

Review

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Review

Critical Knowledge Gaps for Shellfish Allergies: Insights from Global Market Presence and Trade of Shellfish

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Abstract

With the increasing popularity of seafood in human diets, managing allergic reactions to shellfish has become more critical. Our review offers a comprehensive analysis of shellfish allergens, focusing on their relationship to global shellfish production and market presence. According to Food and Agriculture Organization data, global Mollusca production exceeds that of Crustacea. Despite this, progress in molecular allergen characterization and the development of diagnostic and analytical tools for Mollusca remains underdeveloped. Additionally, food allergen labeling regulations for shellfish are inconsistently applied across countries. Key allergens have been identified in several shellfish species, particularly Crustaceans, but more allergens must be discovered to enhance diagnostic tools. Within Mollusca, Cephalopoda remains understudied, with only one allergen identified despite dominating the shellfish trade. Lack of molecular studies on Molluscan allergens hinders further development of diagnostic tools and accurate allergen detection. Given the high consumption rates and the prevalence of Molluscan allergies, large populations are at risk. Therefore, systematic research on Molluscan allergens is essential for improving diagnostics, food safety regulations, and public health measures worldwide. Our review summarizes the knowledge gaps of the economically most relevant species of shellfish based on their market presence and trade and provides guidance for further research in the area.

Keywords: food allergies; diagnostics; shellfish; production; trade

1. Introduction

Blue foods, including shellfish, are a key source of nutrition worldwide (Tigchelaar et al., 2022), making 17% of the animal protein supply (Figure S1A), and reaching over 50% in several countries in Asia and Africa ("Food and Agricultural Organization. The State of World Fisheries and Aquaculture 2022. Towards Blue Transformation. Rome. <https://doi.org/10.4060/cc0461en> ", 2022). Growing interest has been put on blue foods in terms of current and future transitions to more sustainable food systems since the way in which blue foods are produced has been considered more environmentally sustainable than terrestrial animal-sourced foods (Jones, Alleway, McAfee, Reis-Santos, Theuerkauf, & Jones, 2022). Considering all these factors, in a high-production scenario, driven by increased financial investment and innovation in aquaculture production, annual global production of aquatic animal-source food is predicted to increase by 8% in 2030 compared to the baseline scenario in which moderate growth in aquaculture production is assumed (Golden et al., 2021).

Fisheries and aquaculture, according to the Food and Agriculture Organization of the United Nations (FAO), comprise food groups: Marine and freshwater fishes, Crustaceas, Mollusk (excluding Cephalopodes) and Cephalopodes, with fishes contributing around 70% of the total aquatic animals produced globally (Figure S1B).

Crustaceas are invertebrates in possession of exoskeleton and a segmented body of the phylum Arthropoda, class Malacostraca. Crustacea shellfish relevant in human diet are shrimps/prawns, crayfish, lobster and crabs. Mollusks are any soft-bodied invertebrate of the phylum Mollusca, usually wholly or partly enclosed in a calcium carbonate shell secreted by a soft mantle covering the body, represented classes of Bivalvia, Gastropoda and Cephalopoda. The molluscan shellfish relevant in human diet are gastropods (including abalones, limpets, land and marine snails, whelks), bivalves (including oysters, mussels, scallops) and cephalopods (including squids, octopuses) (Ruethers et al., 2018). Both Crustaceas and Mollusks are reported as causing allergic reactions. In food allergy studies, shellfish allergens primarily come from two major groups, crustaceans and mollusks.

Increased awareness of the high nutritional value of crustaceans and molluscs has led to a rise in shellfish consumption, and this has been associated with more frequent reports of allergic reactions (Dramburg et al., 2023). In contrast to allergens such as egg and cow's milk, shellfish allergy does not in general resolve with age, and thus lifelong dietary avoidance is necessary (Lopata & Lehrer, 2009). Seafood allergy is regarded to persist for life in up to 90% of patients (Zotova et al., 2019). On the other hand, adults can also develop new food allergies, and certain food allergies, such as shellfish allergies, are more likely to develop during adulthood than others (Kamdar, Peterson, Lau, Saltoun, Gupta, & Bryce, 2015).

Shellfish seems to be the most common trigger of immunoglobulin E (IgE)-mediated food allergy among adults in United States (C. Warren, Nimmagadda, Gupta, & Levin, 2023). The prevalence of shellfish allergies is estimated to be up to 3% of the adult population in United States based on self-report survey studies (Gupta et al., 2019; C. M. Warren, Aktas, Gupta, & Davis, 2019). In Europe prevalence assessed by questionnaire-based methods was 0.1% to 5.5% for crustacean allergy, 0.4% to 1.5% for mollusk, and 0.1% to 1.5% for shellfish allergy, while food challenges confirmed a 0% to 0.9% prevalence of crustacean allergy and 0.1% prevalence of mollusk allergy (Moonesinghe et al., 2016).

Shellfish allergies have one of the highest rates of severe reaction to ingested food, known as food-induced anaphylaxis. Data from the European Anaphylaxis Registry demonstrated that shellfish and wheat were identified as major triggers of food-induced anaphylaxis in adults, where shrimp was the main food trigger (Dölle-Bierke et al., 2023). In adults and children's shellfish-induced anaphylaxis has a prevalence of 0.41% and 0.11% in Asia, 1.9% and 0.72% in North America, and 0.27% and 0.55% in Europe (Baseggio Conrado, Patel, & Turner, 2021). Recent study showed 8.3% of European patients with asthma or atopic diseases aged 1-18 years experienced anaphylaxis after shrimp ingestion (Miraglia del Giudice et al., 2023) with prawn and crab (Crustaceans) being the major causes of anaphylaxis in both children and adults. In Singapore, Thailand, and Hong Kong, a majority of the food-induced anaphylactic cases were attributed to shellfish, at frequencies of 24.6% (Goh et al., 2018), 45.2% (Lertnawapan & Maek-a-nantawat, 2011) and 71.2% (Smit, Cameron, & Rainer, 2005), respectively.

The epidemiology of shellfish allergies varies across countries. Based on a cross-sectional food allergy prevalence survey, in United States the prevalence of shellfish allergies in children was 1.3%, with more children allergic to crustacean (1.2%) than mollusk (0.5%) (H. T. Wang, Warren, Gupta, & Davis, 2020). Combined crustacean and mollusks allergy self-reportedly affects as many as 5.5% of French children (5–17 years old) and 9.0% of American adults (Moonesinghe et al., 2016). The prevalence of crustacean allergy alone is considerably higher, with the highest reported prevalence of 10.3% determined among Italian adults who were confirmed positive by Skin Prick Test (SPT) (Burney, Summers, Chinn, Hooper, Van Ree, & Lidholm, 2010). Self-report survey study in USA adults reported 2.4% crustacean allergy prevalence (C. M. Warren et al., 2019), as well as 1.9% for shrimp, 1.3% for lobster and 1.3% for crab (Gupta et al., 2019).

The prevalence of shellfish allergy is generally higher among Asians based on questionnaire-based surveys: in China 15.3%, 13.9% and 11.1% 7.3% for crab, shrimp and shellfish (Hao et al., 2018), 7.3% in Taiwanese children and adults (Wu et al., 2012), in Hong Kong 1.3% for preschool (T. F. Leung, Yung, Wong, Lam, & Wong, 2009) and 1.7% for children aged below 15 years (Ho, Lee, Wong, Ip, & Lau, 2012), 5.2% in Singapore and 5.1% in Philippines teenagers (Shek et al., 2010).

Although numerous clinical cases of sensitized patients to mollusc are often reported, there are still no reliable clinical diagnostic approaches of isolated mollusc allergy due to undefined allergens and extensive immunological cross-reactivity with other allergen sources containing similar proteins in different species (Dhruve, Ratrey, Lowanshi, Chandravanshi, Kashyap, & Pandey, 2024; Yan, Yao, Jiao, Yang, Liu, & Zhang, 2026). In addition, the wide variety of mollusc species available in different regions of the world, and cross-reactivity within mollusc species make a diagnosis of mollusk allergy even more complicated (Yu et al., 2022). Mollusks allergy was reported in several studies across Europe and Asia (Osterballe, Mortz, Hansen, Andersen, & Bindselev-Jensen, 2009; C. Y. Y. Wai, Leung, Leung, Wong, & Leung, 2021), but its prevalence seems to be lower when confirmed using available *in vitro* and *in vivo* tests (Ruethers et al., 2018). Based on self-report survey study in USA adult's molluscan allergy prevalence was 1.6% (Gupta et al., 2019; C. M. Warren et al., 2019). Approximately 45% of individuals with a crustacean allergy are also allergic to mollusk, while 70–80% of mollusk-allergic patients also experienced allergic reactions to crustaceans (Giannetti, Pession, Bettini, Ricci, Gianni, & Caffarelli, 2023; C. M. Warren et al., 2019). The patients with crustacean or mollusk allergy should avoid all shellfish species not only due to cross-reactivity, but also due to contamination of each other. In addition, patients with allergy to shrimp are at risk of developing clinical allergy to edible insects (De Marchi, Wangorsch, & Zoccatelli, 2021), which are frequently consumed in Asia, and since recently also in Europe and North America.

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) (Taylor, 2008). Of 45 Spanish patients with mollusk allergy, 55% were allergic to cephalopods (squid 40%, cuttlefish 11%, octopus 11%), 31% to bivalves (clam 18%, mussel 9%, razor fish 7%, cockle 2%), and 24% to gastropods (limpet 15%, snail 9%), demonstrating heterogeneity in allergy to mollusks. Although not known with certainty, the prevalence of molluscan shellfish allergy is likely to parallel consumption patterns being more frequent in locales where consumption is frequent (Taylor, 2008). Therefore, although awareness of mollusk allergies is growing, its prevalence still remains uncertain (Mederos-Luis, Poza-Guedes, Pineda, Sánchez-Machín, & González-Pérez, 2024).

Besides, Asian countries have distinct ways of seafood processing and dietary habits, introduce seafood early into the infants' diet, seafood is often consumed raw, and consume some seafood species that are not being consumed in other parts of the world (Christine Y. Y. Wai et al., 2021). Previous studies of coastal Asian populations reported high rates of shellfish allergy, suggesting a relationship between greater shellfish allergen exposure and shellfish allergy risk. Shellfish allergy was very common in the local Singapore (4-6 years, 1.19%; 14-16 years, 5.23%) and Philippine (14-16 years, 5.12%) (Shek et al., 2010). According to meta-analysis, including studies with questionnaire-based surveys, in China, prevalence of shellfish allergy was observed in 19% of the total patients with food allergy (Luo et al., 2022). Interestingly, in Asia, the patients have shellfish and fish allergies are more common than those have peanuts, nuts, and wheat allergies (Hill et al., 1997).

Thus, several studies point that shellfish is the dominant food allergen among Asian populations (A. S. Y. Leung, Leung, Wai, Leung, & Wong, 2019; Shek et al., 2010). Shellfish allergy is characterized by pan-allergenic molecule, tropomyosin, discovered in numerous species of Crustacea and Mollusca and described as abundant, thermostable, muscle protein, tropomyosin (TPM) which shows high structural homology between phylogenetically related species (Ayuso, Reese, Leong-Kee, Plante, & Lehrer, 2002; Ruethers et al., 2018; Shanti, Martin, Nagpal, Metcalfe, & Rao, 1993). Interestingly, although over 80% of European shellfish-allergic subjects were sensitized to tropomyosine (TPM) as the main shellfish allergen, recent study suggested that only half of Asian subjects with challenge-

proven shrimp allergy were sensitized to TPM (Christine Y. Y. Wai et al., 2021). Low sensitization rate to TPM was also reported in Singapore (34.2%) (Thalayasingam et al., 2015) and Japan (37%) (Tsedendorj, Chinuki, Ueda, Kohno, Adachi, & Morita, 2018). Similarly, Chinese patients were shown to be sensitized to multiple shrimp allergens, supporting opinion that TPM might not be the major allergen in Asians (Christine Y. Y. Wai et al., 2021). Diversified allergen sensitization in Asians is explained by consumption practice for shrimp and crab non-muscle body parts of (cephalothorax, containing brain, heart, stomach and bladder, ovaries and hepatopancreas) together with muscles (Christine Y. Y. Wai et al., 2021).

Despite the large number of edible shellfish, only 62 shellfish allergens, of which 52 crustacean and 10 mollusks have been identified, characterized and registered in the WHO/IUIS Allergen nomenclature database by October 2024. Knowing that there are thousands of species in human diet of which more than 800 species of only Mollusca Bivalvia in human diet (Huang, Edie, Collins, Crouch, Roy, & Jablonski, 2023), prioritization is a must.

This review aims to provide a comprehensive overview of shellfish production, regulatory landscape, allergens, diagnostic and analytical repertoire of available tools and provides insight into the most relevant gaps to be filled to improve shellfish allergy diagnosis, management and public health measures worldwide.

2. Methodology

Production data was retrieved from FAO FishStat, FAO global fishery and aquaculture statistics, for 2021 (<https://www.fao.org/fishery/en/fishstat>), using FAO's Fisheries and Aquaculture statistics software FishStatJ (<https://www.fao.org/fishery/en/statistics/software/fishstatj>). For each species, there are one or several entries for each producing country as production data are separately provided for different FAO major fishing areas (such as Northern regions, central regions, Southern regions), as well as for type of production (such as capture production and aquaculture production). In order to get information on total production of shellfish live weight for given species by given country, if there was more than one entry tons produced in different FAO major fishing areas and different types of production were summed. Total production of shellfish live weight for given species by given country was calculated as % of total production of shellfish live weight for given species by all countries. Allergens listed in WHO/IUIS were retrieved in October 2024. Allergome data as of October 2024 were retrieved to collect information on non-registered allergens. Publications were additionally reviewed manually until September 2024 to add to the list on non-registered allergens based on reported IgE reactivity. Blast similarity search was performed with sequence information in UniProt available as of November 2024.

3. Overview of Global Production and Regulatory Landscape

3.1. Production of Shellfish

Of the 494 taxonomically recognized species ever farmed in the world of aquaculture and fisheries, 88 species are molluscs and 49 species are crustaceans. Crustaceans' production in 2021 amounts to nearly 18 million tons of live weight (LW) (Figure 1). In comparison, FAO reported the annual production of crustaceans across the world at approximately 16.9 million tons in 2020 ("Food and Agricultural Organization. The State of World Fisheries and Aquaculture 2022. Towards Blue Transformation. Rome. <https://doi.org/10.4060/cc0461en>", 2022).

Data for 2021 show that Mollusk and Cephalopodes with 24,8 million LWT produced globally account for nearly 60% of global production of shellfish foods (Figure 1). FAO FishStat gives separate production data for Cephalopodes: they contribute around 10% of the global production of all shellfish foods. Among the produced Mollusk, on top are oysters and clams (Supplementary information, Table S1).

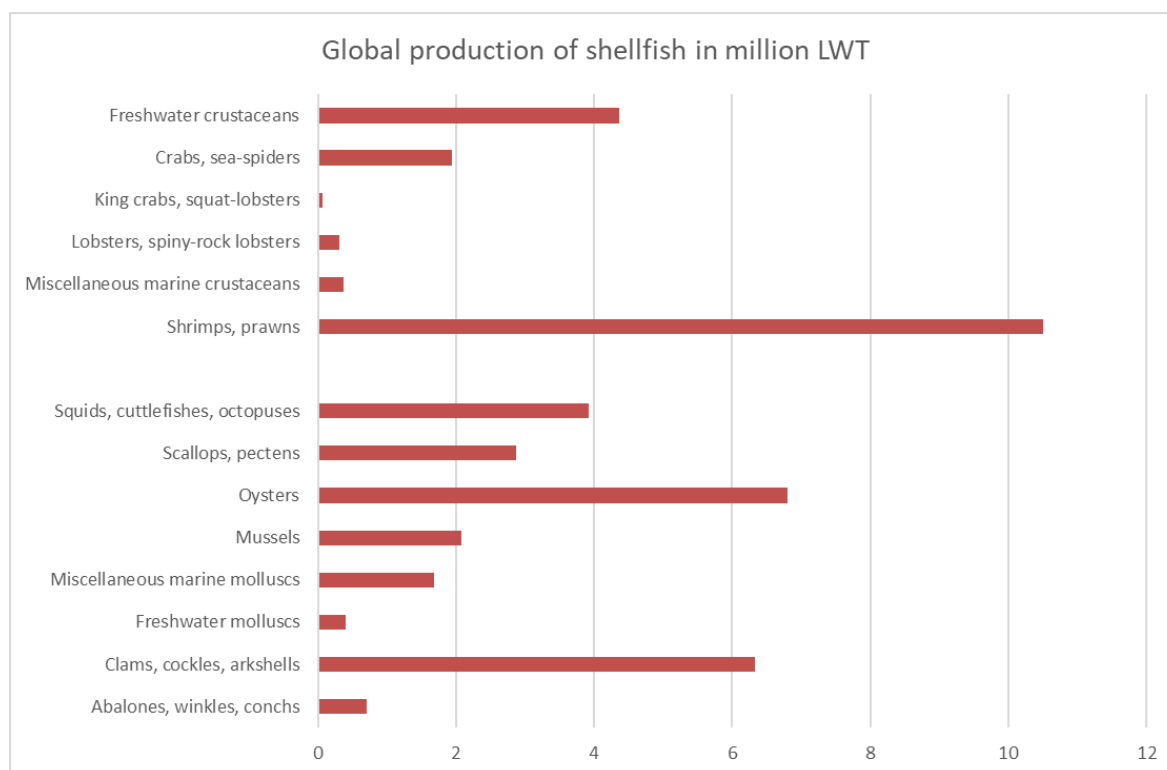


Figure 1. Global production of shellfish in 2021 in million LWT according to FAO database. Production includes both captured and aquacultured shellfish.

China mainland is the main producer of Crustaceans, Mollusca and Cephalopoda in 2021 (Figure 2, Supplementary Tables S2, S3, S4). Marine shrimps dominate the global production of crustaceans, and they are an important source of foreign exchange earnings for a number of developing countries in Asia and Latin America (Supplementary Table S5). Supplementary Table S5 gives an overview of the most important Crustacean shellfish in 2021, including aquaculture and capture production. The species produces in >1000 tones and their main producers are presented. The top produced marine Crustacean species is whiteleg shrimp (*Penaeus vannamei/Litopenaeus vannamei*), while red swamp crawfish is the top products among freshwater crustaceans. Among Mollusan shellfish, various cupped oysters and Japanese carpet shell (*Ruditapes philippinarum*) are main products (Table S6).

Jumbo flying squid (*Dosidicus gigas*) is a top Cephalopode produced globally, amounting to nearly 1 million LWT annually, just from the top two producers. Cephalopods production is dominated by squids, quite opposite to the production of Molluscs, where various oysters, mussels, clams, scallops are made to the top 10 produced foods (Supplementary Table S6).

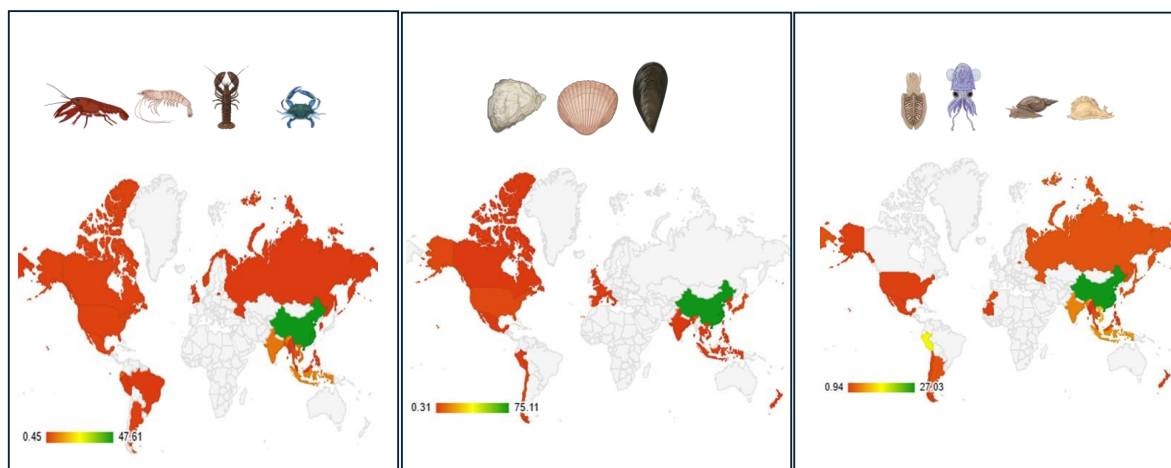


Figure 2. Global shellfish production in 2021. A. Geochart of top 20 countries with the highest Crustaceans production in 2021. B. Geochart of top 20 countries with the highest Mollusca (ex. Cephalopoda) production in 2021. C. Geochart of top 20 countries with the highest Cephalopoda production in 2021. The data are mined from FAO. Created in BioRender. Velickovic, T. (2025) <https://BioRender.com/r99t719>.

Of the shellfish produced globally, global trade of Crustaceans dominates the market (Figure 3). Mollusca (ex. Cephalopodes), though making the top produced group, accounts for the minor fraction of global trade of exported commodities. Export comprises live, frozen, chilled, dried, cured, meat of shellfish etc. (Supplementary Table S7-S12).

Mollusca makes 48% of all shellfish being globally produced but only 7% is exported (with a similar % of imported commodities based on Mollusca), most of the produced Mollusca are in fact consumed in the countries producing them. China produces over 80% of the world's bivalves, but domestically consumes almost all of this production (Supplementary Table S7-S12).

Mollusca, a heterogeneous group of species, grouped according to FAO into Mollusca ex. Cephalopodes and Cephalopodes (such as squids) rational finds in quite different trading pattern. Mollusca ex. Cephalopodes are mostly consumed in the producing country, while Cephalopodes trade accounts for nearly 64% of the production, with import equally dominating the shellfish market. Thus, production of Mollusca (ex Cephalopodes) could, with a 5% margin of error, be related to the consumption in the producing country (oysters, clams, mussels).

European market is characterized by the highest import of all commodities based on Mollusca and Crustaceans.

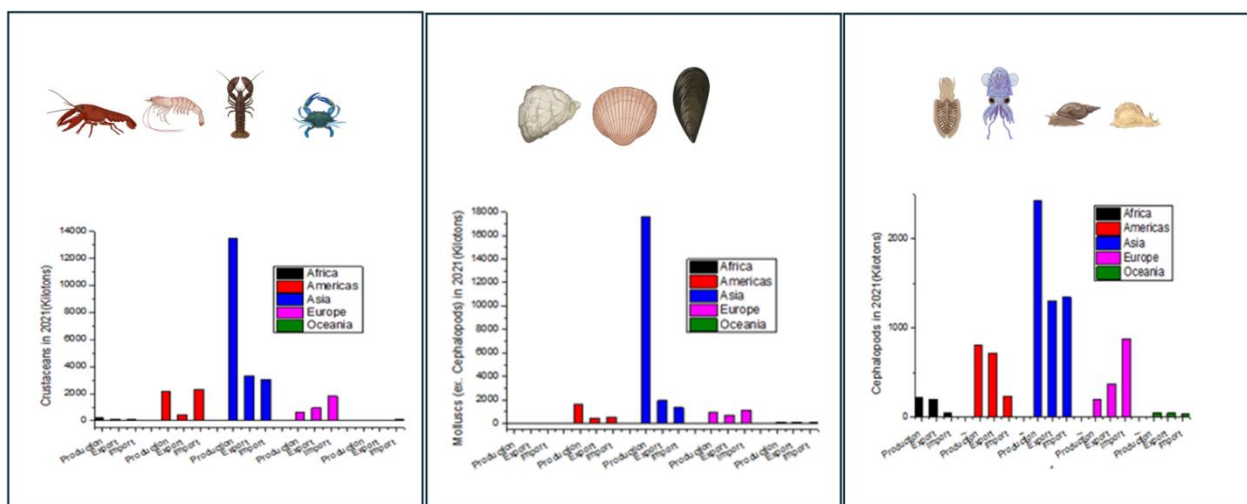


Figure 3. Overview of shellfish trade. A. Production, export and import of Crustaceans. B. Mollusc (ex, Cephalopods) and C. Cephalopods, in different regions of the world for 2021. The data are mined from FAO database using FishStat. Created in BioRender. Velickovic, T. (2025) <https://BioRender.com/w04q952>.

3.2. Shellfish Supply per Capita

According to 2021 FAO data, although Asia is the highest producer, importer and exporter of all shellfish groups (Figure 2), its supply quantity per capita, e.g. availability for consumption, is relatively low, particularly Cephalopodes (Figure 4 and Section S2.2.).

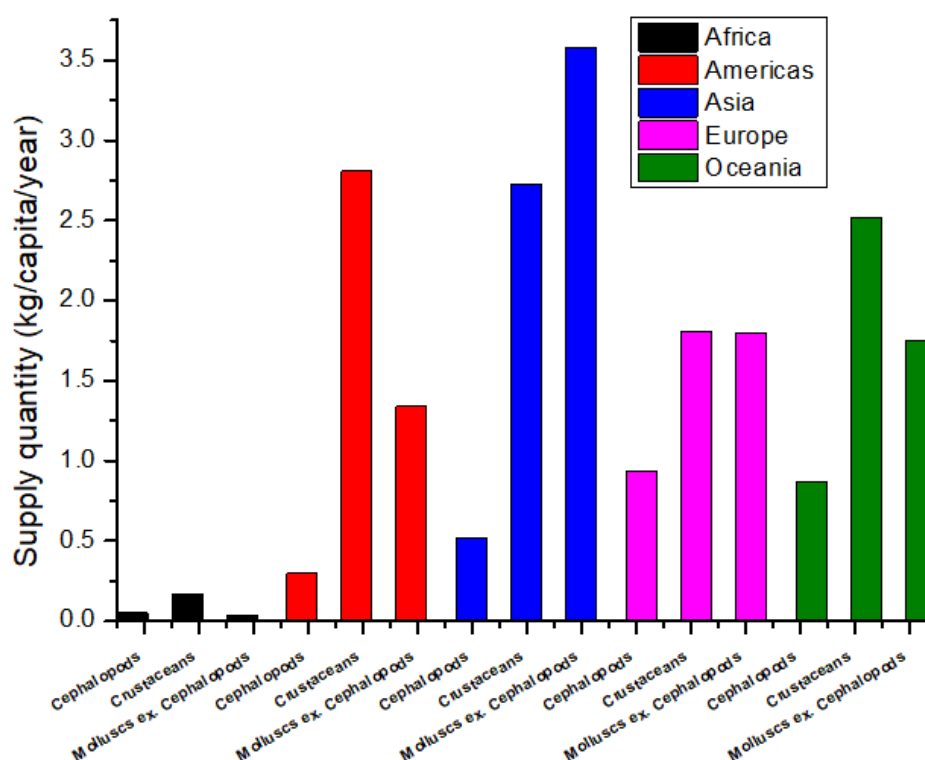


Figure 4. Supply quantity (kg/capita/year) of Cephalopods, Crustaceans and Mollusc (x, Cephalopods) per region in 2021.

Although Asia is far the highest producer, importer and exporter of all shellfish groups (Figure 3), only several Asian countries are in the top 20 countries with the highest shellfish supply quantity per capita in 2021 (Table S13). China and its SARs/Provinces, and Republic of Korea have the highest shellfish supply quantity per capita, suggesting in general the highest consumption of shellfish per capita. Although China mainland is the highest producer (Table S1), exporter (Table S2) and importer (Table S3) of Cephalopoda, its supply quantity, and thus consumption per capita per year, is not in the top 20 countries for Cephalopoda (Table S13).

3.3. Consumption of Shellfish

Although there are available consumption data for fish and seafood as a whole, data on shellfish consumption is still scarce, particularly for different shellfish species and for different regions/countries. Another issue is the regular updating of shellfish consumption data which fastly changes due to changes in eating habits, as well as shellfish availability. Shellfish consumption data are of great importance not only for food allergy risk assessment, but also for exposure and risk assessments of different environmental contaminants found in shellfish.

Available data from 2019 show that of the 20.5 kg of seafood per capita consumption, nearly 75 percent came from finfish and the remainder came from shellfish, of which 12% were mollusks (excluding cephalopods), 11% crustaceans and 2% cephalopods (“Food and Agricultural Organization. The State of World Fisheries and Aquaculture 2022. Towards Blue Transformation. Rome. <https://doi.org/10.4060/cc0461en>”, 2022). Countries with the highest seafood consumption include coastal nations such as Iceland or the Maldives, at more than 80 kg per capita per year on average, while landlocked countries such as Afghanistan, Ethiopia and Tajikistan consume less than 1 kilogram per year.

According to the European Market Observatory for Fisheries and Aquaculture Products, EU is a major world market for fishery and aquaculture products: in 2021, apparent consumption amounted to 10,60 million tons in live weight equivalent (LWE), corresponding to 24 kg LWE per capita. Consumption, however, varies greatly across the EU, from 56 kg LWE per capita in Portugal to 6 kg LWE per capita in Hungary. Portugal still stands out as the major EU consumer of fishery and aquaculture products. The main products consumed are tuna (mostly canned), salmon, cod, Alaska pollock, shrimps, mussel, hake and herring (<https://www.eumofa.eu/the-eu-market#euFishMarket>). Of that, consumption of shellfish species per capita in Europe was: Shrimps 1.47 kg, Mussel 1.23 kg, Squid 0.62 (European Commission: Directorate-General for Maritime & Fisheries, 2022). For US, according to data from the National Oceanic and Atmospheric Administration (NOAA) in 2020, the average American consumption of fresh and frozen seafood products was 14.6 pounds, of which shellfish accounted for a total of 6.3 pounds per capita (“National Marine Fisheries Service (2022). Fisheries of the United States, 2020. U.S. Department of Commerce, NOAA Current Fishery Statistics No.2020. Available at: <https://www.fisheries.noaa.gov/national/sustainable-fisheries/fisheriesunited-states>,” 2022). US National Fisheries Institute’s (NFI) recently released top 10 list of seafood consumption in 2021(<https://aboutseafood.com/about/top-ten-list-for-seafood-consumption/>). Of total seafood consumption per capita per year (20.50 pounds) in 2021, the consumption of top 10 seafood is 15.67 pounds, of which 6.75 pounds consumed are shellfish (0.26 clams, 0.59 crab and 5.9 shrimp).

Relatively to production, Asian countries, particularly China, have low shellfish consumption per capita per year (Table 1). Moreover, although China mainland is the highest producer of Cephalopoda, its supply quantity, and thus consumption per capita per year, is not in the top 20 countries, e.g. its consumption is only 0.56 kg/capita/yr. On the other hand, small coastal countries, although globally negligible producers of shellfish, have high consumption per capita per year. Similarly, relatively to production, European countries are also very high consumers of shellfish.

4. Regulatory Landscape

The best management of food allergic diseases is avoidance of food containing causative allergens. With raw agricultural materials, avoiding allergens is simple. However, in processed foods, allergens can be hidden or added unintentionally to food products as a processing residue, or a contaminant. Therefore, processed food should be labelled for intentionally added allergens. In addition, food businesses may voluntarily provide information about the unintentional presence of allergens to fulfil legal obligations to provide safe food. This precautionary allergen labelling (PAL) is usually in the form “may contain x” or “not suitable for consumers with a x allergy”. Unintentionally added allergens may be present in food products due to allergen cross-contamination, when there is a risk that an allergen can enter the product accidentally during the production process, manufacturing, handling, transport, or storage of foods. Legislation in the EU and USA enforces regulations requiring companies to list ingredients on foods and beverages prepacked for direct sale, as well as food sold in loose form in i.e. restaurants, food from a takeaway and foods sold loose in retail outlets. For labeling of allergens in EU the name of the allergen or allergenic ingredient must be clearly highlighted from the rest of the text, e.g. with different letters, styles or colors in the background. In USA allergen’s food source name must be declared at least once on the food label in one of two ways, in parentheses following the name of the ingredient in the

ingredient list or immediately after or next to the list of ingredients in a “contains” statement. For certain foods or substances that cause allergies or other hypersensitivity reactions, there are more specific labeling requirements. In the USA legislation requires listing for Big 9 causative allergen sources), and in EU for 14 sources of allergens.

Analytical detection of allergens from Crustaceans is part of USA regulation on food allergens labelling. FDA enforces regulations requiring companies to list ingredients on packaged foods and beverages. For certain foods or substances that cause allergies or other hypersensitivity reactions, there are more specific labeling requirements. Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) identified eight foods as major food allergens: milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. On April 23, 2021, the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act was signed into law, declaring sesame as the 9th major food allergen recognized by the United States. The change was effective on January 1, 2023. However, although under section 201(qq) of the Federal Food, Drug, And Cosmetic Act (As Amended Through P.L. 118–15, Enacted September 30, 2023), Crustacean shellfish (such as crab, lobster, or shrimp) and ingredients that contain protein derived from Crustacean shellfish are regarded as major food allergens, molluscan shellfish (such as oysters, clams, mussels, or scallops) are not (Administration, 2024) .

EU lists 14 allergenic sources that must be declared according to the legislation of the European Union (Regulation (EU) N° 1169 / 2011 of the European Parliament and of the Council 2014) (“Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, Official Journal of the European Union L 304, 2011, p. 18-63, <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AL%3A2011%3A304%3ATOC>).,” 2011), including fish, Crustaceans and Molluscs and products thereof.

In China, there is no national legal regulation regarding food allergen labeling in China. In 2008, Beijing Municipal Government issued the Local Standard (DB11/Z5-21-2008) “Olympic Food Safety - Food Allergen Labeling” (“Beijing Bureau of Quality and Technique Supervision. (March 28,2008). Food safety for Beijing Olympic Games food allergens labeling DB11/Z521-2008,” 2008). Food safety for Beijing Olympic Games food allergens labeling DB11/Z521-2008), which was the earliest regulation on food allergen labeling in China and was abolished after the Olympics. In April 2011, National Standards Committee of China issued the National Standard (GB7718-2011) “National food safety standard-General rules for the labeling of prepackaged foods” (“National Standards Committee. GB7718-2011 National food safety standard-General rules for the labeling of prepackaged foods[S]. Beijing: Standards Press of China, 2011,” 2011). According to this standard, any food or its products contain the eight major categories of “allergic foods” defined by FAO/WHO, it is advisable to use an easily recognizable name in the ingredient list or to indicate it in a nearby location. But this is recommended labeling.

Within Food Allergy Research and Resource Program (FARRP), Institute of Agriculture and Natural Resources of University of Nebraska (updated in August 2024, <https://farrp.unl.edu/IRChart>) provided information on international food allergen labeling regulations. This database with 42 entries includes countries, unions (EU, 27 EU countries and 6 non-EU countries adopting EU allergen labeling regulations), GSO (6 countries), Central America (5 countries) and CARICOM (21 member states), e.g. in total 105 countries and their regulatory requirements. The most of African countries do not have regulation on labelling of food allergens. There are big differences in food allergen legislation among non-EU European countries. Some non-EU European Countries adopted EU allergen labeling regulations: Iceland, Liechtenstein, Norway, Macedonia, Switzerland, United Kingdom (UK).

Out of 42 entries listed, all regulate Crustacean shellfish, except Israel (38 all Crustacea, Japan and South Korea only shrimp and crab, Thailand only crab, shrimp), but only 13 entries, e.g. 52 countries, regulate Mollusca shellfish (11 entries, e.g. 44 countries, regulate all Mollusca, 7 GSO countries only clams, and South Korea only abalone, mussel, oyster and squid). Although Molluscan

allergen labelling is not obligatory, in Japan there is recommend labeling for abalone and squid, while in Thailand recommended is labeling for cuttlefish, neritic squid, octopus, escargot, mussel, clam, oyster, scallop, mytilus, meretrix lusoria and abalone. Countries not included in the overview of University of Nebraska, such as non-EU European Countries of the West Balkan all regulate fish, Crustaceans and Mollusca (Montenegro (“ Regulation on informing consumers about food, Official gazette of Montenegro, No. 22 (2018), <https://www.gov.me/en/documents/c815ddd1-d101-43d1-9202-e78da8f57976>,” 2018), Serbia (“Regulation on food declaration, labeling and advertising, Official Gazette of the Republic of Serbia, No. 41 (2009) and 17 (2019), <https://www.pravno-informacioni-sistem.rs/SlGlasnikPortal/eli/rep/sgrs/ministarstva/pravilnik/2017/19/3/reg>,” 2019):), except Bosnia which does not regulate Mollusca (“Rules on general declaration or labeling packaged foods, Official Gazette of Bosnia and Herzegovina, No. 87 (2008), https://fsa.gov.ba/wp-content/uploads/2020/01/hr-Pravilnik_o_opcem_deklariranju_ili_oznacavanju_upakirane_hrane_87-08.pdf,” 2008).

Thus, of top ten the most populated countries (India, China, USA, Indonesia, Pakistan, Nigeria, Brazil, Bangladesh, Russian Federation and Ethiopia), only in Russian Federation Molluscan shellfish allergen labelling is regulated (there is no data for Pakistan and Ethiopia). This means that in these countries, which are contributing to 50% of world population, Molluscan shellfish allergen labelling is not regulated.

Each country regulates a list of the most relevant food allergens for labeling, based on epidemiological screening and dietary habits of its population. Proper legislation and control of food products for allergen labeling, as well as unintentionally added food allergens (as contaminants) by state regulatory agencies are a major step towards better management of food allergic diseases that may prevent unwanted severe allergic reactions, especially for the vulnerable pediatric population.

These data show that most countries still do not regulate Molluscan shellfish allergen labelling, presenting health risk for the large portion of world population. With increasing rates of molluscan shellfish allergies worldwide, recognition of molluscan allergens by policy makers in these countries is urgently needed to ensure that people living with food allergies can safely purchase and consume foods. This is particularly important for people from countries with Molluscan shellfish allergen labelling legislation who travel to countries without it. However, more and more countries include Molluscan shellfish as allergens in their updated regulatives.

5. Allergens of Shellfish

The two invertebrate groups of crustacean and molluscan are, for culinary reasons, often combined as shellfish but belong to two very different phyla. The evolutionary and taxonomic diversity of the various consumed seafood species poses a challenge in the identification and characterization of the major and minor allergens critical for reliable diagnostics and therapeutic treatments. Allergens in various crustacean and mollusks species are mainly found in the edible portions of meat. Several crustacean allergens have been identified over the past two decades, due to the advances in protein identification and allergen characterization techniques.

5.1. Shellfish Allergens Nonregistered in WHO/IUIS

WHO/IUIS registered 57 Arthropoda (e.g., 52 crustacean allergens and 5 allergens of *Bombyx mori* (Silk moth)) and 10 molluscan (including one allergen of *Helix aspersa* [*Cornu aspersum*] (Brown garden snail) food allergens (Table S13 and Table S14). A comprehensive review on shellfish allergens in 2018 (Ruethers et al., 2018) reported 31 crustacean and 6 mollusks allergens, suggesting that progress has been made mostly with regards to new crustacean allergens. Currently, of 61 shellfish molecules registered as allergens by the WHO/IUIS Allergen Nomenclature Sub-Committee, only 9 belong to mollusks. Taking into account for example, that molluskan major allergen tropomyosin (TPM), a highly homologues protein across species, shares only up to 60% amino acid sequence identity with the crustacean TPM (Emoto, Ishizaki, & Shiomi, 2009), identification and registration of more mollusk's shellfish allergens is urgently needed.

Crustacean allergens are proteins found mostly in muscle tissue, cephalothorax or in roe. Their physiological functions are involved in muscle movement and energy metabolism. Several allergens have also been identified from edible parts of mollusks species. Three allergenic proteins: tropomyosin, arginine kinase and triosephosphate isomerase, have also been identified in both shellfish groups (Figure 5).

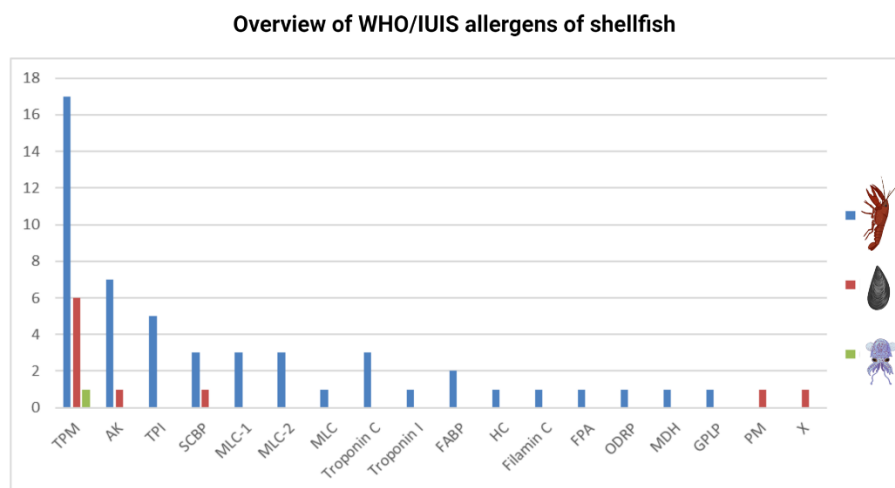


Figure 5. Overview of WHO/IUIS registered allergens of shellfish. Allergic proteins registered in Crustacea and Mollusca are grouped according to protein type. TPM – tropomyosin, PM paramyosin, AK –arginine kinase, X - unknown, SCBP - Sarcoplasmic Calcium-binding Protein, HC – hemocyanin, PPH - Phosphopyruvate Hydratase, PK - Pyruvate Kinase, MLC - Myosin Light Chain, MDH - Malate dehydrogenase, FPA - Fructose 1,6-bisphosphate Aldolase, ODRP – ovary development related protein, GPLP – glycoposphrylase like protein, FABP – fatty acid binding proteins. Blue (Crustacea), Red (Mollusca ex Cephalopodes), Green (Cephalopodes). Created in BioRender. Velickovic, T. (2025) <https://BioRender.com/b38o566>.

Of identified food allergens from Phylum Arthropoda, sub-Phylum Crustacea, all originate from blue food, e.g. from Class Malacostraca and Order Decapoda, including freshwater and marine shrimps, prawns, crabs, lobsters and crayfishes. Of the identified food allergens from Phylum Mollusca, except allergens from brown Garden snail *Helix aspersa*, all originate from marine blue food, from Classes Bivalvia (oysters), Gastropoda (abalone and whelk) and Cephalopoda (squid).

Of 52 Crustacea shellfish food allergens and their isoforms (52 allergens and 2 isoforms), majority are tropomyosins (Figure 5). Of 10 Molluscan shellfish food allergens and one isoform, 6 allergens are TPMs. Of all Mollusca, Cephalopods, with only one registered allergen (from Japanese flying squid) represent significantly understudied allergenic seafood source.

Of class Bivalvia there are no registered allergens of clams, cockles, mussels, scallops and numerous other families that live in saltwater, as well as a few families that live in freshwater.

Only in the period 2019-2021 more than 106 new allergens have been added to the WHO/IUIS (Sudharson, Kalic, Hafner, & Breiteneder, 2021). Important discoveries included paramyosin, Rap v 2, an allergenic paramyosin in molluscs. Paramyosins were previously known mainly as arthropod allergens (Sudharson et al., 2021). However, although there are hundreds of commercially important edible shellfish species, in WHO/IUIS allergens from only 22 Crustacean and from only 8 Molluscan species are currently registered.

5.2. Shellfish Allergens Nonregistered in WHO/IUIS

In addition to 52 TPM Crustacea shellfish allergens registered in WHO/IUIS, 72 allergens from different Crustacea species, which are IgE reactive, were reported (Figure 6), of which, one third are TPMs. This is similar to registered Crustacea allergens, of which, one third are TPMs. These nonregistered allergens need to be further tested in order to be approved by WHO/IUIS.

Nonregistered proteins with IgE reactivity in Mollusca are 52, of which 9 are described in Cephalopoda (Figure 6, In detail data available at <https://cherry.chem.bg.ac.rs/handle/123456789/7052>). In addition to 6 TPM Mollusca allergens registered in WHO/IUIS, 43 TPMs from different Mollusca species, which are IgE reactive, were reported. As for registered Mollusca allergens, the vast majority are TPMs, this suggests that in Mollusca shellfish, allergen repertoire is poorly characterized.

Overview of non WHO/IUIS allergens of shellfish

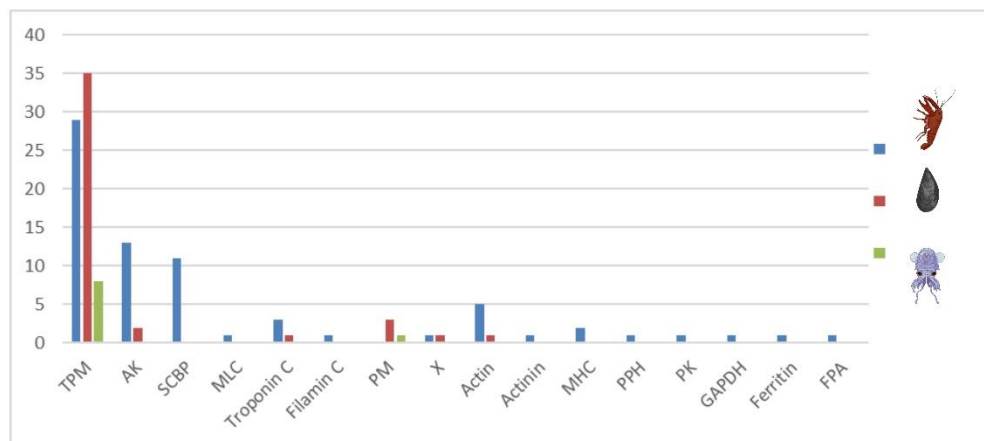


Figure 6. Overview of non WHO/IUIS registered allergens of shellfish grouped according to protein type. Blue (Crustacea), Red (Mollusca ex Cephalopodes), Green (Cephalopodes). TPM – tropomyosin, PM paramyosin, AK – arginine kinase, X – nonavailable, SCBP - Sarcoplasmic Calcium-binding Protein, MLC- Myosin Light Chain, MHC - Myosin Heavy Chain, HC – hemocyanin, GAPDH – glyceraldehyde hehydrogenase, FPA – Fructose 1,6-bisphosphate Aldolase. Overview of all non registered allergens, their available sequences and availability as recombinant allergen is given at <https://cherry.chem.bg.ac.rs/handle/123456789/705> . Created in BioRender. Velickovic, T. (2025) <https://BioRender.com/b38o566>.

In contrast to registered shellfish Molluscan TPMs encompassing only oyster, abalone, whelk and squid species, unregistered IgE reactive allergens were also shown in clam, sea snail, cockle, mussel, scallop, as well as in Cephalopoda octopus and cuttlefish species. All these nonregistered TPMs are solid candidates for future approval by WHO/IUIS, as TPM has shown to be major and the most dominant molluscan allergen. Besides TPM, there are numerous IgE reactive shellfish allergens, which are still nonregistered in WHO/IUIS, including paramyosin, arginine kinase, sarcoplasmic calcium-binding protein, myosin light chain, myosin heavy chain, hemocyanin, glyceraldehyde hehydrogenase, fructose 1,6- bisphosphate aldolase and allergens with unknown function (**Figure 6 and Section S3**).

5.3. Availability of Natural and Recombinant Shellfish Allergens

Based on the WHO/IUIS allergen registry, the most comprehensive allergen profile was delineated from *Penaeus monodon*, comprising nine registered shrimp allergens, including TM, AK, MLC2, SCBP, Troponin, HC, TIM, FABP, and GP. These allergens are mostly identified by conventional immunodetection methods. The availability of the genome assembly data of penaeid shrimp was indispensable for studies of penaeid shrimps allergenic proteins (Li, Chu, & Wai, 2023)

as it allowed production of recombinant molecules and their allergenicity testing. Similarly, with more genome assembly data, particularly from Mollusca, research will make significant progress.

Beside these listed IgE reactive allergens, not yet registered, there is high number of shellfish proteins that have been identified in different species and/or in silico predicted as allergens, but IgE reactivity was not demonstrated yet. In addition, there are numerous shellfish species for which potential allergens have to be identified in the future. This implies that identification of potential allergens in neglected shellfish species and testing of their IgE reactivity is also huge gap in shellfish allergy field, particularly important for species consumed worldwide, and/or consumed by globally high population, such as Asian. All submitted requests for allergen inclusion in WHO/IUIS list must fulfil the molecular and immunological requirements for inclusion into the allergen nomenclature database including IgE binding data using purified natural or recombinant allergens.

It implies that further testing of these nonregistered allergens and their registration is urgently needed in order to widen a list of shellfish allergens approved by WHO/IUIS. This is particularly important for Molluscan allergens, where there is nearly five times higher number of Molluscan IgE reactive nonregistered allergens than registered ones (Figure 6). A necessary prerequisite is the availability of natural or recombinant allergens of shellfish.

5.3.1. Availability of Natural Shellfish Allergens

Unfortunately, purified natural shellfish allergens are currently hardly available. The only commercially available is shrimp TPM by InBio (<https://inbio.com/>). However, not only that it is costly, but also it does not originate from single species. According to the manufacturer, depending of the season, this preparation originates from *L.setiferus*, *F. aztecus* and *F. duorarum*. Therefore, in order to obtain natural shellfish allergens research groups have to isolate and purify them. This includes development of methods for isolation and purification, which is usually multistep and complex, and characterization of purified protein. In addition, usually very low yields are obtained, with several isoforms present, and preparations may differ from batch to batch. Thus, isolation and purification of natural shellfish allergens could be very time consuming and costly, as reflected in commercially poor availability of natural shellfish allergens.

5.3.2. Availability of Recombinant Shellfish Allergens

In contrast to natural allergens, production of recombinant allergens is cost effective, preparations contain only one isoform and with no batch-to batch differences. The most of shellfish allergens registered in WHO/IUIS are commercially available as recombinant proteins produced in different expression systems (*E. coli*, yeast, baculovirus-infected insect cells, mammalian cells, and *in vitro E. coli*) (Section S3).

In order to be registered in WHO/IUIS, IgE binding data must be obtained using sufficiently purified (natural or recombinant) allergens (<https://allergen.org/submission.php>). Therefore, commercial availability of much wider palette of recombinant nonregistered shellfish allergens would enable IgE testing of much higher number of shellfish allergens and their faster registration, particularly Molluscan allergens which are currently scarce (only 10 registered). As obtaining highly purified natural shellfish allergens is complex and costly, commercial availability of recombinant allergens is key prerequisite for more efficient and up-to-date introduction of shellfish allergens in WHO/IUIS list in the future.

6. Diagnostic and Therapy Tools for Shellfish Allergies

According to the recently published European Academy of Allergy and Clinical Immunology guideline, providing recommendations for diagnosing IgE-mediated food allergy, food allergy diagnosis starts with an allergy-focused clinical history followed by tests to determine IgE sensitization: skin prick test (SPT), serum allergen-specific IgE (sIgE) to extracts, sIgE to allergen components and basophil activation test (BAT). SPT and sIgE to allergen extracts are recommended

as first-line tests, and sIgE to individual allergen molecules is second line. If available, BAT can be undertaken in equivocal cases, should standard allergy tests be insufficient to provide a diagnosis. Oral food challenge (OFC) remains the reference standard and should be reserved for cases that cannot be clarified with SPT, sIgE and/or BAT, while double-blind placebo-controlled food challenge (DBPCFC) can be used if open OFC are equivocal or for research purposes (Santos et al., 2023) For in vivo allergy diagnosis several types of skin tests are used, including skin prick Test (SPT), Intradermal Test (IDT) and Patch test, while in vitro diagnosis includes total IgE assay, serum specific IgE assays against allergen sources/molecules and basophil activation test (BAT) (Ansotegui et al., 2020). Besides clinical assessment, the current clinical shellfish allergy diagnosis includes SPT, sIgE testing, and OFC.

Despite OFC being the diagnostic standard for food allergy, there are no standardized protocols for shellfish allergies, as observed in international multicenter cohorts of patients from United Kingdom and USA (Nakonechna et al., 2024).

6.1. Shellfish Allergens Within Skin Prick Test Diagnostic Tools

There are several issues related to SPT for shellfish allergies. Firstly, commercially available shellfish extracts are limited compared to the wide variety of dietary shellfish. From the Table S16, it could be observed that three most reputable manufacturers of allergen extracts (ALK-Abelló, STALLERGENS GREER and HollisterStier Allergy) offer a very narrow palette of only several shellfish extracts. These manufacturers do not offer extracts of freshwater crustacean, mussels, squids, octopuses, abalones. In contrast, Chinese manufacturer Beijing Macro-Union Pharmaceutical Limited Corporation offers only extracts from two species, but for which China is the highest producer (>95%). Some manufacturers, such as HollisterStier Allergy, do not provide information of shellfish species.

This problem could be partially solved by in-house preparation of extracts from fresh shellfish for SPT, as done by Asero et al. (Asero et al., 2017), or by prick-to-prick test using fresh or cooked food, as done by Scala et al. (Scala et al., 2022). However, both approaches lack standardization.

Secondly, even commercially available shellfish allergen extracts for SPT still lack standardization. Several studies demonstrated that commercial shellfish SPT extracts from different manufacturers have different compositions and heterogeneous proteins profiles. Moreover, Asero et al. (Asero et al., 2017) demonstrated that five commercially available crustacean SPT extracts displayed a dramatic loss of protein bands compared to fresh shrimp extract when analyzed by SDS-PAGE. These authors also found a heterogeneous abundance of three shellfish allergens in these commercial extracts, resulting in 32 clinical profiles among 157 shrimp-allergic patients. Ruthers et al. (Ruthers et al., 2023) examined 11 commercial crustacean and 5 molluscan SPT extracts, utilizing biochemical and immunological methods and mass spectrometry. They showed that not only that total protein content varied up to 14-fold (0.1–1.4 mg/mL), but also in the SDS PAGE profiles 1–15 distinct bands were visible, suggesting huge differences in antigen repertoire, as well as their content in extracts, between different manufacturers. Besides, authors realized that some proteins may have been degraded into smaller fragments in some extracts. In addition, utilizing serum from five shellfish-allergic subjects, IgE-binding patterns to 14/16 extracts underlined high variance in anticipated in vitro and in vivo potency, and no IgE binding to 2 of tested extract due to low protein and allergen content, concluding that there is a high risk of false-negative SPT results with these extracts. In addition, a recent study investigated influence of geographic location of capture or aquaculture on allergenic protein profiles of black tiger shrimp (*Penaeus monodon*), and demonstrated that ten of the twelve known shrimp allergens were detected, but with considerable differences between locations, while tropomyosin abundance varied by up to 13 times between locations (Nakonechna et al., 2024). This shows that shrimp origin might directly impact the readout of commercial crustacean allergen detection kits, most of which target tropomyosin. In addition, as in Asia shrimp is always served head-on and shell-on, for Asian population shrimp cephalothorax extracts should be standardized and made available for the clinical diagnosis of seafood allergy (C.

Y. Y. Wai et al., 2021). Therefore, standardization of allergen extracts is urgently needed to improve the accuracy and reliability of SPT. On the other hand, in vitro component-resolved diagnostic tools might be beneficial and enable better predictions regarding cross-sensitization, especially for individuals sensitized to only one shellfish allergen (Ruethers et al., 2023).

6.2. Shellfish Allergens Within Diagnostic Tools for Measurement of Allergen-Specific IgE

Several manufacturers produce shellfish allergen extracts that can be used for specific IgE, IgG4, IgG determination, degranulation tests, BAT, cell tests, lymphocyte transformation tests, kit-manufacturing (such as, DST and Labor Dr. Weyers, Table S17). However, even these manufacturers offer extracts from limited number of shellfish species, and many species with highest global production and consumption are neglected. For example, there is no commercially available extract of whiteleg shrimp, whose production and consumption is the highest of all shellfish species.

Shellfish allergen-specific IgE in human sera can be measured in vitro by several ELISA kits, or by using singleplex and multiplex measurement platforms. The most of ELISA kits are seafood or shellfish allergy tests, thus measuring total IgE to mixture of all seafood (fish and shellfish) or shellfish allergens from several species. Although these tests are useful, they can not measure specific IgE to separate shellfish species.

Component-resolved diagnosis (CRD) that involves the detection of sIgE to individual allergenic molecules and/or allergen peptides has emerged to possibly resolve ambiguities of extract-based SPT and sIgE analysis. Molecular diagnosis using single allergens, instead of whole food extracts, to quantify sIgE levels were shown to more accurately reflect the clinical reactivity. However, the relevant allergen components fit for diagnosis may, however, vary among different geographical locations depending on the dietary habits and disease prevalence.

There are several platforms that measure shellfish specific IgE levels against a chosen allergen analyte, which can be recombinant or purified native allergen component or allergen extract from one or several species (Table S17). Singleplex platforms, such as ImmunoCAP (Phadia/Thermo Fisher Scientific, Uppsala, Sweden), IMMULITE (Siemens Healthcare Diagnostics, Los Angeles, CA, USA), FABER (Centri Associati di Allergologia Molecolare) measure specific IgE levels against a single chosen allergen analyte. Multiplex platforms, such as Alex2 Allergy (Macroarray Diagnostics, Wien, Austria) and ImmunoCAP ISAC 112 (Thermo Fisher Scientific) use a fixed array of more than hundred allergen analytes.

In ImmunoCAP System 17 shellfish extracts (including 4 different shrimps under single test code f24) are available for routine sIgE quantification (Table S16), including 8 for Crustacea and 9 for Mollusca (4 from Bivalvia, 3 Cephalopoda and 2 Gastropoda class) (https://www.abacusdx.com/media/PU_Product%20Catalogue%202022.pdf). Unfortunately, currently there is only one ImmunoCAP with allergen component, rPen a 1 Tropomyosin from shrimp (*Penaeus aztecus*). IMMULITE 1000/2000/Xpi offers 11 shellfish extracts (4 for Crustacea and 7 for Mollusca) and also only one allergen component, nPen m 1 from *Penaeus monodon* (shrimp). In FABER there are available 6 shellfish extracts and three allergen components, Lit v 1 from *Litopenaeus vannamei* (shrimp), Ven ga 1 from *Venus gallina* (clam) and Uro du 1 from *Uroteuthis duvauceli* (squid). In multiplex Alex2 Allergy Explorer, of array of 288 allergens, 10 extracts and 5 allergen components are from shellfish. All allergen components are from shrimps (nPen m 1, nPen m 2, nPen m 3 and rPen m 4 from *Penaeus monodon*, rPen a 1 from *Penaeus aztecus* and rCra c 6 from *Crangon crangon*). ImmunoCAP ISAC 112 platform contains 112 allergen components, of which only 3 allergens are from shellfish (nPen m 1, nPen m 2 and nPen m 4 from *Penaeus monodon*).

This data also shows that different platforms offer shellfish extracts from different species, and that shellfish extracts palettes in all these platforms are still very limited. In addition, extracts from many shellfish species with the highest global production and consumption are still missing, particularly species with highest consumption in Asia (Supplementary Table S5 and S6). Therefore, singleplex and multiplex platforms should widen shellfish extract palettes, and for choosing further species for extracts production they should be guided also by monitoring global production, and

particularly consumption. For example, only FABER offers extract and one allergen component from *Litopenaeus vannamei* (whiteleg shrimp), species with the highest global production/consumption among all shellfish.

On the other hand, in spite of the fact that there are 62 (52 Crustacean and 10 Molluscan) food allergens in database of WHO/IUIS, only 7 Crustacean and 2 Molluscan allergens are commercially available as allergen components within singleplex and multiplex diagnostic tools. Therefore, detection of mollusks hypersensitivity must still rely on molluscan extracts, or on indirect molecular diagnosis based on the presumption of cross-reactivity with crustaceans, unless proven with the oral food challenge. The total amount and repertoire of shellfish consumed has increased worldwide, particularly in the last 10 years, due to increased availability of shellfish in supermarkets, increased consumption of shellfish because of its nutritional values and health benefits, as well as due to increased travel to countries where seafood is a common part of the diet. As consequence there is a growing prevalence of shellfish allergies. Therefore, manufacturers of diagnostic tools for shellfish allergies should follow this trend and expand the palette of diagnostic tools in a timely manner. For example, in spite of the fact that available ImmunoCAP shellfish extracts are very limited compared to the variety of dietary shellfish, this repertoire was not widened by Phadia/Thermo Fisher Scientific in last 9 years, even not for single one shellfish extract (Catalog for 2022 https://www.abacusdx.com/media/PU_Product%20Catalogue%202022.pdf vs Catalog for 2013 <https://www.abacusdx.com/wp-content/uploads/2015/05/Phadia-Allergy-Autoimmunity-Product-Catalogue.pdf>).

For example, ImmunoCAP ISAC, containing only three shrimp allergens (Pen m 1, Pen m 2 and Pen m 4) allowed to diagnose only 44% of patients (Ukleja-Sokołowska, Gawrońska-Ukleja, Lis, Żbikowska-Gotz, & Bartuzi, 2020), while by using comprehensive panel of 11 recombinant shrimp allergens Wai et al. (Christine Y. Y. Wai et al., 2022) achieved detection rate of >80%. In addition, although TM is a common sensitizing allergen across populations, the major shrimp allergens could differ among populations (Christine Y. Y. Wai et al., 2022) Therefore, a much wider repertoire of allergen components for measurement of allergen-specific IgE is needed for more accurate and reliable shellfish allergy diagnostics, particularly for Molluscan shellfish.

Developing countries are the the most significant producers and consumers of shellfish. However, although food allergies in general are currently a significant health care problem in the developing world, food allergies are under-recognized as a clinical specialty which compromises the chance for accurate diagnosis. The main challenges are: lack of reliable data on the prevalence of food allergies, skin testing issues, in vitro test accessibility, settings and personnel for testing, as well as management issues with respect to local circumstances (Hossny et al., 2019).

6.3. Quantification of Shellfish Allergens for Food Safety and Monitoring

Analytical methods for detection and quantification of shellfish allergens have mostly been developed for Crustacean tropomyosin and target either the whole protein, peptide fragment or gene segment coding tropomyosin. Sensitivity of some of methods for quantification of TPM protein are so high reaching limit of detection down to even 20-30 pg/ml; (Radomirović, Gligorijević, Stanić-Vučinić, Rajković, & Ćirković Veličković, 2023; Y. Wang, Rao, Zhou, Zheng, & Fu, 2019). Most of the methods for detection and quantification of shellfish TPM are based on tropomyosin recognition by specific antibodies. ELISA sandwich assay is the most frequently used method for the detection and quantification of TPM (Lin, Lee, Huang, Sheu, & Yu, 2018; Seiki et al., 2007; Zhao et al., 2022). Methods based on liquid chromatography-mass spectrometry (LC-MS) use TPM peptide fragment as target (Fan et al., 2022; Korte, Monneuse, Gemrot, Metton, Humpf, & Brockmeyer, 2016; S. Wang, Pang, & Liang, 2021). In all mentioned studies Crustacean TPM was target, and there are only a few studies reporting methods for quantification of Molluscan TPM specific recognition. There is only one published method based on TPM recognition by specific Molluscan TPM antibodies. (Zhang, Lu, Ushio, & Shiomi, 2014) developed a sandwich ELISA method for the detection of TPM from molluscan bivalves (clam, scallop, and cockle), based on monoclonal antibody against a C-terminal

peptide of TPM, which is conserved across crustacean and molluscan species. The multiplex polymerase chain reaction (PCR) method with capillary electrophoresis for the detection of TPM from oyster, mussel, abalone (gastropod species), and clam was developed by Sathe and Sharma (Sathe & Sharma, 2009). Similarly, Suh et al. (Suh, Kim, Kim, Kim, & Kim, 2020) developed multiplex PCR assay combined with capillary electrophoresis for the simultaneous detection of TPM allergens from oyster, mussel, abalone, and clam mollusk species. Unfortunately, methods developed for quantification of Crustacean TPM cannot be applied for quantification of Molluscan TPM. It has been shown that clam residues were detected quite weakly using commercial crustacean tropomyosin kit, quantifying only 0.4 g/g of tissue, in contrast to shrimp where it detected 3389 g/g of tissue (Koppelman, Lardizabal, Niemann, Baumert, & Taylor, 2021).

Currently there are not commercially available pure natural Molluscan TPM, nor antibodies against it. Commercially available are 5 recombinant TPMs registered in WHO/IUIS and ready to ready-to-use ELISA kit for detection of Molluscan TPM based on tropomyosin from *Helix aspersa* (garden snail) TPM.

7. Cross-Reactivity of TPM from Economically Most Relevant Species of Shellfish with WHO Registered Allergens

It is usually considered that cross-reactivity between 2 proteins is probable if their sequence identity is >70% which also implies that the proteins have a similar 3D fold (Sharma & Vitte, 2024). In such cases, linear sequence alignment methods (i.e. BLAST) are frequently used to predict cross-reactivity between allergenic proteins.

Based on the global production of shellfish (FAO FishStat for 2021) presented in Supplementary material (Table S6), top 5 economically most relevant species or groups of Crustacea and Mollusca grouped into: freshwater crustacea, crabs, lobsters, shrimps/prawns, oysters, mussels, clams, scallops, squids and freshwater Mollusca have been included in the cross-reactivity search. For economically most relevant species without any TPM registered (or reported as IgE-binding), information on the sequence availability for TPM was collected. Furthermore, for those TPMs, BLAST search was performed to identify the homologues proteins among existing allergens. Detailed results of homology search between registered TPM of shellfish and corresponding proteins of the most economically relevant species are presented in supplementary Data available online. Only the top homologous allergen is presented in the overview given in Table 4. Sequence identity refers to the percentage of amino acids that show a direct match with the compared sequence during alignment.

Table 4. Alignment of major economically relevant species/genera/families/orders of Crustacean shellfish with the information on existing shellfish allergens (WHO/IUIS and non WHO/IUIS), cross-reactivity of TPM (if PubMed information was available) with registered TPM, availability of any diagnostic tools (in vivo, in vitro) or pure component (allergen) for *in house* allergenicity testing. For entries such as group of species (genus, family, etc.) % homology was presented for all species of specified group with available complete sequence in UniProt. Details are shown in data available at https://hdl.handle.net/21.15107/rcub_cherry_7008.

| Comm on name/ Latin name | Produc ers | Produc tion [LWT] | WHO/IUIS Allergens | nonWHO/ IUIS IgE reactive allergens | TPM as allergen or putative allergen (% homology with shellfish TPM | Commerci ally available extract or allergen |
|--------------------------------------|---------------|-------------------------|-----------------------|---|--|---|
|--------------------------------------|---------------|-------------------------|-----------------------|---|--|---|

| | | | | | | |
|--|-------------------|--------------------------------|--|---|--|--|
| | | | | | allergens approved by WHO/IUIS) | componen t for in vivo or in vitro diagnosis |
| Freshwater crustaceans | | | | | | |
| Red swamp crayfis h/ <i>Procam barus clarkii</i> | China (96.92%) | 2,717,18 3.83 | Pro c 1 (TPM), Pro c 2 (AK), Pro c 5 (MLC) and Pro c 8 (TIM) | Pro c 210 kDa (Ferritin), Pro c 4 (Sarcoplas mic Calcium- binding Protein, SCBP), pPro c 3.0301 (MLC2), pPro c 6.0201(tro ponin C) | > 91.9% with all Crustacean (with Hom a 1 98.24%) and > 60.56% with all Molluscan (with Hal l 1 1 63.38%) | f178 <i>Procambar us clarkii</i> extract; rProc 1, rProc 2, rProc 5, rProc 8 |



| | | | | | | |
|--|--|------------|---|-------------------------------|---|--|
| Chinese mitten crab <i>Eriocheir sinensis</i> | China (99.99%) | 833,313.75 | Eri s 2 (ovary development related protein) | Eri s 1 (TPM), Eri s 4 (SCBP) | > 91.55% with all Crustacean (with Scy p1 99.65%) and > 60.56% with all Molluscan (with Tod p 1, Cra g 1 and Hal l 1 63.0.3%) | <i>Eriocheir sinensis</i> extract; rEri s 2 |
| Giant river prawn <i>Macrobrachium rosenbergii</i> | China (52.24%), Bangla desh (15.48%), Thailan d (13.25%) | 327,827.88 | Mac r 1 (TPM), Mac r 2 (AK) | Mac r HC (Hemocyanin) | > 92.25% with all Crustacean (with Cra c 1 99.65%) and > 61.27% with all Molluscan (with Tod p 1, Cra g 1 and Hal l 1 63.38%) | rMar c 1 |
| Oriental river prawn | China (100%) | 273,493.50 | | TPM, MLC | > 91.55% with all Crustacean (with Hom a 1 98.24%) | rTPM , rMLC |

| | | | | | | |
|---|----------------|-----------|---|---|--|-------------------|
| Macrobrachium nipponense | | | | | and > 60.92% with all Molluscan (with Hal 1 1 64.08%) | |
| Freshwater prawns, shrimp <i>Penaeus Palaemonidae</i> | China (63.60%) | 67,297.23 | Exo m 1 (TPM) from <i>Exopalaemon modestus</i> ; Mac r 1 (TPM) and Mac r 2 (AK) from <i>Macrobrachium rosenbergii</i> | Mac r HC (Hemocyanin) from <i>Macrobrachium rosenbergii</i> | All homologies listed for <i>Macrobrachium rosenbergii</i> and <i>Macrobrachium nipponense</i> | rExo m1, rMac r 1 |
| | | | | | TPM <i>Macrobrachium lanchesteri</i> : > 92.25% with all Crustacean (with Mac r 1 100%) and > 61.27 with all Molluscan (with Cra | |

| | | | | | | | |
|---|---|------------------------------|---------------|----------------|--|--|---|
| | | | | | | g 1, Hal l 1 and Tod p 1 with 63.38) | |
| Crabs, sea-spiders | | | | | | | |
| Gazami crab <i>Portunus trituberculatus</i> | China (95.48%) | 476,026. 45 | | Por tr 1 (TPM) | | > 91.2% with all Crustacean (with Scy p 1 99.65%) and > 60.56% with all Molluscan (with Tod p 1, Cra g 1 and Hal l 1 63.03%) | <i>Portunus trituberculatus</i> extract |
| Blue swimming crab <i>Portunus pelagicus</i> | Indonesia (39.58%), China (27.26%), Philippines | 251,440. 12 | Por p 1 (TPM) | Por p 2 (AK) | | > 91.9% with all Crustacean (with Pan s 1 98.54%), > 60.21% with all Molluscan (with Tod p 1 and Hal l 1 63.03%) | rPor p 1 |

| | | | | | | |
|---|---|-------------|--|-----------------------------|---|--|
| | (12.81%) | | | | | |
| Green mud crab <i>Scylla paramamosain</i> | China (100%) | 152,065,000 | Scy p 1 (TPM), Scy p 2 (AK), Scy p 3 (MLC), Scy p 4 (SCBP), Scy p 8 (TPI), Scy p 9 (Filamin C) | | > 91.55% with all Crustacean (with Hom a 1 97.18%) and > 60.56% with all Molluscan (with Tod p 1, Cra g 1 and Hal l 1 63.03%) | rScy p 1, rScy p 2, rScy p 3, rSci p 4, rScy p 8, rScy p 9 |
| Indo-Pacific swamp crab <i>Scylla serrata</i> | Viet Nam (62.29%), Philipp ines (20.34%), Indone sia (14.00%) | 130,276,780 | | Scy s 1 (TPM), Scy s 2 (AK) | > 91.55% with all Crustacean (with Scy p 1 100%) and > 60.56% with all Molluscan (with Tod p 1, Cra g 1 and Hal l 1 63.03%) | |

| | | | | | | |
|--|--------------------------------|-----------|---|--|---|---|
| Queen crab <i>Chionoecetes opilio</i> | Canada (63.16%) | 121,643.2 | | Chionoecetes (TPM), Chionoecetes (AK), Chionoecetes (SCBP), Chionoecetes (Troponin C), Chionoecetes alpha_Actin (alpha actin), Chionoecetes SERCA (SERCA) | > 87.96% with all Crustacean TPM allergens (with Scy p 1 94.72%) and > 59.15% with all Molluscan (with Tod p 1, Cra g 1 and Hal l 1 61.27%) | f23 <i>Chionoecetes</i> spp extract; rChionoecetes 1, rChionoecetes 6 |
| King crabs, squat-lobsters | | | | | | |
| Red king crab <i>Paralithodes</i> | Russian Federation (92.66%) | 28,911.00 | Paralithodes (Mitochondrial malate dehydrogenase) | Paralithodes (TPM) | > 90.14% with all Crustacean (with Hom a 1 98.24%) and > 59.51% homology with all | <i>Paralithodes</i> s <i>camtschatica</i> extract |

| | | | | | | |
|--|------------------------------------|-----------------|--|--|---|--|
| <i>camtschatica</i> | | | | | Molluscan TPM allergens (with Top 1 63.73%) | |
| Blue king crab <i>Paralithodes platypus</i> | Russian Federation (100%) | 8,365.00 | | | | |
| Southern king crab <i>Lithodes santolla</i> | Chile (67.76%), Argentina (32.22%) | 6,630.73 | | | | |
| Carrot squat lobster <i>Pleuron</i> | Chile (100%) | 6,176.00 | | | | |

| | | | | | | |
|---|--|------------------------|--|-------------------|---|---|
| <i>codes</i> | | | | | | |
| <i>monodo</i> | | | | | | |
| <i>n</i> | | | | | | |
| Blue squat lobster <i>Cervim unida johni</i> | Chile (100%) | 3,114.00 | | | | |
| Lobsters | | | | | | |
| St.Paul rock lobster <i>Jasus paulensi s</i> | French Souther n Terr (100%) | 219,709. 00 | | | | |
| Americ an lobster <i>Homaru s</i> | Canada (63.37%) , USA (36.62%) | 166,815. 04 | Hom a 1 (TPM) , Hom a 3 (MLC), Hom a 6 (Troponin C) | Hom a 4 (SCBP) | > 92.96% with all Crustacean (with Pan s 1 98.91%) and > 60.92% with | F20 <i>Homarus americanus</i> extract, rHom a 1, |

| | | | | | | |
|---|---|-----------------------------|--|-------------------------------|--|-----------------------|
| <i>america nus</i> | | | | | all Molluscan (with Hal l 1 63.73%) | rHom a 3, rHom a 6 |
| Norwa y lobster <i>Nephro ps norvegic us</i> | United Kingdo m Ireland (11.80%) Denma rk (9.99%) | 54,228.3 3 | | Nep n DF9 (unknown) | | |
| Caribb ean spiny lobster <i>Panulir us argus</i> | Brazil (24.90%) Baham as (22.31%) Cuba (12.24%) | 29,316.9 5 | | | | |

| | | | | | | |
|---|--|------------------------------------|--|--|---|---|
| Tropical spiny lobsters nei Panulir us spp | Indone sia (25.56% , Nigeria (18.45% , Mexico (12.70%) | 27,131.1 6 | Pan s 1 (TPM) from Panulirus stimpsoni | Pan ho 1 (TPM) from Panulirus homarus; Pan j 1 (TPM) from Panulirus japonicus | TPM Panulirus stimpsoni: > 92.34 with all Crustacean (with Hom a 1 98.91) and > 60.58 with all Molluscan (with Cra g 1 and Hal l 1 62.77) | f71 <i>Palinurus</i> <i>elephas</i> <i>extract; f</i> 304 <i>Palinurus</i> spp extract ; F71 <i>Palinurus</i> <i>vulgaris</i> extract; rPan s 1 |
| Shrimps, prawns | | | | | | |
| Whitele g shrimp <i>Penaeus</i> <i>vannam</i> <i>ei/Litope</i> <i>naeus</i> | China (31.15% , India (15.71% , Ecuado r | 6,348,62 1.71 | Lit v 1 (TPM), Lit v 2 (AK), Lit v 3 (MLC), Lit v 4 (SCBP), Lit v 13 (Fatty Acid Binding Protein) | Lit v HC (Hemocya nin) | > 92.61% with all Crustacean (with Pen m 1 and Pen a 1 100%) and > 60.92% with all Molluscan (with Hal l 1 63.38%) | <i>Litopenaeu</i> <i>s vannamei</i> extract; rLit v 1, rLit v 2, rLit v 3, rLit v 4 |

| | | | | | | |
|---|---|------------------------------|--|--|---|---|
| <i>vannam</i> | (14.06% | | | | | |
| <i>ei</i> |) | | | | | |
| Giant tiger prawn <i>Penaeus</i> <i>monodon</i> <i>n</i> | Viet Nam (30.14%) Indone sia (16.84%) , China (11.84%) | 883,686. 29 | Pen m 1 (TPM), Pen m 2 (AK), Pen m 3 (MLC), Pen m 4 (SCBP), Pen m 6 (Troponin C), Pen m 7 (Hemocyanin), Pen m 8 (TPI), Pen m 13 (Cytoplasmic fatty acid binding protein), Pen m 14 (Glycogen phosphorylase- like protein) | | > 92.61% with all Crustacean (with Lit v 1 and Pen a 1 100%) and > 60.92% with all Molluscan (with Hal l 1 63.38%) | f24 <i>Penaeus</i> <i>monodon</i> extract; rPen m 1, rPen m 2, rPen m 3, rPen m 4, rPen m 6, rPen m 7, rPen m 8, rPen m 14 |
| Natanti an decapo ds nei | China (25.23%) , Viet Nam | 758,903. 87 | All allergens listed for <i>Penaeus</i> spp, Met e 1 (TPM) from | All allergens listed for <i>Penaeus</i> | All listed homologies of <i>Penaeus</i> spp | All recombina nt allergen |

| | | | | | | | |
|---------|----------|--|--------------------------|------------|----------------------------|----------|---------------------|
| Natanti | (20.47% | | Metapenaeus | spp; Pan e | TPM | Pandalus | extracts |
| a |), India | | ensis; Cra c 1 | 1 (TPM) | borealis: > | 92.25% | and |
| | (25.20% | | (TPM), Cra c 2 | from | with all Crustacean | | componen |
| |) | | (AK), Cra c 4 | Pandalus | (with Mac r 1 | | ts listed |
| | | | (SCBP), Cra c 5 | eous; Sol | 98.94%) and > | | for |
| | | | (MLC), Cra c 6 | me 1 | 61.62% with all | | Penaeus |
| | | | (Troponin C) and | (TPM) | Molluscan (with Hal | | spp; |
| | | | Cra c 8 (TIM) | from | l and Tod p 1 | | F241 |
| | | | from Crangon | Solenocer | 63.73%) | | <i>Pandalus</i> |
| | | | crangon; Pan b 1 | a | | | <i>borealis</i> |
| | | | (TPM) from | melantho; | TPM Pandalus eous: | | extract, |
| | | | <i>Pandalus borealis</i> | | > 92.25% with all | | F23 |
| | | | | | Crustacean (with | | <i>Crangon</i> |
| | | | | | Pan b 1 100%) and > | | <i>crangon</i> |
| | | | | | 61.62% with all | | extract; |
| | | | | | Molluscan (with Hal | | <i>Parapenaeu</i> |
| | | | | | l 1 and Tod p 1 | | s |
| | | | | | 63.73%), | | <i>longirostris</i> |
| | | | | | | | extract; |
| | | | | | TPM Crangon | | rCra c 1, |
| | | | | | crangon: > 92.25% | | rCra c 2, |
| | | | | | with all Crustacean | | rCra c 4, |

| | | | | | | |
|---|---|------------------------------|--|--|---|---|
| | | | | | (with Mac r 1 rCrac c 5, r 99.65%) and > 61.62% with all Molluscan (with Cra g 1, Hal l 1 and Tod p 1 63.38%), | Cra c 6, rCrac c 8, natural shrimp TPM |
| Akiami paste shrimp <i>Acetes japonicu s</i> | China (94.75%) | 379,695. 95 | | TPM | nonavailable TPM sequence | |
| Penaeu s shrimp s nei Penaeu s spp | China (39.62%) , Peru (11.52%), Camer oon (10.76%) | 295,115. 19 | Lit v 1 (TPM), Lit v 2 (AK), Lit v 3 (MLC), Lit v 4 (SCBP) and Lit v 13 (Fatty Acid Binding Protein) from Litopenaeus vannamei (syn. Penaeus vannamei); Mel l | Fen me 2 (AK) and Fen me 4 (SCBP) from Fennerope naeus merguiens is (syn. Penaeus | All homologies listed for Penaeus monodon, Penaeus vannamei TPM Penaeus chinensis: > 92.61% with all Crustacean (with Pen m 1, Pen a 1 and Lit v 1 100%) | f24 Penaeus monodon extract; Litopenae us vannamei extract; F34 Farfantepe |

| | | | | | |
|--|--|--------------------|------------|----------------------------|------------|
| | | 1 (TPM) from | merguiens | and > 60.92% with | naeus |
| | | Melicertus | is); Lit v | all Molluscan (with | aztecus; |
| | | latisulcatus (syn. | HC | Hal l 1 63.38%), | rLit v 1, |
| | | Penaeus | (Hemocya | Penaeus aztecus | rLit v 2, |
| | | latisulcatus); Pen | nin) from | TPM: > 92.61% with | rLit v 3, |
| | | a 1 (TPM) from | Litopenae | all Crustacean (with | rLit v 4, |
| | | Farfantepenaeus | us | Pen m 1 and Lit v 1 | rMel l 1, |
| | | aztecus (syn. | vannamei | 100%) and > 60.92% | rPen a 1, |
| | | Penaeus aztecus); | (syn. | with all Molluscan | rPen i 1, |
| | | Pen i 1 (TPM) | Penaeus | (with Hal l 1 1 | rPen m 1, |
| | | from | vannamei) | 63.38%), | rPen m 2, |
| | | Farfantepenaeus | ; Mar j 1 | Metapenaeus ensis | rPen m 3, |
| | | indicus (syn. | (TPM), | TPM: > 92.34% with | rPen m 4, |
| | | Penaeus indicus); | Mar j 4 | all Crustacean (with | rPen m 6, |
| | | Pen m 1 (TPM), | (SCBP), | Pen m 1, Pen a 1 and | rPen m 7, |
| | | Pen m 2 (AK), | Mar j | Lit v 1 99.64%) and > | rPen m 8, |
| | | Pen m 3 (MLC), | Enolase | 60.22% with all | rPen m 14, |
| | | Pen m 4 (SCBP), | (enolase) | Molluscan (with Cra | rMar j 2 |
| | | Pen m 6 | and Mar j | g 1 and Hal l 1 | |
| | | (Troponin C), Pen | PK | 62.41%) | |
| | | m 7 | (Pyruvate | | |
| | | (Hemocyanin), | Kinase) | | |

| | | | | | |
|--|--|--------------------|-------------|----------------------|--|
| | | Pen m 8 (TPI), | from | Penaeus japonicus | |
| | | Pen m 13 | Marsupen | TPM: > 92.61% with | |
| | | (Cytoplasmic | aeus | all Crustacean (with | |
| | | fatty acid binding | japonicas | Pen m 1, Pen a 1 and | |
| | | protein) and | (syn. | Lit v 1 100%) and > | |
| | | Pen m 14 | Penaeus | 60.92% with all | |
| | | (Glycogen | japonicas); | Molluscan (with Hal | |
| | | phosphorylase- | Met j 2 | l 1 63.38%) | |
| | | like protein) from | (AK) from | Penaeus latisulcatus | |
| | | Penaeus | Metapena | TPM: > 91.55% with | |
| | | monodon; | eus | all Crustacean (with | |
| | | | joyneri,(sy | Pan b 1 95.42%) and | |
| | | | n. Penaeus | > 61.62% with all | |
| | | | joyneri); | Molluscan (with Cra | |
| | | | Pena o 1 | g 1, Hal l 1 and Tod | |
| | | | (TPM) | p 1 64.08%) | |
| | | | from | Penaeus | |
| | | | Penaeus | merguiensis TPM: > | |
| | | | orientalis; | 92.61% with all | |
| | | | | Crustacean (with | |
| | | | | Pen m 1, Pen a 1 and | |
| | | | | Lit v 1 100%) and > | |

| | | | | | | |
|--|--|--|--|--|---------------------|--|
| | | | | | 60.92% with all | |
| | | | | | Molluscan (with Hal | |
| | | | | | l 1 63.38%) | |

From Table 4 it can be concluded that TPMs of the most economically relevant Crustacean shellfish have >90% of homology with all Crustacean TPM allergens registered in WHO/IUIS, and half of them have homology >98%. On the other hand, homology with all Molluscan TPM allergens registered in WHO/IUIS is > 60%.

Table 4 shows that the most economically relevant Molluscan shellfish TPMs for which sequence information exists show >70% of homology with all Molluscan TPMs, and >50% homology with all Crustacean TPM allergens registered in WHO/IUIS (not considering homologies with only available partial sequences). The highest homologies of the most economically relevant Molluscan shellfish TPMs are with Sac g 1 and Hal l 1. The only exception is flat oyster, *Ostreus edulis*, for which partial TPM sequence information exists, showing only 55% homology with TPM of closely related Pacific cupped oyster *Crasostrea gigas* (*Magelana gigas*) (Figure S2).

Identification of Critical Knowledge Gaps on Shellfish Allergens

Based on the global production of shellfish (FAO FishStat for 2021) presented in Supplementary material (Table S6), top 5 economically most relevant species or groups of Crustacea and Mollusca have been included in the overview table (Table 6), grouped into: freshwater crustacea, crabs, lobsters, shrimps/prawns, oysters, mussels, clams, scallops, squids and freshwater mollusca. Information presented in the overview for each species/genera include: production data and main producers, availability of in vivo and in vitro diagnostic tools and commercially available individual allergens, regardless of whether natural or recombinant; allergens in WHO/IUIS (and nonWHO/IUIS). If no information on the allergens was available, availability of genomic information on TPM sequences was searched in UniProt database for the species or species representing genera. Finally, BLAST linear sequence similarity search results are shown as described above.

For all entries without availability of any of the most critical information on allergenicity, diagnostic tools availability, nor sequence information, species was marked in red to highlight critical information missing.

In general, several critical gaps have been identified related to shellfish allergy (**Figure 7**):

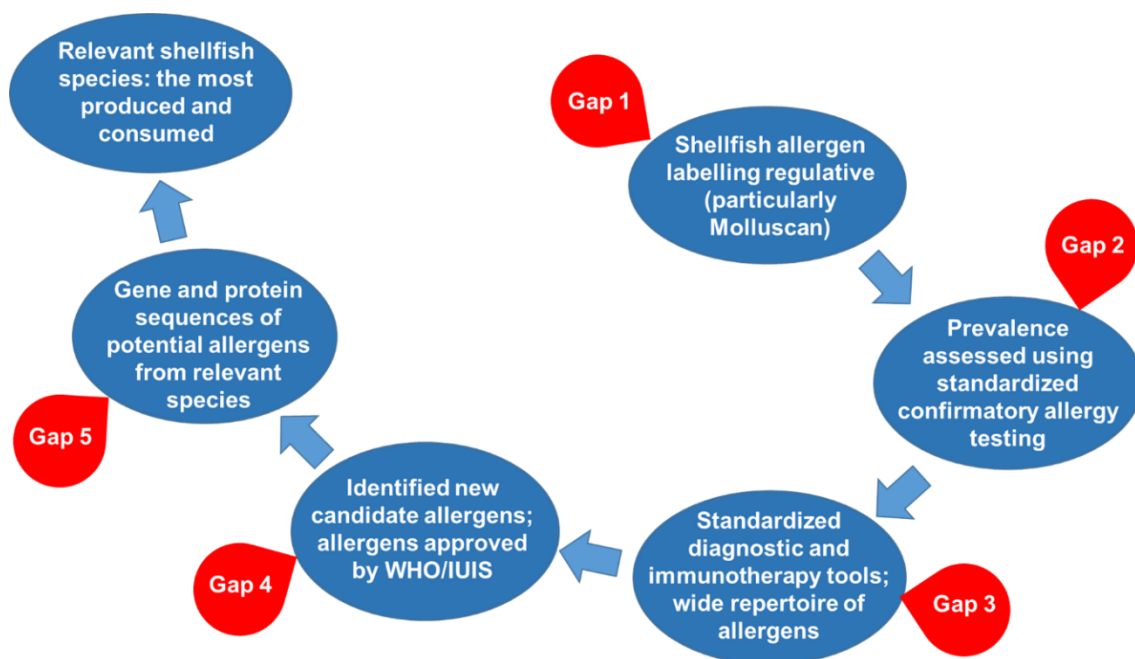


Figure 7. Overview of critical gaps in shellfish allergy and their dependency relationships.

Shellfish allergen labelling regulative gaps: Of 195 countries in the world today, only 105 regulate Crustacean shellfish allergen labelling, while Molluscan shellfish is regulated only by 52 countries. The reason for absence of molluscan allergen labelling in most countries is probably the fact that molluscan shellfish is not in Codex Alimentarius priority allergen list (FAO and WHO. 2022. <https://doi.org/10.4060/cb9070en>) due to the lack of data on prevalence, severity and/or potency. Therefore, legislation on shellfish allergen labelling, particularly for molluscan shellfish, is urgently needed, which is of increasing importance due to globalization in terms of trading and traveling. Prerequisites for introducing regulation of shellfish labelling are reliable data on prevalence, severity and potency, particularly data obtained based on standardized confirmatory allergy testing, as well as warning epidemiology of shellfish-induced anaphylaxis, primarily for molluscan shellfish.

Prevalence, severity and potency gaps: Unfortunately, in most studies shellfish allergy prevalence was assessed using self-reported questionnaire-based methods, and there are limited number of studies with assessment using sensitization (SPT and sIgE), and very few studies have established the prevalence of shellfish allergy using the gold standard challenge criteria.. Moreover, studies for isolated molluscan allergy prevalence are scarce, and, except few, in all of them self-reported questionnaire-based methods. The reason for this is the huge diagnostic gap for molluscan allergy, and this gap may result in underestimation of prevalence for isolated molluscan allergy. Beside, existing gap is also in more comprehensive epidemiology of severity of manifestation of molluscan-induced allergies, particularly life threatening anaphylaxis, which is necessary to alarm policy makers on risk level of molluscan allergen ingestion. FAO and WHO (FAO and WHO. 2022. <https://doi.org/10.4060/cb9070en>) rated crustacean shellfish with higher proportion of anaphylaxis 3+ regions, and Mollusca with higher proportion of anaphylaxis 1+ regions. In addition, there is also a gap in the level of potency of shellfish allergens. For Crustacea there are limited data only for shrimps, which are rated by FAO and WHO with low potency (ED10 mg range > 100 mg protein, and ED50 mg range > 1000 mg protein), and there is no data for other crustaceans. There is no data for any molluscan shellfish.

Therefore, to obtain reliable prevalence, severity and potency data, particularly for molluscan allergy, further studies incorporating standardized confirmatory allergy testing are urgently needed. For this, standardized diagnostic tools and wide repertoire of shellfish allergens (extracts and allergen components), particularly for molluscan species, is prerequisite.

Diagnostic gaps: Tables 4 and 5 show that for the top 5 economically most relevant species/genera of each group, only for few of them extracts/and or allergen component for allergen diagnostics are commercially available. This is particularly pronounced for species/genera for which most of production is in Asia, especially China. This clearly demonstrates that the main global manufacturers of allergy diagnostics tools are mainly focused on patients from Europe and North America. Moreover, even for many species for which Europe and North America are main producers/consumers allergen extract/components are commercially unavailable. The main consequence of these gaps is that diagnostic tools for shellfish allergies are mainly based on shellfish extracts or even mixtures of shellfish extracts, instead of allergen components. As these extracts are not standardized and may lack a sufficient amount and diversity of important shellfish allergens, shellfish allergy diagnostics are not quite reliable. Furthermore, false negative testing results can put patient's lives at risk. For top economically relevant Molluscan shellfish there are only several extracts available for SPT or within in vitro diagnostics tools. The most critically missing component for diagnostic repertoire are extracts from the group of clams, cockles, arkshells, with *Ruditapes philipinarum* as the most striking example. Furthermore, low sequence similarity between TPMs of flat oyster (*Ostrea edulis*) and cupped oyster (*Crasostrea gigas*) should be taken into account and further examined particularly as *Ostrea edulis* is a component of in vitro diagnostic tools (Table 4, 5), while *Crasostrea gigas* is a component of in vivo diagnostic tools (Table 4).

This is of particular importance for patients monosensitized to molluscan shellfish or to specific molluscan species, where diagnosis using current tools could be false negative, putting these patients at risk. This is also important for patients monosensitized to crustacean shellfish, with the aim to reduce the unnecessary avoidance of mollusks. Therefore, for precise and unambiguous diagnostics of shellfish allergy and personalized recommendations, expanding of repertoire of allergen components from one species, as well as expanding of repertoire of different species with their allergen components, particularly the most relevant species, is urgently needed. For this identification of new candidate allergens, confirmation of their IgE reactivity and their approval by WHO/IUIS is prerequisite. Beside, standardized immunotherapy preparations using recombinant allergen components are essential for developing consistent immunotherapy protocols.

Allergenicity gaps: For the top economically relevant species, there are several gaps. Firstly, for most species or groups there are **no allergens** approved by WHO/IUIS, or there is only **one allergen**. Secondly, for many species even nonregistered IgE reactive allergens were not described yet. This gap is again particularly great for Molluscan shellfish. Table 5 shows that allergens are registered for only five economically relevant Mollusca (mostly TPMs). Although for several species nonregistered TPMs and other allergens IgE reactivity was documented, for the top 5 economically relevant Molluscan shellfish species no allergens have been described yet. Within Mollusca shellfish, the most economically relevant species of oysters (*C. gigas*) are well characterized at the molecular level. All top 5 freshwater Mollusk species do not have a single allergen described, nor available sequences for the top 3 species. For mussels, scallops and clams there are only several nonregistered allergens with IgE reactivity and no registered allergens. Squids have only one registered and several nonregistered allergens with IgE reactivity described. In contrast to Crustacea shellfish (Table 4), there are only several recombinant allergens currently commercially available, and none of them (except nonregistered allergens Ven ga 1 and Uro du 1) are present within diagnostics tools (Table 3). Moreover, although many recombinant allergens currently are commercially available, they are not present within diagnostics tools, particularly allergens other than TPM. Other than TPM, only the top shrimp and prawns (white leg shrimp and giant tiger prawn) species, crabs (green mud crab) and freshwater crustaceans (red swamp crayfish) allergens are well described at the molecular level (Table 4). However, for few species (such as queen crab and kuruma shrimp/ *Marsupenaeus japonicus*) several allergens other than TPM have demonstrated IgE reactivity. The data presented in Table 6 clearly demonstrate that for the most economically relevant Crustaceans shellfish not only that allergens approved by WHO/IUIS are still missing, but for many of them allergenicity were not sufficiently investigated. Therefore, for the development of reliable diagnostic tools faster and more

comprehensive identification of new candidate allergens, particularly from the most relevant species and for molluscan species, their testing and subsequent approval by WHO/IUIS, is needed. For identification of new potential allergens and their testing for IgE reactivity eligible by WHO/IUIS, recombinant allergens are necessary, taking into account difficulties related to purification and standardization of natural allergens. Consequently, obtaining recombinant allergens requires available gene or protein sequences.

Genomic/proteomic gaps: For many species there is limited number of available gene or protein sequences of potential allergens, not only for TPM but also sequences of other potential allergens, such as AK, SCBP, etc. For Molluscan species sequences of potential allergens are very scarce, particularly for freshwater Mollusca, marine Gastropoda and marine Cephalopoda shellfish (Table 7). For example, there are available protein sequences of TPM for only about 10 marine Gastropoda, or Cephalopoda, shellfish species, including unreviewed sequences. Similarly, for paramyosin, as the second relevant allergen in Mollusca, there are protein sequences from only several Gastropoda and Cephalopoda shellfish species. For flat oyster, *Ostrea edulis* (a frequent component of in vitro diagnostic tools), only a partial, unreviewed, sequence of TPM exist.

For economically highly relevant species of: Chilean mussels (0.5 billion tones produced), jumbo flying squids (1 billion tones produced annually), Akiami paste shrimp *Acetes japonicus* (0.3 million tons produced annually), Blood cockle *Tegillarca granosa* (0.4 billion tones produced annually), Peruvian calico scallop, *Argopecten purpuratus*, Argentine shortfin squid, *Illex argentinus* there are no in vitro diagnostic tools available, registered allergens, nor sequence information on the most common allergen of shellfish, tropomyosin (Tables 4 and 5).

For research on gene or protein sequences of potential shellfish allergens, the list of most relevant shellfish species is prerequisite to direct this research. Thus, part of this review is focused on global production, supply and consumption of shellfish, providing an overview of the relevant shellfish species.

Very recent publication is nice example of significant progress in the allergen profile of relevant shellfish species, which is crucial for developing CRD-based tests and preventive immunotherapy based on molecular allergens (Ng et al., 2025). Based on assembled *P. clarkii* (crayfish) genome using both long-read and short-read sequencing data, this study identified a total of 11 putative allergen groups, including all isoforms or homologs for each allergen group based on the genome, identified 2 previously unknown allergens (pPro c 3.0301 and pPro c 6.0201) with IgE reactivity of E reactivity of 33.3% and 20%, respectively, and additionally identified 3 putative allergens through 2D mass spectrometry. This comprehensive approach could be applied to other relevant shellfish species and may be particularly useful for relevant molluscan species.

In summary, the most urgent research on genomic, proteomic, allergenicity and improvement of diagnostic and immunotherapy tools is necessary for the identified species. Progress in these aspects would allow obtaining more comprehensive and more reliable prevalence, severity and potency data, which in turn would be convincing for policy makers to introduce regulation on shellfish allergen labelling worldwide. Finally, reliable unequivocal diagnostics of shellfish allergy and shellfish allergen labelling together would reduce risk of shellfish-induced allergic reactions and anaphylaxis. This is of particular importance for still undefined molluscan allergy resulting in allergic risks associated with the consumption of molluscan shellfish. This review, providing lists of the most economically relevant shellfish species, may serve as a guide not only for directions of research needed, but also for clinicians, diagnostic and immunotherapy tools manufacturers, as well as for policy makers.

Table 5. Alignment of major economically relevant species/genera/families/orders of Mollusca shellfish with the information on existing allergens (WHO/IUIS and non WHO/IUIS), cross-reactivity of TPM (if PubMed information was available) with registered TPM, availability of any diagnostic tools (in vivo, in vitro) or pure component (allergen) for *in house* allergenicity detection. For entries such as group of species (genus, family, etc.) % homology was presented for all species of specified group with available complete sequence in UniProt.

| Common name/ Latin name | The main producers (% of total production) | Production [LWT] | Allergens | nonIUIS allergens with IgE reactivity | TPM as allergen or putative allergen (%) homology with shellfish TPM allergens approved by WHO/IUIS)* | Commercially available extract or allergen component |
|----------------------------------|--|------------------|-----------|---------------------------------------|---|--|
| Freshwater molluscs | | | | | | |
| Freshwater molluscs nei Mollusca | China (76.32%), Philippines (14.61%), Korea, Republic of (3.81%) | 212,045.18 | | | Homology presented for <i>Corbicula japonica</i> <i>Dreissena polymorpha</i> TPM: > 71.73% with all Molluscan (with Hal 1 1 | |



| | | | | | |
|--|--|--|--|--|--|
| | | | | | <p>75.97%) and ></p> <p>55.31% with</p> <p>all</p> <p>Crustacean</p> <p>(with Pan b 1</p> <p>and Hom a 1</p> <p>57.24%)</p> <p><i>Biomphalaria</i></p> <p><i>glabrata</i> TPM</p> <p>(Uniprot ID</p> <p>P42636): ></p> <p>76.76% with</p> <p>all Molluscan</p> <p>(with Hal 1 1</p> <p>82.39%) and ></p> <p>60.22 with all</p> <p>Crustacean</p> <p>(with Pan b 1</p> <p>and Hom a 1</p> <p>61.62%)</p> |
|--|--|--|--|--|--|

| | | | | | | |
|--|--|-----------|--|--|--|--|
| Chinese mystery snail <i>Cipangopaludin a chinensis</i> | China (100%) | 98,420.00 | | | | |
| Chinese pond mussel <i>Sinanodonta woodiana</i> | China (100%) | 54,628.00 | | | | |
| Asian clam <i>Corbicula fluminea</i> | China (84.31%), Taiwan Province of China (15.69%) | 26,385.74 | | | | |
| Japanese corbicula <i>Corbicula japonica</i> | Japan (93.51%), Russian Federation (6.48%) | 9,560.00 | | | > 72.18% with all Molluscan (with Hal I 77.11%) and > 55.11% with all Crustacean | |

| | | | | | | |
|---------------------------|---|----------------|---|---|---|--|
| | | | | | (with Hom a 1, Scy p 1 and Pan b 1 57.39%) | |
| Abalones, winkles, conchs | | | | | | |
| Sea snails | China | 299,620 | Rap v 2 | | | rRap v |
| Rapana spp | (100%) | .00 | (paramyosi n) from Rapana venosa, | | | 2 |
| Abalones nei | China | 245,567 | Hal l 1 1 | Hal d 1 (TPM) | Haliotis | f935 |
| Haliotis spp | (88.71%), Korea, Republic of (9.49%) | .51 | (Haliotis laevigata x Haliotis rubra), TPM Hal m 1 (Haliotis midiae (Perlemoen abalone)), TPM | Hal d 1 (TPM) from Haliotis diversicolor , Hal di 1 (TPM) from Haliotis discus, Hal di PM (paramyosin) from Haliotis discus, Hal r 1 (TPM) from Haliotis | Haliotis discus discus TPM: > 78.17% with all Molluscan (with Hal l 1 99.65%) and > 62.41% with all Crustacean (with Cra c 1, Pan b 1 and | Haliotis japonica extract; f346 Haliotis spp. Extract; rHal l 1, rHal m 1, rHal di 1 |

| | | | | | |
|--|--|--|--|-------------------------------|--|
| | | | | laevigata x Mel 1 1 | |
| | | | | Haliotis rubra, 63.73%) | |
| | | | | Hal r 49 kDa | |
| | | | | (unknown Haliotis | |
| | | | | protein) from diversicolor | |
| | | | | Haliotis TPM: > | |
| | | | | laevigata x 77.46% with | |
| | | | | Haliotis rubra, all Molluscan | |
| | | | | (with Hal 1 1 | |
| | | | | 98.94%) and > | |
| | | | | 61.68% with | |
| | | | | all | |
| | | | | Crustacean | |
| | | | | (with Cra c 1 | |
| | | | | and Mel 1 1 | |
| | | | | 63.03%) | |
| | | | | Haliotis | |
| | | | | rufescens | |
| | | | | TPM: > 75.7% | |
| | | | | with all | |



| | | | | | |
|--|--|--|--|--|---|
| | | | | | <p>Molluscan</p> <p>(with Hal 1 1</p> <p>96.13%) and ></p> <p>60.22% with</p> <p>all</p> <p>Crustacean</p> <p>(with Cra c 1</p> <p>and Pan b 1</p> <p>61.97%)</p> <p>Haliotis</p> <p>asinine TPM:</p> <p>> 76.06% with</p> <p>all Molluscan</p> <p>(with Hal 1 1</p> <p>94.37%) and ></p> <p>60.22% with</p> <p>all</p> <p>Crustacean</p> <p>(with Cra c 1,</p> <p>Pan b 1 and</p> |
|--|--|--|--|--|---|

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|---------------------------------|--------------------|-----------------------------|--------------------------------|--|---|------------------------|
| | | | | | <p>Mel 1 1 61.62%)</p> <p>Haliotis laevigata x Haliotis rubra TPM: > 77.82% with all Molluscan (with Cra g 1 82.39%) and > 62.41% with all Crustacean (with Mel 1 1 64.08%)</p> | |
| Gastropods nei Gastropoda | Mexico (34.56%) | 40,514. 86 | All allergens listed for | All allergens listed for Rapana spp | All homologies listed for | All recombi nant |

| | | | | | | |
|--|--|--|-----------------------------|--|--|--|
| | | | Rapana spp and Haliotis spp | and Haliotis spp | Rapana spp and Haliotis spp | allergen extracts and compon ents listed for Rapana spp and Haliotis spp, |
| | | | | (TPM), Tur c 1 PM (paramyosin) ftom Horned turban (Turbo cornutus) | TPM: > 75.7% | rTur c 1 |
| | | | | | with all Molluscan (with Hal 1 1 85.21%) and > 62.04% with all Crustacean (with Mel 1 1 63.73%) Elysia crispata TPM: > 50.18% with all Molluscan (with Hal 1 1 | |



| | | | | | | |
|--|--|--|--|--|---------------|--|
| | | | | | 54.8%) and > | |
| | | | | | 40.18% with | |
| | | | | | all | |
| | | | | | Crustacean | |
| | | | | | (with Met e 1 | |
| | | | | | 46.62%) | |
| | | | | | Elysia | |
| | | | | | chlorotica | |
| | | | | | TPM: > | |
| | | | | | 72.18% with | |
| | | | | | all Molluscan | |
| | | | | | (with Hal 1 1 | |
| | | | | | 84.45%) and > | |
| | | | | | 63.03% with | |
| | | | | | all | |
| | | | | | Crustacean | |
| | | | | | (with Pan b 1 | |
| | | | | | 64.08%) | |
| | | | | | Neptunea | |
| | | | | | polycostata | |

| | | | | | | |
|---|--|-----------------------------|--|--|--|--|
| | | | | | TPM: > 73.24% with all Molluscan (with Hal 1 1 77.46%) and > 59.15% with all Crustacean (with Mel 1 1 61.62%) | |
| Whelk Buccinum undatum | United Kingdom (49.46%), France (31.29%), Ireland (15.16%) | 38,276. 59 | | | | |
| Stromboid conchs nei Strombus spp | Nicaragua (50.36%), Belize (12.27%), Turks and | 32,588. 57 | | | | |

| | | | | | | |
|-----------------------------------|-----------------------|--------------|---|--|--|--|
| | Caicos Is. (6.47%) | | | | | |
| Oysters | | | | | | |
| Cupped oysters Crassostrea spp | China (99.33%) | 5,858,347.36 | Crassostrea gigas (TPM) <i>Crassostrea gigas</i> (Pacific cupped oyster); Crassostrea 1 (TPM) Crassostrea 2 (AK) Crassostrea 4 (SCP) Portuguese Crassostrea angulata | | All homologies for Crassostrea gigas and Crassostrea virginica | Crassostrea 1 f23 Crassostrea virginica extract; |



| | | | | | | |
|---|--|---------------------------|--|--|--|------------------|
| | | | <p>Sac g 1</p> <p>(TPM)</p> <p>from</p> <p>Saccostrea</p> <p>glomerata</p> <p>(syn.</p> <p>Crassostre</p> <p>a</p> <p>glomerata)</p> | | | |
| <p>Pacific cupped</p> <p>oyster</p> <p><i>Crassostrea</i></p> <p><i>gigas</i></p> | <p>Korea,</p> <p>Republic</p> <p>of</p> <p>(50.60%),</p> <p>Japan</p> <p>(24.29%),</p> <p>France</p> <p>(13.06%)</p> | <p>652,011</p> <p>.94</p> | <p>Cr a g 1.01</p> <p>(TPM)</p> <p>Cr a g 1.02</p> <p>(AK)</p> | | <p>> 71.83% with</p> <p>all Molluscan</p> <p>(with Cr a 1</p> <p>94.74%) and ></p> <p>60.95% with</p> <p>all</p> <p>Crustacean</p> <p>(with Pan s 1,</p> <p>Hom a 1and</p> <p>Mel 1 1</p> <p>66.23%)</p> | <p>rCr a g 1</p> |

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|--|--|--------------------------------------|---------------------------------|--|---|---|
| <p>American cupped oyster <i>Crassostrea virginica</i></p> | <p>USA (75.07%), Mexico (20.51%), Canada (4.42%)</p> | <p>226,485 .41</p> | | | <p>> 80.77% with all Molluscan (with Cra g 1 88.24%) and > 65% with all Crustacean (with Pen m 1, Pen a 1, Lit v 1, Met e 1, Pan b 1, Mac r 1 Pan s 1 and Mel 1 1 68.78%)</p> | <p>f23 <i>Crassostr ea virginica</i> extract;</p> |
| <p>Slipper cupped oyster <i>Crassostrea Iredalei</i></p> | <p>Philippine s (100%)</p> | <p>40,799. 75</p> | | | | |
| <p>Flat and cupped oysters nei</p> | <p>Australia (100%)</p> | <p>8,051.3 2</p> | <p>All allergens listed for</p> | | <p>All listed homologies of <i>Crassostrea</i></p> | <p>F177 <i>Ostrea</i></p> |

| | | | | |
|----------------------|--|------------|-----------------------|---------------|
| (flat – Ostrea) | | Crassostre | <i>virginica,</i> | <i>edulis</i> |
| Ostreidae | | a spp | <i>Crassostrea</i> | extract |
| <i>Ostrea edulis</i> | | | <i>gigas</i> and | |
| | | | <i>Crassostrea</i> | |
| | | | <i>rhizophorae</i> | |
| | | | <i>Saccostrea</i> | |
| | | | <i>glomerata</i> | |
| | | | TPM: > 75% | |
| | | | with all | |
| | | | Molluscan | |
| | | | (with Cra a 1 | |
| | | | and Cra g 1 | |
| | | | 96.48%) and > | |
| | | | 60.21% with | |
| | | | all | |
| | | | Crustacean | |
| | | | (with Cra c 1, | |
| | | | Pan b 1 and | |
| | | | Mel 1 1 | |
| | | | 61.62%) | |
| Mussels | | | | |

| | | | | | | |
|------------------------------|---|---------------------|--|--|--|--|
| Sea mussels nei Mytilidae | China (78.07%), Spain (19.13%) | 1,062,460.81 | | Myt e 1 (TPM) from Mytilus edulis; Myt g PM (paramyosin) from Mytilus galloprovincial is; | All listed homologies of Mytilus edulis and Perna viridis TPM Mytilus galloprovinci alis: > 70.77% with all Molluscan (with Sac g 1 80.99%) and > 56.2% with all Crustacean (with Cra c 1 and Mel l 1 58.45%) | rMyt g 1, r Myt g PM, rMyt e 1 f 37 Mytilus edulis extract; |
| Chilean mussel | Chile (100%) | 425,833.00 | | | | |

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|--------------------------------------|--|----------------------------------|--|--|---|--|
| <i>Mytilus chilensis</i> | | | | | | |
| Blue mussel <i>Mytilus edulis</i> | France (29.23%), Denmark (17.64%), Netherlands (Kingdom of the Netherlands) (17.41%) | 188,669 .96 | | Mytilus edulis (TPM) from <i>Mytilus edulis</i> | > 70.42% with all Molluscan (with Saccharina 80.63%) and > 55.84% with all Crustacean (with Crustacean 58.1%) | f 37 Mytilus edulis extract; rMytilus edulis |
| Green mussel <i>Perna viridis</i> | Thailand (44.28%), Indonesia (21.18%), Philippines (20.18%) | 117,603 .10 | | Perna viridis (TPM) | > 69.37% with all Molluscan (with Saccharina 80.63%) and > 54.74% with all Crustacean (with Melissoidia 57.39%) | rPerna viridis |

| | | | | | | |
|---|--------------------|--------------|--|--|--|---|
| New Zealand mussel <i>Perna canaliculus</i> | New Zealand (100%) | 98,151.73 | | | | |
| Scallops, pectens | | | | | | |
| Scallops nei Pectinidae | China (99.75%) | 1,834,531.33 | | Pat y 1 (TPM) from Yesso scallop (Patinopecten yessoensis) | Homology presented for Patinopecten yessoensis Chlamys nipponensis akazara TPM: > 69.72% homology with all Molluscan (with Cra g 1 73.94%) and > 55.84% with all Crustacean | f 338 Pecten spp. extract; f328 Chlamys varia extract; f32 Placopec ten magella nicus extract; f338 Pecten maximu s extract |



| | | | | | |
|--|--|--|--|--|--|
| | | | | | (with Mel 1 1 58.8%) Mimachlamy s nobilis TPM: > 70.07% homology with all Molluscan (with Cra g 1 73.94%) and > 56.2% with all Crustacean (with Hom a 1 58.8%) Argopecten irradians TPM: > 69.72% homology with all |
|--|--|--|--|--|--|

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|---|--|------------------------------|--|---------------|--|
| | | | | | <p>Molluscan (with Cra g 1 and Sac g 1 74.3%) and > 54.74% with all Crustacean (with Mel l 1 57.75%)</p> |
| Yesso scallop <i>Patinopecten</i> <i>yessoensis</i> | Japan (93.88%), Russian Federation (5.10%) | 554,409 .08 | | Pat y 1 (TPM) | <p>> 69.37% homology with all Molluscan (with Cra g 1 73.94%) and > 55.47% with all Crustacean (with Mel l 1</p> |

| | | | | | | |
|---|---|-----------------------|--|--|-----------------------|---|
| | | | | | and Scy p 1 58.1%) | |
| American sea scallop <i>Placopecten magellanicus</i> | USA (73.99%), Canada (26.%) | 220,861 .24 | | | | f32 Placopecten magellanicus extract |
| Peruvian calico scallop <i>Argopecten purpuratus</i> | Peru (96.55%) | 112,904 .15 | | | | |
| Great Atlantic scallop <i>Pecten maximus</i> | France (54.20%), United Kingdom (38.62%), Ireland (3.79%) | 72,447. 55 | | | | f338 Pecten maximus extract |
| Clams, cockles, arkshells | | | | | | |

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|--|-----------------|--------------|--|--|---|
| Japanese carpet shell <i>Ruditapes philippinarum</i> | China (98.15%) | 4,358,635.76 | | Venerupis philippinarum (TPM) (syn. Venerupis philippinarum) | > 73.14% with all Molluscan (with Hal 1 1 77.03%), > 57.51% with all Crustacean (with Mel 1 1 59.86%) |
| <i>Sinonovacula constricta</i> | China (100%) | 859,651.00 | | Sin c 1 (TPM) | > 68.9% with all Molluscan (with Hal 1 1 73.5%) and > 55.68% with all Crustacean (with Hom a 1 58.3%) |
| Blood cockle | China (68.61%), | 496,118.64 | | | > 72.18% with all Molluscan |

| | | | | | | |
|---------------------------|---|-------------|--|--|---|---|
| <i>Tegillarca granosa</i> | Indonesia (18.74%), Thailand (7.47%) | | | | (with Hal 1 1 and Sac g 1 80.28%) and > 58.76% with all Crustacean (with Cra c 1 and Pan b 1 60.56%) | |
| Clams, etc. nei Bivalvia | Korea, Dem. People’s Rep (49.98%), Japan (18.87%), Korea, Republic of (7.69%) | 124,038 .51 | | Ana br 1 (TPM) from Anadara broughtonii; Lut p 1 (TPM) from Lutraria philippinarum; Pin a 1 (TPM) from Pinna atropurpurea; Sin c 1 (TPM) from Sinonovacula constricta; Sol | All homologies listed for Tegillarca granosa, Ruditapes philippinaru m, Sinonovacula constricta Anadara broughtonii | F10 Mercena ria mercena ria extract; F328 Chlamys varia extract; F176 Venus |

| | | | | | | |
|--|---|---------------------|--|---|---|--------------------|
| | | | | st 1 (TPM) from Solen strictus; Spi sa 1 (TPM) from Spisula sachalinensis; Tre ke 1 (TPM) from Tresus keena; Ven ph 1 (TPM) from Venerupis philippinarum; | TPM: > 71.83% homology with all Molluscan (with Sac g 1 79.93%) and > 58.76% with all Crustacean (with Pan b 1 60.21%) | gallina extract |
| Ocean quahog <i>Arctica islandica</i> | USA (99.99%) | 85,521,000 | | | | |
| Squids, cuttlefishes, octopuses | | | | | | |
| Jumbo flying squid <i>Dosidicus gigas</i> (genus: Dosidicus) | Peru (51.55%), China (42.02%), | 1,004,277.76 | | | | |

| | | | | | | |
|--|---|------------------------------|--|---|---|----------|
| | Chile (5.33%) | | | | | |
| Various squids nei Loliiginidae, Ommastrephi dae | China (62.51%), India (13.93%), Morocco (5.40%) | 542,466 .49 | Tod p 1 (TPM) from Tadarodes pacificus | All allergens listed for Loligo spp; Omm b 1 (TPM) from Ommastrephes bartramii; | All listed homologies for Loligo spp (Loligo bleekeri and Ommastrephes bartramii) | rTod p 1 |
| | | | | | TPM Tadarodes pacificus: > 75% with all Molluscan (with Hal 1 1 80.99%) and > 62.04% with all Crustacean (with Mel 1 1 64.08%) | |

| | | | | | | |
|--|---|------------|---|---|--|--|
| Argentine shortfin squid <i>Illex argentinus</i> | Taiwan Province of China (32.61%), China (31.25%), Argentina (29.57%) | 447,091.58 | | | | |
| Cephalopods Cephalopoda | Viet Nam (84.87%), China (10.51%), Madagascar (2.48%) | 423,596.21 | Tod p 1 (TPM) from <i>Todarodes pacificus</i> | All allergens listed for Loliginidae, Ommastrephidae; Enteropneust (TPM) from <i>Enteroctopus dofleini</i> ; Oct f 1 (TPM) and Oct f 2 (AK) from <i>Octopus fangsiao</i> ; Oct l 1 (TPM) from | All listed homologies for Loliginidae and Ommastrephidae <i>Octopus bimaculoides</i> TPM: > 75.7% with all Molluscan (with Tod p 1 | rTod p 1; F176 Loligo spp extract; F819 Octopus vulgaris extract; F108 Todarodes pacificus extract; |

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|--|--|--|--|--|
| | | | | <p><i>Octopus luteus</i>; 91.2%) and > F120</p> <p>Oct v 1 (TPM) 62.77% with Sepia</p> <p>from Octopus all officinali</p> <p>vulgaris; Sep e Crustacean s</p> <p>1 (TPM) from (with Pan b 1</p> <p><i>Sepia esculenta</i>; 64.79%)</p> <p>Sep m 1 (TPM)</p> <p>from Sepia <i>Sepioteuthis</i></p> <p>madokai <i>lessoniana</i></p> <p>TPM: > 75%</p> <p>with all</p> <p>Molluscan</p> <p>(with Tod p 1</p> <p>96.48%) and ></p> <p>61.68% with</p> <p>all</p> <p>Crustacean</p> <p>(with Mel l 1</p> <p>63.73%)</p> |
|--|--|--|--|--|

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|--------------------------------|---|------------------------------|--|---|--|-------------------------------------|
| | | | | | <p><i>Sepia esculenta</i></p> <p>TPM: ></p> <p>75.35% with</p> <p>all Molluscan</p> <p>(with Tod p 1</p> <p>97.54%) and ></p> <p>62.41% with</p> <p>all</p> <p>Crustacean</p> <p>(with Mel l 1</p> <p>and Scy p 1</p> <p>64.44%)</p> | |
| Common squids Loligo spp | Indonesia (61.46%), Thailand (19.60%), Philippine s (13.98%) | 332,201 .68 | | Lol b 1 (TPM) from Loligo bleekeri; Omm b 1 (TPM) from Ommastrephes bartramii (syn. Lologo bartramii); Uro ed 1 (TPM) | <p>Loligo <i>bleekeri</i></p> <p>TPM: ></p> <p>76.41% with</p> <p>all Molluscan</p> <p>(with Tod p 1</p> <p>92.96%) and ></p> <p>60.58% with</p> <p>all</p> | . F176 Loligo spp extract; |

| | | | | | | |
|--|--|--|--|-----------------------|--|--|
| | | | | from Loligo edulis | Crustacean (with Crac 1, Mac r 1, Scy p 1 and Hom a 1 61.97%) <i>Ommastrephes bartramii</i> TPM: > 74.65% with all Molluscan (with Tod p 1 96.13%) and > 61.68% with all Crustacean (with Mel l 1 and Scy p 1 63.73%) | |
|--|--|--|--|-----------------------|--|--|

8. Conclusion

Despite the growing popularity of shellfish, improvement of diagnostics and better standardization of shellfish allergenic extracts is a very challenging task. The great diversity of

shellfish species consumed is an obvious obstacle. Furthermore, the contents, concentrations, and ratios of the individual allergens vary greatly depending on a large variety of factors. Allergens frequently occur as different isoforms in varying quantities and the presence of proteases in allergen extracts results in allergen degradation, contributing to heterogeneity of allergenic extracts (Valenta et al., 2018). Therefore, for more reliable shellfish allergy diagnosis, tools should be based on implementation of recombinant allergen molecules, and their mixtures, that are defined regarding purity and biological activity. The prerequisite for wide implementation of recombinant allergen molecules of shellfish is investigation of allergen molecules in, at least the most frequently and /or widely consumed, species, as well as availability of their protein sequences.

Shellfish Crustacean species are taxonomically highly related, belonging to the same order Decapods, resulting in high sequence homology (>90%) of pan-allergen TPM. In contrast, Molluscan shellfish belong to different classes (Bivalvia, Cephalopoda and Gastropoda) resulting in much lower sequence homology (>70%) of TPM. Moreover, even molluscs belonging to the same order have TPM sequence homology <90%, e.g. only molluscs belonging to the same genus have sequence TPM homology >90%. The most striking example are oysters, cupped oysters and flat oysters' TPM share only about 55% of homology (Figure S2). This implies that by using recombinant TPM allergen from one Crustacea species allergy to other crustacean shellfish can be more reliably diagnosed than by using recombinant TPM from one Mollusca species to diagnose allergy to other molluscan shellfish. Furthermore, regarding the sensitization rates to TPM, studies do not show that 100% of patients react to it, meaning that additional allergens are necessary for precise diagnosis. The identification of TPM, AK, SCBP, in several shellfish species as allergens are all important contributions, but additional allergens are required for the development of a complete set of reagents for component resolved diagnosis and the exploration of novel vaccination strategies, particularly in Mollusca. Based on the WHO/IUIS allergen registry, the most comprehensive allergen profile exists from black tiger shrimp, *P. monodon*, comprising nine registered allergens, including TPM, AK, MLC2, SCP, Tn, Hc, TIM, FABP, and GP. The number of bivalve species known to be exploited by humans for food is about 800 (Huang et al., 2023) while only 5 Bivalvia allergens are registered by WHO/IUIS from only 3 species. Moreover, in UniProt database there are TPM sequences from about only 30 Bivalvia species.

Our review provided a comprehensive analysis of shellfish allergens in relation to the abundance of the food source on the global market. We have shown that production of shellfish, such as Mollusca, is overweight production of Crustacea globally, while lagging in view of not only molecular characterization of allergens, but also availability of in vivo and in vitro diagnostic tools based and molecular information on potential allergens. There are economically highly relevant species, present on the market, that are not presented in diagnostic tools. Therefore, sensitization rate to those species cannot be known. Furthermore, regulation of food allergen labelling in a wide range of countries affected by shellfish/Molluscan allergies is inconsistent with the supply/capita of the shellfish.

Within the group of Mollusca, particular attention should be given to Cephalopoda, because of their dominance on the global trade market and rather minimal knowledge of causative allergens. Cephalopodes trades (squids being on top) represent 60% of the global production of shellfish, while only 1 allergen of Cephalopodes out of 50 allergenic shellfish allergens is included so far in the WHO/IUIS.

The scarcity of molecular studies on Mollusca and Cephalopodes allergens leads to the absence of reference for precise allergy diagnostics and accurate allergen immunodetection. In view of the widespread high consumption and allergy prevalence of Mollusca shellfish, that would hazard the health of large populations. Thus, more systematic research studies of Molluscan allergens are essential for future development of diagnostic tools and improvement of food legislation and safety. The knowledge gaps identified through our study may represent a useful guide for further research and improvement of diagnostic tools and better management of shellfish allergies.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author statement: T.C.V. and D.S.-V. were involved in conception and design of the study, analysis and interpretation of the data; the drafting of the paper, revising it critically for intellectual content; and the final approval of the version to be published; M.S., X.W. and M.R. were involved in analysis and interpretation of the data; the drafting of the paper, revising it critically for intellectual content; and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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Data Availability: Data on the cross-reactivity of tropomyosins are available from the Cherry repository of the University of Belgrade-Faculty of Chemistry, from the link: https://hdl.handle.net/21.15107/rcub_cherry_7008. Data on the nonregistered allergens of shellfish are available from the Cherry repository of the University of Belgrade-Faculty of Chemistry, from the link: <https://cherry.chem.bg.ac.rs/handle/123456789/7052>.

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