between molluscan and crustacean shellfish is not invariably found. In a telephone-based survey of individuals with seafood allergies, only 14% reported allergic reactions to one or more crustaceans and one or more mollusks (Sicherer *et al.*, 2004). This finding may be partially attributed to avoidance and lack of experience with many of the species following discovery and diagnosis of the original shellfish allergy. Among 70 individuals sensitized to shellfish on the basis of positive SPTs, 25 were sensitized to crustaceans only, 18 were sensitized to mollusks only, and 27 were sensitized to both crustacean and molluscan shellfish (Wu and Williams, 2004). In a study of 24 shellfish-allergic children, Crespo *et al.* (1995) identified 23 with crustacean allergy but only 10 with allergies to molluscan shellfish. However, 9 of these 10 patients with molluscan shellfish allergy were also allergic to crustacean shellfish (Crespo *et al.*, 1995). Laffond (1996) evaluated 38 shellfish-allergic subjects and determined that 25 were sensitized to both crustaceans and mollusks, 12 to crustaceans only, and only 1 to mollusks only.

Several investigators have noted that tropomyosin is a common allergen among both crustacean and molluscan shellfish and have demonstrated *in vitro* cross-reactivity with IgE antibodies from patient sera (Leung and Chu, 1998; Leung *et al.*, 1996; Motoyama *et al.*, 2006; Reese *et al.*, 1999). The tropomyosins of crustacean species share only 56–68% amino acid sequence identities with tropomyosins of molluscan shellfish species (Fig. 4.1). This is high enough to explain the *in vitro* cross-reactivity in IgE binding. However, the existence of true clinical cross-reactivity has not been documented by oral food challenge in most cases. Certainly, the cross-reactions between the molluscan and crustacean shellfish species require much more careful and definitive study. However, minor differences in the structures of tropomyosin between different molluscan and crustacean shellfish species could account for the noted differences. Sensitization to tropomyosin in a molluscan species, snail, is not always accompanied by sensitization to tropomyosin in a crustacean species, shrimp (Van Ree *et al.*, 1996a). A second possibility is that unique allergens, other than tropomyosin, are involved with some species. More clinical studies on the cross-reactions between molluscan and crustacean shellfish species are needed to better define the frequency of cross-reactions and the identity of the allergens involved. Cross-reactions have been studied in so few patients with shellfish allergy that it is impossible to make generalizations about the ideal avoidance diets for such individuals, although the avoidance of both molluscan and crustacean shellfish is probably prudent in the absence of other information.

C. Between molluscan shellfish and mites or insects

Tropomyosin is also a major allergen in dust mites, known as Der p 10 and Der f 10, and in several species of cockroaches, *Periplaneta americana* — Per a 7 — and *Blatella germanica* — Bla g 1 (Aki *et al.*, 1995; Asturias *et al.*, 1998, 1999; Pomes *et al.*, 1998; Santos *et al.*, 1999). Clinically, a strong correlation exists between snail allergy and house dust mite allergy (Ardito *et al.*, 1990; Banzet *et al.*, 1992; DeMaat-Bleeker *et al.*, 1995; Pajno *et al.*, 2002; Sidenius *et al.*, 2001; Van Ree *et al.*, 1996a; among others). In most cases, it appears as though sensitization to dust mite occurred first (Meglio *et al.*, 2002). However, a few cases exist where sensitization to snail occurred first (Martins *et al.*, 2005; Van Ree *et al.*, 1996a). This cross-reactivity occurs with amino acid sequence identity of 65% for tropomyosins of mite and snail. Clinically relevant cross-reactivity has also been observed for limpet and dust mite (Azofra and Lombardero, 2003).

The tropomyosins of mite and insect species show some sequence identity (63–65%) with snail tropomyosin and share similar epitopes (EFSA, 2006; Fig. 4.1). Still, tropomyosin appears to play a minor role in the cross-reactivity of dust mites and snails (Asturias *et al.*, 2002; Guilloux *et al.*, 1998; Van Ree *et al.*, 1996a). Other non-tropomyosin allergens are likely to be involved including Der p 4 (amylase), Der p 5, Der p 7, and hemocyanin (Martins *et al.*, 2005; Mistrello *et al.*, 1992; Van Ree *et al.*, 1996). While snail is the main molluscan shellfish species involved in cross-reactions with dust mites, some patients allergic to dust mites and snails are also sensitized to mussels (DeMaat-Bleeker *et al.*, 1995; Van Ree *et al.*, 1996b). In their study of 70 patients sensitized to molluscan shellfish, Wu and Williams (2004) noted that 90% were also sensitized to dust mites. However, the clinical significance of this sensitization was not documented.

D. Effect of processing on allergenicity of molluscan shellfish

Little research has been conducted on the effect of processing on the allergenicity of molluscan shellfish. Empirical evidence suggests that molluscan shellfish are allergenic in both the raw and cooked states since they are commonly eaten in both forms. Tropomyosin is known to be heat stable and water soluble (Daul *et al.*, 1994). The IgE-binding ability of scallop tropomyosin was enhanced by Maillard browning induced by heating in the presence of reducing sugars (Nakamura *et al.*, 2005). In contrast, the IgE-binding ability of squid tropomyosin was decreased markedly by Maillard browning induced by heating in the presence of ribose, a reducing sugar (Nakamura *et al.*, 2006). The interpretation of these findings is difficult because IgE binding may not always correlate with clinical allergenicity. The Maillard reaction may alter the solubility of proteins which could affect the assessment of *in vitro* IgE binding. The amount of tropomyosin extractable from squid, octopus, and cuttlefish was diminished by treatment with either 2.5 or 4.7 kGy of cobalt-60 gamma radiation (Sinanoglou *et al.*, 2007). Although the cephalopod tropomyosin was less extractable and thus less detectable, its residual allergenicity remains unknown in the absence of clinical challenges of allergic patients.

E. Detection of residues of molluscan shellfish

The only proven therapy for molluscan shellfish allergy is strict dietary avoidance. Problems may arise with avoidance diets when clam is present due to mislabeling or to cross-contact during food processing (Taylor and Hefle, 2005; Taylor *et al.*, 1986, 1999). The food industry typically develops allergen control programs to prevent the occurrence of undeclared allergenic residues in other foods (Taylor *et al.*, 2006). The industry often uses enzyme-linked immunosorbent assays (ELISA) for the detection of residues of allergenic foods (Taylor and Nordlee, 1996). At present, no commercially available assays exist for the quantification of mollusk tropomyosin or other molluscan allergens (EFSA, 2006). An ELISA test kit has been developed and is currently in market for the detection of crustacean tropomyosin (Poms *et al.*, 2004), but its ability to detect molluscan tropomyosin is not known. Sinanoglou *et al.* (2007) developed an ELISA for the detection of tropomyosin from squid, octopus, and cuttlefish with a detection limit of 0.05 ppm. However, the specifics of this ELISA were not provided and it is not commercially available for use by the food industry.

VII. CONCLUSION

Molluscan shellfish allergy is assuming more public health importance since molluscan shellfish are designated as commonly allergenic foods in Canada and the European Union. Despite that designation, the prevalence of molluscan shellfish allergy appears to be relatively low in most geographic locales. The allergenicity of molluscan shellfish have been more poorly studied than their crustacean counterparts. Allergic reactions have been documented to most molluscan shellfish species and particularly to snail, abalone, whelk, limpet, clam, mussel, oyster, scallop, squid, octopus, and cuttlefish. Tropomyosin, a muscle protein, is likely the major allergen of molluscan shellfish allergen, although other proteins may also play important roles in allergenicity. More research on molluscan shellfish allergy seems warranted to better understand this condition and to improve the advice given to individuals with molluscan shellfish allergy with regard to their avoidance diets.

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