

# THE XPLORER



JUNE 2023

EDITION # 3

## ALLERGY AGAINST SHELLFISH AND FISH

Sensitisation,  
reactions, diagnosis

[More on page 3](#)

## CEO INTERVIEW: HUMAN CAPITAL

With Dr. Christian Harwanegg

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## ADVERSE REACTIONS TO SEAFOOD

[madx.com](http://madx.com)

**MAD**  
MACRO ARRAY DIAGNOSTICS

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## EDITORIAL



DEAR READERS,

welcome to the third issue of THE XPLORER. One year has passed since we launched this magazine, and we have received lots of positive feedback about the digital and print version – we want to say thank you for that.

This feedback motivates us to publish two more issues with interesting and educational contents this year. The third summery issue of THE XPLORER is dedicated to the topic of seafood allergy. Seafood is one of the “big 8” food groups causing the most adverse reactions after consumption. Detection of sensitisation to corresponding allergens that fall into this category is not easy due to frequent cross-reactions and poor standardisation in extract-based tests.

In the second part of this issue, we want to inform you about two big developments at MADx: The introduction of the new hardware system MAX 9k, as well as the product launch of the first quantitative IgE-test specifically developed for pets: the PAX pet allergy Xplorer. Finally, you will find an overview of the most important events and congresses MADx will be represented at this year.

I hope you enjoy the third issue of THE XPLORER!

**Christian Harwanegg**

CEO Macro Array Diagnostics



# Seafood allergy

## INTRODUCTION

Seafood plays an important role in human nutrition, but it can also provoke adverse reactions in susceptible people. Seafood and seafood products are becoming increasingly popular. The global per head consumption is estimated at 22.3 kg. The leaders in seafood consumption are the Republic of Korea (78.5 kg per capita), followed by Norway (66.6 kg) and Portugal (61.5 kg).<sup>1</sup>

Regarding the diversity of seafood consumed, patients with adverse reactions to seafood may fail to identify the offending species. However, in-vitro diagnostic tests have the potential to identify the culprit allergenic molecules and thus contribute to an improved and more differentiated diagnosis of seafood hypersensitivity reactions.

## CLASSIFICATION OF SEAFOOD

The term seafood refers to different groups of edible aquatic animals including fish and shellfish, i.e., crustaceans and mollusks.

Fish are divided into bony and cartilaginous fish. Bony fish have bony endoskeletons and include, e.g., cod, salmon, and catfish. The endoskeleton of cartilaginous fish, which include sharks and rays, consists of cartilage. Despite pronounced cross-reactivity between allergens from different fish species, there also seem to be epitopes which are specific to distinct fish species, reflected in "mono-sensitisation" to specific groups, such as salmon and trout.<sup>2</sup>

Shellfish, in the context of culinary seafood consumption, constitutes a diverse group of species subdivided into crustaceans and mollusks.

Crustaceans are aquatic arthropods with an exoskeleton (i.e., lobsters, prawns, shrimps, and crabs) and are closely related to arachnids (e.g., dust mites, spiders) and insects (e.g., cockroach, edible insects such as house cricket or mealworm). This might provide an explanation for molecular and clinical cross-reactivity.

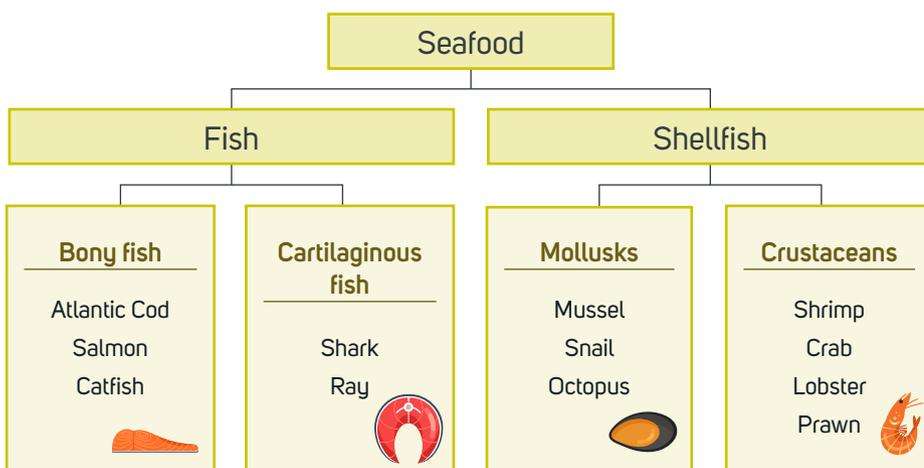
Mollusks are edible invertebrates living in aquatic or damp habitats, characterised by a soft unsegmented body often covered by an external calcareous shell. They include snails,

clams, oysters, mussels, scallops, squids, etc.<sup>3</sup> Like for fish allergens, both extensive cross-reactivity and species specific IgE-reactivities were described for allergens of crustaceans and mollusks. Most allergens responsible for shellfish allergy, including the major allergen tropomyosin, are heat-stable proteins.

Although several hundred different types of mussels are consumed worldwide, almost 80% of all allergic reactions to shellfish involve crab or shrimp. This is partly due to the high production and consumption compared to other shellfish species. Biologically, all edible shellfish species are invertebrates belonging to the Arthropoda or Mollusca family.

## ADVERSE REACTIONS

Different mechanisms were described that can account for adverse reactions to seafood. However, regardless of the underlying mechanisms, the clinical appearance of the different disease entities might be similar.



Classification of seafood

### Immunological reactions

Immunological reactions include IgE-mediated seafood allergy as well as non-IgE-mediated reactions such as food intolerance or FPIES (food protein-induced enterocolitis syndrome).

#### IgE-mediated reactions

##### (type I seafood allergy)

The prevalence of IgE-mediated hypersensitivity reactions to seafood, also known as seafood allergy, is usually higher when the consumption plays a greater part in the diet of the observed community. In general, the consumption of seafood has increased worldwide. It is considered that crustaceans and fish are among the four food groups most commonly provoking severe food anaphylaxis.<sup>4</sup>

#### Non-IgE-mediated reactions

Food intolerances are food-specific IgG-reactions to seafood, where the body produces an inflammatory response to seafood proteins. Unlike seafood allergy, the effects of seafood intolerance are usually delayed, and are not life-threatening but influence the well-being of the patient.

Food protein-induced enterocolitis syndrome (FPIES), is a delayed, non-IgE-mediated allergic reaction of the gut to food, usually presenting in the first two years of life.

In contrast to foods mostly implicated in FPIES in infants and young children (such as milk, soy, rice and other grains, meat and poultry, eggs, and certain fruits and vegetables), FPIES in older children and adults is often triggered by seafood.

### Non-immunological reactions

Among non-immunological types of adverse reactions to seafood, intoxications as well as Anisakis infestations are the main pathomechanisms.

#### Biotoxins

Marine biotoxins are contaminations that are mainly present in filter feeding species.

Biotxin-producing algae are eaten by shellfish, and biotoxins are usually found at very low concentrations in our shellfish dishes. Thus, biotoxins pose no concern for most people that eat moderate amounts of shellfish. However, when the quantities of algae increase in the marine environment, higher quantities of biotoxin can accumulate in species feeding on such algae. Since biotoxins are heat tolerant, they are not destroyed by cooking or other types of heat processing. Therefore, a toxic reaction to biotoxins is dose-dependent and relates to the amount of shellfish consumed.

#### Ciguatera toxin

The ciguatera toxins leading to ciguatera poisoning are incorporated by eating fish that has been contaminated by algae-derived toxins. Those substances are highly resistant to heat, freezing, drying or low pH and do not cause any perceptible changes (taste, smell, colour) of the dish. Ciguatera toxins are only present in fish, particularly large reef fish in the tropics. Symptoms can be highly diverse, including



gastrointestinal, neurological, or dermatological manifestations.

### **Puffer fish poisoning**

In Japan, fugu or puffer fish is a long-established delicacy, despite of its known potential for toxicity. Tetrodotoxin (TTX) is the naturally occurring toxin that is mainly responsible for the risk. TTX is water soluble and heat stable, cooking even increases toxicity of this substance.

Great care must be taken, and only specially trained chefs are allowed to prepare them in such a way so consumers can experience only a small tingle or numbness to their lips when eating. They must ensure that the hazardous parts of the fish (specifically the liver, ovaries, and skin) are removed before serving.

Nevertheless, human intoxications are still not uncommon and even deaths have been linked to the consumption of puffer fish.<sup>5</sup>

### **Scombroid fish poisoning**

Scombroid fish poisoning is an allergy-like reaction that occurs after eating fish that have been improperly refrigerated after capture. Bacteria in and on the fish break down proteins into histamine, one of the major mediators of allergic reactions. Affected fish often have a metallic or peppery taste. Symptoms usually commence within 30 minutes of eating, and include flushing, itching, hives (urticaria), nausea, vomiting, stomach cramps, dizziness,

palpitations, and headache. Scombroid poisoning can be diagnosed based on the pattern of symptoms and negative results in skin or blood allergy testing.

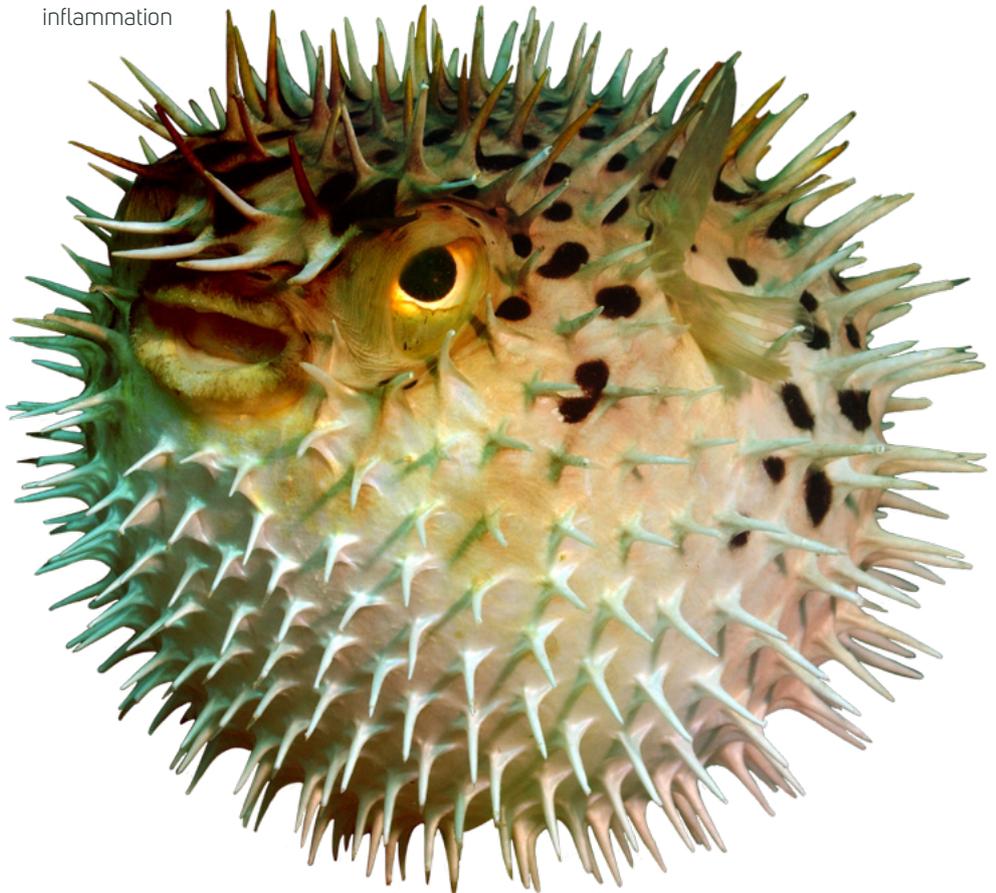
### **Anisakis simplex**

*Anisakis simplex* is a nematode (worm) that was described as a fish parasite. It is found in most parts of the world. Cooking at temperatures above 60°C or storage in industrial freezers for two days is required to kill the parasite. *Anisakis* can cause two major problems in humans:

1. *Anisakis* infestation (anisakiasis) can result from eating raw, pickled, or undercooked seafood such as sushi. Infection may cause nausea, vomiting, stomach pain, and sometimes appendicitis, bowel blockage or bleeding. Symptoms can occur due to inflammation

in the gut at the site of entry of the parasite. Diagnosis requires endoscopy of the stomach and bowel with direct visual detection of the parasite. The parasite usually gets destroyed by our immune system after three weeks.

2. *Anisakis* allergy resembles other allergic reactions to food. In this case, the allergy is directed against the fish parasite, not to the fish itself. Reactions thus mainly occur after eating seafood that is infested with *Anisakis*. The allergens of *Anisakis simplex* appear not to be destroyed by heat or cooking and so allergic reactions may be triggered by dead parasites in fish meat that has been well cooked. Serological allergy testing is available to confirm suspected sensitivity to this parasite.





# Shellfish allergy

## ROUTES OF SENSITISATION

Some shellfish allergens can sensitise via the oral and inhalation route but also via the skin. However, the most common route of exposure and thus sensitisation to shellfish is through ingestion. Many allergens, such as tropomyosin and arginine kinase are abundant in shellfish meat and preserve their structure when exposed to heat. Consequently, these allergens often lead to severe allergic reactions.

Allergic symptoms may also be triggered from inhaling cooking vapour and handling seafood in the domestic sphere but particularly in the occupational setting. In the seafood processing industry, workers are constantly exposed to aerosolised shellfish particulate matters arising from different processing activities leading to the inhalation of airborne allergens and/or cooking fumes. Such occupational exposure to shellfish allergens (tropomyosin, arginine kinase, triosephosphate isomerase) may be a primary route of sensitisation to shellfish, and

upon re-exposure can elicit upper and lower respiratory tract symptoms such as cough, wheeze, laryngeal symptoms, and rhinitis. Occupational exposure may also result in contact urticaria or contact dermatitis. Workers with shellfish-induced occupational symptoms are at risk of developing allergic reactions upon ingestion of seafood (secondary food allergy).

## PREVALENCE

The shellfish group is included among the “Big Eight” food groups which are responsible for more than 90% of all food allergy cases. It is estimated that up to 3% of the general population and less than 1% of children are affected by food allergy to shellfish, including crustaceans and mollusks. Shellfish allergy, particularly to shrimp, has one of the highest rates of food-induced anaphylaxis with nearly 42% of shellfish allergic adults and 12-20% of allergic children reporting anaphylaxis.<sup>6 7</sup>

## SYMPTOMS

The pattern of allergic symptoms after ingestion of shellfish is like that of other foods. Most reactions are immediate and occur within two hours. However, also late-phase reactions have been reported up to eight hours after ingestion of mollusks. Particularly after ingestion of crustaceans, symptoms occur within minutes and include itching and angioedema of the lips, mouth, and pharynx (oral allergy syndrome). Shrimp has also been implicated in food-dependent exercise-induced anaphylaxis. It seems that atopic individuals are at a higher risk of developing anaphylactic reactions.

Respiratory allergy symptoms manifest mainly as upper and lower airway respiratory symptoms, whereas anaphylaxis is rarely seen with this type of exposure. The prevalence of occupational asthma ranges from 7 to 36% and for occupational contact dermatitis, from 3 to 11%.

## DIAGNOSIS

As for any other food allergy, diagnosis of shellfish allergies includes a detailed anamnesis, skin prick testing and serological tests. In unclear cases, provocation testing needs to be performed.

If shellfish extracts are used in skin prick or serological testing, one must consider that these extracts usually comprise a high concentration of tropomyosin. However, other important allergens are frequently missing, or their concentration is too low, which can lead to false-negative test results.<sup>8</sup>

Furthermore, skin prick tests bear the risk of triggering severe allergic reactions (e.g., anaphylactic reactions) in patients that have already experienced severe symptoms. In these patients, serological tests should be preferred.

## MOLECULAR ALLERGY DIAGNOSTICS

Any serological test result should be interpreted in the context of the patient's history. Due to strong cross-reactivity among shellfish, mites, and insects, it is sometimes difficult to identify the primary sensitising allergen source. Unfortunately, there is no unique marker allergen specific for sensitisation to shellfish or a particular shellfish species.

Since cross-reactivity varies among different species, multiplex tests offer the advantage of detecting the respective specific IgE simultaneously, provided that the used allergen panel covers most relevant allergens. The ALEX<sup>2</sup> allergen panel comprises several allergens

from different species from the northern and southern hemisphere.

Tropomyosin is regarded as a major allergen, detecting more than 60% of shellfish sensitisations. It demonstrated much higher specificity than extract-based testing (skin prick and serological testing) and, thus, is a better predictor of shrimp allergy. If IgE antibodies against tropomyosin are detected, broad cross-reactivity to other shellfish and arthropod sources is likely. A diagnosis can be made if the history matches the serology.

Furthermore, it has been shown that a combination of the determination of sIgE to Pen m 1 (Tropomyosin) and Pen m 4 (Sarcoplasmic calcium-binding protein) increases the sensitivity and specificity of shrimp allergy diagnosis.<sup>9</sup>

If shellfish allergic patients are not sensitised to tropomyosin, then sensitisation to other shellfish allergens needs to be evaluated. If no IgE-reactivity to all tested extracts and molecular allergens is found, but the anamnesis indicates shellfish allergy, in some cases food challenge tests are necessary.

## SHELLFISH ALLERGENS

Most of the identified shellfish allergens belong to a common set of protein families that is shared across a diverse range of species. All the currently identified shellfish allergens demonstrate common properties such as low molecular weight (15-75 kDa),

good aqueous solubility and they frequently form dimers or other oligomers.

The major allergen of shellfish allergy is the muscle protein tropomyosin, which occurs both in crustaceans and mollusks. In addition to tropomyosin, other allergens have been identified and characterised in crustaceans such as the 40 kDa arginine kinase, which might be a new class of invertebrate pan-allergen and may be of high clinical relevance. However, previous studies have demonstrated the clinical relevance of IgE-reactivity to additional seafood allergens including myosin light chain, sarcoplasmic calcium-binding protein, troponin C, triosephosphate isomerase and hemocyanin. (Table 1) These less investigated shellfish allergens have also been demonstrated to play a role in clinical cross-reactivity to other invertebrate allergen sources, including dust mites and cockroaches.<sup>10</sup> Interestingly, some shellfish allergens can sensitise not only via the oral route but also via the inhalation route (tropomyosin, arginine kinase, triosephosphate isomerase, hemocyanin).

The major allergens found across all shellfish species belong to the tropomyosin family which are mainly present in the edible



Protein family	Examples	IgE-sensitisation	Heat stability	Route of exposure
<b>Tropomyosin</b>	Pen m 1	62% (16 subjects)	Highly heat stable	Ingestion Inhalation
	Pen a 1	51% (45 subjects)		
	Cra c 1	68% (31 subjects)		
	Lit v 1	94% (34 children) 61% (19 adults)		
<b>Arginine kinase</b>	Pen m 2	50% (16 subjects)	Moderately heat stable	Ingestion Inhalation
	Cra c 2	29% (31 subjects)		
	Lit v 2	67% (34 children) 21% (19 adults)		
<b>Myosin light chain</b>	Pen m 3	31% (16 subjects)	Heat stable	Ingestion
	Cra c 3	19% (31 subjects)		
	Lit v 3	70% (34 children) 31% (19 adults)		
<b>Sarcoplasmic calcium-binding protein</b>	Pen m 4	19% (16 subjects)	Heat stable	Ingestion
	Cra c 4	19% (31 subjects)		
	Lit v 4	59% (34 children) 31% (19 adults)		
<b>Troponin C</b>	Pen m 6	19% (31 subjects)	Heat stable	Ingestion
	Cra c 6			
<b>Triosephosphat isomerase</b>	Pen m 8	19% (16 subjects)	Heat stable	Ingestion Inhalation
	Cra c 8	23% (31 subjects)		
<b>Hemocyanin</b>	Pen m 7	29% (58 subjects)	Heat stable	Ingestion Inhalation
		47% (40 subjects)		

Table 1: Shellfish allergens, adapted from MAUG 2.0<sup>12</sup>

Abbreviations: Pen m: *Penaeus monodon* (Black tiger shrimp), Pen a: *Penaeus aztecus* (Brown shrimp), Cra c: *Crangon crangon* (North sea shrimp), Lit v: *Litopenaeus vannamei* (White shrimp)

meat. It is one of the most abundant proteins representing up to 20% of the total protein content in a shrimp. Allergens from the tropomyosin family have a highly conserved primary structure, and this is the main reason for immunological and clinical cross-reactivity not only among crustaceans and mollusks but also among insects, mites, and nematodes. However, cross-reactivity is higher between tropomyosins from different arthropod species than

between arthropods and mollusks, and even species-specific tropomyosins sometimes play an important role.

Tropomyosin is the major sensitising allergen family in shellfish allergy. Over 60% of shellfish allergic subjects are positive to tropomyosins.<sup>5</sup> As it is highly heat stable and relatively resistant to proteases, severe allergic reactions are often observed.

### Arginine kinase

Arginine kinase is a minor allergen in most populations and belongs to the phosphotransferase family while myosin light chain, sarcoplasmic calcium-binding protein, and troponin C belong to the EF-hand domain family.

Arginine kinase has been identified in several crustaceans and one mollusk species and has been implicated in cross-reactivity between

shellfish and edible insects. It was found to be susceptible to heat treatment or thermal food processing but, however, its capacity to bind IgE is preserved to a certain extent. This is an important fact to consider while using in-vitro diagnostics which is often based on heated shrimp or crab extract to avoid bacterial contamination and therefore includes mainly heat-stable proteins; molecular in-vitro diagnostics might offer a better solution.

### Myosin light chain

Myosin light chain belongs to the myosin family, is part of the sarcomeric units in muscle tissue and involved in muscle contraction. Allergenic myosin light chains are found in arthropods such as crustaceans, mites (e.g., Der p 26 – house dust mite) and cockroaches (e.g., Bla g 8 – German cockroach) but also in meat from other species, e.g., from chicken (Gal d 7).<sup>11</sup>

### Sarcoplasmic calcium-binding protein (SCP)

SCP is a calcium-binding protein regulating cytosolic calcium concentration. Myosin light chain and Sarcoplasmic calcium-binding protein have a lower IgE binding frequency. However, a higher rate of IgE-sensitisation is observed in children as compared to adults and may be used as diagnostic markers for shrimp allergy in children.

### Troponin C

Troponin C is part of the macromolecular complex composed of troponins, tropomyosin, actin, and myosin, and is involved in muscle contraction. It is the calcium-sensing

component that can attach to and detach from tropomyosin.

Troponin C is recognised as a food allergen in shrimp (Cra c 6 and Pen m 6). Furthermore, allergenic troponin C proteins are found in mites (e.g., Der p 39 – house dust mite) and cockroaches (e.g., Bla g 6 – German cockroach).

### Triosephosphate isomerase

Triosephosphate isomerase is a glycolytic heat-labile protein that catalyses the conversion of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate. It has been identified not only in shrimps and crayfish but also in cockroaches.

### Hemocyanin

Hemocyanin was first identified as an allergen in the giant freshwater shrimp. Hemocyanins are copper-containing, oxygen transport proteins mainly found in the hemolymph of invertebrate animals. Consumption of cephalothorax is common in Asian populations and could lead to higher exposure to this allergen. In a recent study, strong IgE-sensitisation to crab hemocyanin was observed in crab-processing workers by inhalational exposure to aerosolised matter. Therefore, hemocyanin-specific IgE may be a potential diagnostic marker for occupational exposure and symptoms to shellfish allergens.

## CROSS-REACTIVITY WITH OTHER ALLERGEN SOURCES

Patients with shellfish allergy are frequently reported to also have allergic reactions to mites and insects. This cross-reactivity is probably due to the high amino acid homology of invertebrate tropomyosins and may have significant clinical implications. Patients that were never exposed to crustacean allergens can be sensitised to tropomyosin due to a non-crustacean source, such as house dust mites (HDM), cockroaches or both, via inhalation. The primary sensitisation is believed mostly to be caused by respiratory exposure to dust mites, which in some individuals may cause allergic reactions after the consumption of shellfish. This view is supported by recent observations during immunotherapy to HDM in which some patients developed clinical sensitisation to shellfish tropomyosin, which did not exist before therapy. Molecular studies suggest similar IgE-binding epitopes in these very different arthropods. Using synthetic overlapping peptides spanning the entire length of the major shrimp allergen Pen a 1, eight IgE-binding epitopes were identified. Four out of eight epitopes are identical to



homologous regions in Der p 10 and Der f 10 (from mites), and five out of eight are identical to homologous regions in Per a 7 (from cockroach). These immunological findings strongly indicate that the documented cross-reactivity between tropomyosins from different allergen sources can result in IgE-antibody binding and subsequent allergic reactions.

## THERAPY

In case of confirmed, severe shellfish allergy, exposure to any shellfish species (except to those species which the patient tolerates) must be strictly avoided, not only via ingestion, but also via inhalation and skin contact. If severe allergic reactions have been observed in the past, emergency medication is essential. Unfortunately, currently there is no allergen-specific immunotherapy available.<sup>9</sup>



## SUMMARY

- 3% of the general population and 1% of children are affected by food allergy to shellfish.
- Nearly 80% of all allergic reactions to shellfish are due to shrimps or prawns.
- Diagnosis of shellfish allergies includes a detailed anamnesis, skin prick testing and serological tests. In unclear cases, provocation testing needs to be performed.
- Molecular allergy tests (e.g., ALEX<sup>2</sup> Allergy Xplorer) cover a comprehensive set of clinically relevant allergens from different species for accurate diagnosis of shellfish allergy.
- ALEX<sup>2</sup> test includes the clinically relevant allergens tropomyosin, arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein and troponin C.
- Cross-reactive allergen tropomyosin is responsible for allergic reactions to mites and insects in shellfish allergic patients.
- Therapy:
  - No allergen-specific immunotherapy available.
  - Strict avoidance, not only via ingestion, but also via inhalation and skin contact.
  - Emergency medication is essential if severe allergic reactions have been observed in the past.



# Fish allergy

## NUTRITION, BENEFITS, AND RISKS

Fish is a common food consumed all around the world. It is a very important dietary source of proteins, vitamin A, iron, calcium, omega-3 fatty acids as well as antioxidants.<sup>13</sup>

The consumption of fish increased by four times over the last 50 years. In westernised countries the increase in fish consumption is related to trends towards healthy nutrition while in developing coastal countries the consumption is related to availability of the product. At a global level, fish consumption is expected to increase by 14.8% until 2030 with a per capita consumption of 21.2 kg per year.<sup>14</sup>

Despite its health benefits, fish is one of the most common foods responsible for allergic reactions in children and adults. Fish allergy is in fact one of the leading causes of anaphylaxis worldwide!<sup>15</sup> It is estimated that 0.1 – 0.5% of the world's population is allergic to fish and in paediatric populations the prevalence is as

high as 7%.<sup>6 16 17</sup> For this reason, fish became part of the food labelling regulation (EU regulation 169/2011).<sup>37 18</sup>

## ROUTES OF SENSITISATION

Despite the health benefits, fish is one of the most common foods that cause allergic reactions in both children and adults. Most reported allergic reactions are related to bony fish.<sup>19 20</sup> In general, sensitisation occurs through allergen exposure via the gastrointestinal tract when eating fish. However, sensitisation can also occur via the respiratory tract, e.g., by inhaling cooking vapours or by skin contact.<sup>21 22 23</sup>

## CLINICAL MANIFESTATIONS

The adverse reactions to fish can be classified into three categories:<sup>6 24</sup>

1. Immunological adverse reactions: including IgE-mediated allergic reactions to fish allergens and to fish infected by certain parasites

such as *Anisakis simplex*. *Anisakis simplex* is commonly found in European hake, Atlantic mackerel, and anchovies.

2. Toxic adverse reactions: referring to toxic reactions to fish infected by parasites as well as fish contaminated by bacteria or poisonous algae.
3. Food intolerance: caused by vasoactive amines present in the fish.

These three categories of adverse reactions present similar clinical symptoms; but a good diagnostic analysis of IgE-antibody reactivity can distinguish between a true fish allergy and other adverse events.

Common clinical manifestations are oral allergy syndrome (OAS), rhinitis, asthma, gastrointestinal symptoms such as abdominal pain, diarrhoea and vomiting, or skin reactions like urticaria and angioedema. In severe cases anaphylaxis with respiratory and/or circulatory manifestations can occur. The symptoms normally appear immediately after ingestion but sometimes a late reaction (around 2h later) can

occur. A longer delayed reaction is also possible but rare. <sup>25 26 27</sup>

## FISH ALLERGENS

Proteins present in fish muscle, eggs, skin, or blood can give rise to fish allergy.

Based on the WHO/IUIS database and on the database Allergen Online (www.allergenonline.org, version 21), fish allergens are mainly divided into: parvalbumins, aldolase, beta-enolase, tropomyosin, collagen and vitellogenin. <sup>37</sup>

Parvalbumin is the major fish allergen responsible for more than 90% of allergic reactions. This calcium-binding protein is found in fish muscles of many fish such as cod, carp, salmon, herring, mackerel, swordfish, and tuna. <sup>28 29 30 31 32</sup>

Parvalbumins are divided in alpha and beta subtypes. The beta-subtype, found in bony fish, has a higher allergenic potential, while alpha-parvalbumin found in cartilaginous fish is in general well tolerated. Alpha-parvalbumin is also present as a minor allergen in chicken, frog and crocodile meat and cross-reactivity between fish and these types of meat were clinically reported. Interestingly, white meat fish

such as cod, contain a higher concentration of parvalbumin and are therefore more allergenic than dark meat fish species like tuna. Although cross-reactivity is common in fish allergic patients, monosensitisation to salmon, trout, tilapia, and tropical sole has been reported. This is explained by the sequence homology of beta-parvalbumins that can differ from 46 to 99%. <sup>23 33 37</sup>

Enolase and aldolase are present in fish muscles of cod, salmon, and tuna. Parvalbumin sensitised patients may also have IgE-reactivity to enolase and aldolase. However, there are patients that are positive only to these allergens. <sup>32 34 37</sup>

Tropomyosin is a major allergen in shellfish but in recent years has also been identified as a fish allergen in patients with tilapia, salmon, catfish, and Asian seabass sensitisation. <sup>32 35 36 37</sup>

Collagen is an allergen found in fish skin. An Australian study with 100 fish allergic children demonstrated that 21% of them were sensitised to collagen from salmon, tuna, and Asian seabass. Based on these findings, collagen is now suggested to be included in allergy diagnosis. It is important to remember that collagen is commonly added to drugs, food, and

cosmetics products and can therefore act as a hidden allergen. <sup>19</sup>

Vitellogenin is a major allergen in fish eggs like caviar. Interestingly, patients with fish egg allergy often tolerate fish meat and vice versa. <sup>37</sup>

## FOOD PROCESSING AND ALLERGENICITY

Different from other allergenic foods, fish processing such as heating, smoking, drying, frying, and boiling does not affect its allergenic potency. There are reports suggesting that fish allergens enolase and aldolase are more sensitive to heat treatment and seem to be less resistant to food processing than parvalbumin, but more investigations are needed to confirm these findings.

## DIAGNOSIS

At present, diagnosis of fish allergy is based on clinical history, SPT and specific-IgE serological tests. In few cases, oral food challenge may be performed. Although these diagnostic procedures are considered reliable and are commonly used, they carry some problems. SPT is performed with non-standardised commercial extracts and can lack important

allergens. The measurement of fish specific IgE-antibodies can be challenging because people with low levels of IgE can show severe clinical reactions. In

addition, oral food challenge carries a high risk of side effects and anaphylaxis.

The development of component-based tests that measure IgE-antibodies to individual allergen components gives a better picture on specific sensitisation,



Fish popular name	Component	Extract
Atlantic cod	Gad m 1 ( $\beta$ -parvalbumin)	+
Atlantic cod	Gad m 2 + 3 ( $\beta$ -enolase & aldolase)	
Atlantic herring	Clu h 1 ( $\beta$ -parvalbumin)	+
Atlantic mackerel	Sco s 1 ( $\beta$ -parvalbumin)	+
Carp	Cyp c 1 ( $\beta$ -parvalbumin)	
Salmon	Sal s 1 ( $\beta$ -parvalbumin)	+
Swordfish	Xip g 1 ( $\beta$ -parvalbumin)	
Tuna	Thu a 1 ( $\beta$ -parvalbumin)	+
Thornback ray	Raj c ( $\alpha$ -parvalbumin)	+
Anisakis simplex	Ani s 1 (unknown function)	
Anisakis simplex	Ani s 3 (Tropomyosin)	

Table 2: ALEX<sup>2</sup> Allergy Explorer fish allergen list

cross-reactivity and risk of severe reactions. In this context, ALEX<sup>2</sup> provides a broad panel of fish allergens (e.g., parvalbumins from 8 fish species, aldolase and enolase from Atlantic cod, and 6 fish extracts). Thus, ALEX<sup>2</sup> is a diagnostic tool for the accurate detection of allergic sensitisation to fish allergens.

Based on molecular IgE-reactivity profiles, fish allergic patients are categorised into three groups:

- Poly-sensitised patients who react to many types of fish based on the cross-reactions of beta-parvalbumin, enolase and aldolase.
- Oligo-sensitised patients who react to a considerable number of fish based on enolase and aldolase, but without IgE to beta-parvalbumin.
- Mono-sensitised patients who react only to allergens from one species.

Patient care relies on dietary avoidance of fish and prescription of emergency medication in case of accidental exposure. In this case, it is important to remember that any route of exposure – ingestion, inhalation, and skin contact – must be avoided. Moreover, in contrast to other food allergies, fish allergy normally does not resolve with age and therefore, lifelong avoidance is necessary.

Currently, there is no allergen-specific immunotherapy available for the treatment of fish allergy.

## SUMMARY

- Fish allergy affects 0.1 – 0.5% of the world's population.
- Fish allergy does not disappear with age.
- Reactions can occur after ingestion, inhalation, and skin contact.
- Common clinical symptoms: OAS, rhinitis, asthma, abdominal pain, diarrhoea, vomiting and skin reactions.
- Diagnosis is based on: anamnesis, SPT, serum IgE-levels, OFC, and the most advanced is CRD (e.g., ALEX<sup>2</sup> test).
- Fish allergens: parvalbumin (most important allergen family), aldolase, enolase, tropomyosin, collagen, vitellogenin.
- Cross-reactivity between different fish species is frequent.
- ALEX<sup>2</sup> includes a broad panel of parvalbumins and other relevant fish allergens allowing a precise diagnosis of each individual patient.
- Strict avoidance and emergency medication are still the only treatment strategies available.



# Human Capital

## CEO talks #3

To turn MADx's ambitious goals into reality, the company needs to grow. To achieve this, it not only needs more laboratory and office space, but of course also the right people from various disciplines who will work here in the future. Because it is not at all easy to find and retain good employees, we are talking about the so-called "human capital" today.

**How many employees did MADx have in the beginning, and how fast did the company grow?**

**Christian Harwanegg:** We started with one employee in 2016, at the end of 2016 there were three employees. At the end of 2023, we will surpass the 70-employee-mark if our recruiting plans are successful.

**At the beginning, was it easy or hard to find the right employees to build MADx?**

**Christian Harwanegg:** I think it's always difficult to find the right employees. You often don't know what a potential employee is like at the beginning: a job interview is a stressful situation in which a person can present themselves positively or negatively.

In addition, in a fast-growing, dynamic company, the demands on employees change. At the beginning of MADx, extreme multitasking was required: In the first one and a half to two years, six or seven employees covered the entire company area – production, research, logistics, management and so on.

I am an advocate of the guiding principle "first who, then what". This means that if a good candidate actively applies to us and we think that this person could be a good, hard-working, and competent employee, I take the position to hire this person

immediately – even without a concrete job description. We will find the right job in the next step. I prefer that to looking for employees in a very specific and reactive way.

”  
It is important to  
strengthen  
company culture.

“  
It would be desirable to always be slightly ahead of capacity and that employees can later develop into the appropriate positions where they feel most comfortable. This is not always possible, for example in finance, which requires a very specific skillset and where there is not much leeway. But in areas like HR, marketing, and product management, where different skills are required within the department anyway and a

multidisciplinary team is needed, it works because employees often acquire new skills in the course of their employment.

**Is the employee turnover rate in life science companies low or high, and where does MADx stand?**

**Christian Harwanegg:** I don't think this issue is necessarily industry specific. Whether it's life science, hospitality, or any other field, the deeper the knowledge employees need to work in a particular field, and the more specialised and niche that field is, the higher the staff consistency. I believe that on an industry average, we have relatively low turnover of staff. On average, 5-10% of staff leave, however, we backfill 30% – in my experience, that's fine. The most important factor, especially as the company gets bigger, is to strengthen the company culture so that employees feel comfortable and can thrive. That is more decisive than the industry itself.

**What can a company in our field do to keep employees motivated?**

**Christian Harwanegg:** It's a mix of classic hygiene factors: the working environment has to fit, the salary has to fit, the human quality

has to fit. The company location is also very important: We lose or gain employees because they either live very far away or close to the location. This factor is also increasingly important

in terms of work-life-balance. Even though it used to be no problem for many people to commute for an hour and a half every day, it is extremely unpopular nowadays. For many, traveling longer than half an hour is unthinkable – especially if they can choose to do so. Development opportunities are also important for those who want them. This is important to emphasise because not everyone wants to be a team leader and take on more responsibility. Some employees are happy to work undisturbed, while others want active

management. It is important to respond to the personality of the employees and to consider how to strengthen individuals in their position. Private factors should not be forgotten either. If everything runs smoothly at home, it's easier to be satisfied at work than if things go haywire in your private life. The issue of overwork is very important, you

always have to make sure that there are enough resources. If necessary, an employee can perform at 120% for a while, but it's impossible in the long run. It is the responsibility of management and leaders to recognise when overload sets in. When things are going badly, even 80% is often too much for the person concerned.

MADx is a very young company with partly very inexperienced employees who come directly from university or training. On the one hand, this has the advantage that such employees are shaped to the company, and they do not know how it is in other companies. However, such experience is also worth a lot, because otherwise you quickly get the feeling that it could be better somewhere else, you would earn more or work less, the tasks would be more interesting, and so on. Employees who don't have this wealth of experience will eventually seek it out. It's difficult to counteract this – because you can't give this experience to employees who don't have comparative values.

” The issue of overwork is very important.

“

no family obligations because they are pursuing other goals on the side. There are also employees who want to work from home more



because they live far away, or their family situation requires it. If it is possible to reconcile these requirements with the job, it is good for the company.

Issues like working from home naturally create certain inequalities. There are jobs that cannot be done in the home office – keyword lab work. When it comes to travel, some people want to travel a lot, but their job doesn't require it, while others are constantly on the road even though they would rather be at home with their family. There are often life circumstances in which the work-life-balance is no longer compatible with a full-time job at a location with long commutes. I think we are very flexible here, especially when it comes to young mothers and flexible working time models. Of course, there are certain limits here as well, because, to put it bluntly, it doesn't make sense for an employee who occupies a key position in the company to only be available from 8 p.m. to 4 a.m.

As an employer, you also have to insist that employees take responsibility for themselves, so that they communicate in good time where their comfort zone begins and ends. From my point of view, this unfortunately often happens too late: Frustrations then accumulate, causing the employee to leave because they want to change something – without looking for change in the company first.

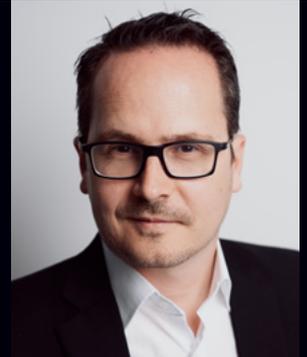


#### ABOUT

#### DR. CHRISTIAN HARWANEGG

studied Molecular Genetics at the University of Vienna, Austria. He joined a team of entrepreneurs in 1999 and graduated with a PhD in 2003. He has spent his entire professional education and career working in the development of all aspects of allergy testing in a multiplexed setup.

” I am an advocate of the principle “first who, then what”. “





# Product innovations for laboratories and veterinarians

## NEW HARDWARE SYSTEM: MAX 9K

The MADx hardware systems have been developed with our customers' needs in mind. Whether it's high throughput, low throughput, a lot of lab space or little lab space – we make sure that one of our systems is the perfect solution for our customers' individual situation. For this reason, in addition to the manual processing system ImageXplorer, which is designed for lower throughput, and the automated processing system MAX 45k, which is designed for high-throughput labs, there is now another system: the MAX 9k.

Like the MAX 45k, the MAX 9k is a fully automated batch analyser that can process 10 samples in one run. It is a smaller benchtop instrument for medium throughput laboratories.

The MADx hardware systems are characterised by their ease of use and can be easily operated together with the MADx software after a short training period. In addition, the MADx hardware systems are connected in real time to our cloud-based software solution, which

means that data can be analysed and managed around the clock.

For a full comparison of all MADx systems, please visit our [website](#).

## PAX PET ALLERGY XPLORER NOW AVAILABLE

MADx is expanding its diagnostic range to pets: Since the beginning of the year, the PAX Pet Allergy Xplorer is exclusively available for dogs from our partner Nextmune. PAX is also based on our proprietary nano-bead technology and is the first quantitative IgE-test specifically designed to detect allergic sensitisations in animals.

Traditional allergy testing in veterinary medicine has not changed for decades and is based on the use of allergen extracts in an enzymatic immunoassay (ELISA). The problem with this method is that results can vary greatly depending on the extract and false-negative results can



often occur due to insufficient protein allergen concentrations.

PAX is based on MADx' revolutionary technology and Nextmune's expertise in the fundamentals of pet allergology. PAX uses allergen extracts and molecular components to identify allergens affecting pets, offering benefits such as improved reproducibility and cross-reactivity identification, improved accuracy, more data (up to 300 results), improved treatment recommendations and more.

MADx CEO Dr. Christian Harwanegg explains: "With PAX, we are finally able to offer accurate and reliable allergy diagnostics not only for human patients, but also for their pets. Pet allergy diagnostics is a growing market, and we are excited to work with a science-based partner like Nextmune to offer this innovative product in the veterinary space."

Nextmune CEO Magnus Kjellberg added: "We value the development collaboration with MADx and are proud to embark on this new journey

together. Nextmune is the only veterinary diagnostic laboratory currently using molecular allergology. We believe this product will allow veterinarians to diagnose pets more accurately, benefiting both the animals and their owners."

PAX is currently available for testing dog sera. Cat and horse sera are also expected to be able to be tested with PAX before the end of 2023. PAX is available from our [partner Nextmune](#) around the world.



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