The Pharma Innovation Journal 2023; 12(6): 1969-1976

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(6): 1969-1976

www.thepharmajournal.com
Received: 17-03-2023
Accepted: 18-04-2023

Domendra Dhruve
College of Fisheries Science, CCSHAU, Hisar, Haryana, India

Ajeet Soni
College of Fisheries Science, CCSHAU, Hisar, Haryana, India

Siddharth Kumar Jatav
College of Fisheries Science, CCSHAU, Hisar, Haryana, India

Satyendra Katara
College of Fisheries Science, NDVSU, Jabalpur, Madhya Pradesh, India

Corresponding Author:
Siddharth Kumar Jatav
College of Fisheries Science, CCSHAU, Hisar, Haryana, India

Naturally occurring marine shellfish and finfish toxins: A review

Domendra Dhruve, Ajeet Soni, Siddharth Kumar Jatav and Satyendra Katara

Abstract
Marine environments host a diverse array of microorganisms that produce a wide range of naturally occurring toxins, many of which pose a significant threat to human health. Among these toxins, those associated with shellfish and finfish consumption have garnered particular attention due to their potential to cause severe poisoning incidents. This review aims to provide a comprehensive overview of the naturally occurring marine toxins associated with shellfish and finfish, including their sources, modes of transmission, and impacts on human health. Shellfish toxins primarily originate from harmful algal blooms (HABs), commonly known as "red tides," which are caused by certain species of phytoplankton. These toxins can accumulate in filter-feeding shellfish such as mussels, clams, and oysters, rendering them toxic to humans upon consumption. The most well-known shellfish toxins include paralytic shellfish toxins (PSTs), amnesic shellfish toxins (ASTs), and diarrhetic shellfish toxins (DSTs). Each class of toxin has distinct chemical properties and targets different physiological systems, leading to varying symptoms in affected individuals. Finfish toxins, on the other hand, are primarily produced by certain species of dinoflagellates and cyanobacteria. These toxins can accumulate in predatory fish species and cause illness in humans upon ingestion. Ciguatera fish poisoning (CFP), saxitoxin (STX), and tetrodotoxin (TTX) are among the most notable finfish toxins. They exhibit neurotoxic effects, leading to symptoms ranging from gastrointestinal distress to neurological impairment. Understanding the characteristics and mechanisms of shellfish and finfish toxins are essential for the development of effective monitoring and surveillance programs.

Keywords: Shellfish toxin, finfish toxins, histamine, saxitoxin, marine toxins

Introduction
The marine toxins, which are harmful substances found in certain seafood that can cause food poisoning. These toxins can contaminate seafood without affecting its appearance, smell, or taste. There are five common types of marine toxins, each causing different symptoms. Bivalve mollusks, like mussels, feed on microscopic algae, and under specific conditions, certain algae species can multiply rapidly, forming dense algae clouds known as blooms. The factors contributing to bloom development are not fully understood, but specific climatic and hydrographic conditions are believed to play a role. While blooms can be beneficial in some cases, more than 40 species of toxic algae, belonging to the classes of dinoflagellates and diatoms, are known to produce phycotoxins (marine toxins). The abundance of these toxic algae can vary significantly. Blooms with high concentrations of toxic algae are called harmful algae blooms (HABs). Some research suggests that certain phytoplankton species produce toxins to compete with others for space. Phycotoxins can accumulate in various marine species, including fish, crabs, and filter-feeding bivalves such as mussels, oysters, scallops, and clams. In shellfish, toxins primarily accumulate in the digestive glands without harming the shellfish itself. However, consuming large amounts of contaminated shellfish can cause severe intoxication in humans. Algae-produced toxins, including freshwater cyanotoxins, are responsible for approximately 60,000 cases of human intoxication annually worldwide. These shellfish toxins also harm wildlife and have negative economic impacts on recreation, tourism, and the shellfish industry. In Europe, the occurrence of algae blooms is estimated to result in an annual loss of 720 million euros for the recreation and tourism industry and 166 million euros for the shellfish industry. To prevent shellfish toxin intoxication, legislation and monitoring programs have been established globally. This review provides an overview of different types of poisoning syndromes, the algae and toxins associated with them, and explore alternative methods to replace animal bioassays currently used for detecting lipophilic marine toxins.

Poisoning Syndromes and Corresponding Toxins

Marine shellfish toxins can be categorized into two main classes based on their chemical properties: hydrophilic toxins and lipophilic toxins. Hydrophilic toxins are associated with the syndromes of amnesic shellfish poisoning (ASP) and paralytic shellfish poisoning (PSP), and they have a molecular weight (MW) below 500 Da. On the other hand, toxins responsible for neurologic shellfish poisoning (NSP), diarrhetic shellfish poisoning (DSP), azaspiracid shellfish poisoning (AZP), as well as other toxins like pectenotoxins, yessotoxins, and cyclic imines, all share a common characteristic of having a molecular weight above 600 Da, reaching up to 2,000 Da. These toxins possess significant lipophilic properties. As a result, they are generally referred to as lipophilic marine toxins.

Paralytic Shellfish Poisoning (PSP)

Paralytic shellfish poisoning (PSP) occurs when individuals consume bivalve mollusks such as mussels, clams, oysters, and scallops that have ingested toxic dinoflagellates (Halstead and Schantz, 1984; Schantz, 1973) [40, 76]. These toxins are absorbed and temporarily stored by the shellfish. In the United States, PSP is mainly a concern in the New England states on the East Coast, as well as in Alaska, California, and Washington on the West Coast. Outbreaks from shellfish harvested in coastal states outside of these regions are rare, which highlights the effectiveness of current testing and control measures for commercially produced shellfish. Most cases of PSP involve mussels, clams, and scallops gathered by recreational collectors, often from closed areas. The Centers for Disease Control and Prevention (CDC) reported 12 outbreaks between 1978 and 1986, involving 134 people and one death. However, it is believed that mild cases resulting from the consumption of marginally toxic clams by recreational diggers are either not reported to health authorities or misdiagnosed.

Paralytic shellfish poisoning is considered highly dangerous because the toxins involved are among the most potent known. Symptoms are primarily neurological and typically manifest within an hour of consuming toxic shellfish. In non-lethal cases, the symptoms usually subside within a few days. Common symptoms include tingling, numbness, and burning sensations in the lips and fingertips, ataxia, dizziness, unsteady movements, drowsiness, dry throat and skin, incoherence, aphasia, rash, and fever. Severe cases can lead to respiratory paralysis, which can cause death, usually within the first 24 hours. However, patients who survive this critical period have a good prognosis for recovery. There is no known antidote for PSP, but respiratory support is administered when paralysis occurs. Patients generally recover fully without any long-term effects. It is important to note that experiencing PSP does not confer immunity, and multiple incidents can occur.

The complex of toxins responsible for paralytic shellfish poisoning (PSP) is known as saxitoxins, which can be considered forms or derivatives of saxitoxin. The structure of saxitoxin was reported by Schantz *et al*. in 1975 [79]. The 12 most commonly encountered toxins in this complex include saxitoxin, neosaxitoxin, gonyautoxins (I, II, III, IV), B1, B2, C1, C2, C3, and C4. These toxins exhibit varying toxic effects on mice, with saxitoxin, neosaxitoxin, and gonyautoxins II and III being roughly equal in toxicity, while the others are somewhat weaker, as documented by Boyer *et al*. in 1978 and Shimizu and Hsu in 1981. The toxigenic dinoflagellates Gonyaulax catenella and G. tamarenses are of particular importance in the United States, with G. catenella dominating the West Coast and G. tamarenses being more prevalent on the East Coast, according to Taylor in 1988 [87]. These microorganisms develop specific toxin profiles that typically consist of six to eight saxitoxins. While shellfish consume all of these toxins during blooms of these Gonyaulax species, they appear to selectively retain or biologically modify certain derivatives, leading to differences in toxin profiles between the shellfish and the Gonyaulax they feed on, as noted by Schantz *et al*. in 1975 [79] and Sullivan *et al*. in 1983 [84-85].

Blooms of toxigenic dinoflagellates, specifically Gonyaulax catenella on the West Coast and G. tamarensis on the East Coast, occur multiple times each year. These blooms primarily take place from April to October along the U.S. West Coast, Alaska, and the East Coast from Long Island Sound to Maine. Similar blooms also occur off the coast of British Columbia and the Canadian Maritime Provinces. The occurrence of these blooms cannot be reliably predicted with current knowledge. When these blooms occur, shellfish become toxic and remain toxic for several weeks after the bloom subsides. In some areas, certain species of bivalve mollusks, such as butter clams in parts of Washington State and Alaska, remain consistently toxic. The responsibility of protecting consumers primarily lies with the state where potentially toxic shellfish originate. This is achieved by closing shellfish harvesting in affected areas. Closures may be long-term and absolute for certain species, such as ocean coast mussels in California, or temporary, such as for most hard-shell clam operations in Washington and Oregon, as described by Nishitani and Chew in 1988.Given that clam digging and oyster gathering from public beaches are popular recreational activities in coastal states, authorities issue warnings through the media when hazardous conditions exist and post multilingual warning notices on public beaches, particularly along the West Coast. Each affected state has a surveillance system that involves regular sampling and testing of shellfish from different areas throughout the bloom season (April to October). Toxicity tests are typically conducted in state public health laboratories using the standardized mouse bioassay, as outlined by the AOAC in 1984. Collection of samples and posting of beach warnings are often the responsibility of local authorities, such as county-level agencies. Commercial shellfish producers are required to submit samples for testing, and many voluntarily send their shellfish to state laboratories for analysis.

Neurotoxic Shellfish Poisoning (NSP)

Neurotoxic shellfish poisoning (also known as brevetoxic shellfish poisoning or BSP) occurs when shellfish contaminated with the red tide organism Gymnodinium breve (formerly Ptychodiscus brevis) are consumed. Red tides occasionally appear in the Gulf of Mexico and off the coast of Florida, and they can be carried by the Gulf Stream to adjacent states. These events are characterized by the observation of red-colored seawater and can cause massive fish die-offs, with dead fish washing ashore. The wind and waves generated during red tides produce irritant aerosols that may lead to respiratory distress. Filter feeding molluscs ingest the dinoflagellates responsible for red tides and retain the toxin in their tissues. Although no cases of Neurotoxic Shellfish Poisoning (NSP) were reported to the CDC between

1978 and 1986, five cases were reported in Florida from 1973 to 1974, according to NETSU. In a red tide incident in North Carolina from 1987 to 1988, 48 individuals fell ill with NSP (Tester and Fowler, 1990) [90]. Reports of respiratory irritation among people in coastal areas were received on October 29 and 30, 1987, and oyster harvesting was subsequently closed on November 2. However, 35 of the reported cases occurred before the shellfish harvesting ban, which lasted from 3 1/2 to 6 months depending on the location. The decision to close harvesting was based on the presence of more than 5,000 G. breve cells per liter of seawater, and reopening was contingent on the absence of brevetoxin in 100-gram samples of shellfish meat as determined by a mouse bioassay (DNR, 1985; FDA, 1989) [21, 24]. Despite this incident resulting from the first reported G. breve bloom in North Carolina, recent evidence suggests that the state-operated surveillance and closure systems are generally effective.

Symptoms of NSP caused by consuming shellfish containing brevetoxins include tingling and numbness in the lips, tongue, throat, and area around the mouth, muscle aches, gastrointestinal disturbances, and dizziness. Although the intoxication is typically not fatal, onset is rapid, and symptoms usually subside within a few hours or, at most, a few days. Unfortunately, there is currently no antidote for this condition.

Diarrhetic Shellfish Poisoning (DSP)

Diarrhetic shellfish poisoning (DSP) is caused by consuming mussels, scallops, or clams that have fed on *Dinophysis fortii*, D. acuminata, and other species of Dinophysis, and possibly Prorocentrum (Edler and Hageltorn, 1990; Yasumoto and Murata, 1990) [22, 94]. While no confirmed outbreaks have been reported in the United States, DSP is prevalent in Japan and has become a problem in Europe. A single confirmed episode of DSP occurred in Canada in 1990.

Symptoms of DSP include diarrhea, nausea, vomiting, and abdominal pain. Onset typically ranges from 30 minutes to a few hours after consuming the toxic shellfish, and the duration of symptoms is usually short, with severe cases lasting a few days at most. Fortunately, the disease is not life-threatening (Yasumoto *et al*., 1984) [95].

Multiple toxins have been identified in dinoflagellates and shellfish associated with DSP. Okadaic acid is the most commonly encountered toxin in Europe, where D. acuminata is the primary culprit, while Japanese cases usually involve D. fortii and exhibit mixtures of okadaic acid, dinophysistoxins, and pectenotoxins (Yasumoto and Murata, 1990) [94]. A mouse bioassay is available for detecting these toxins.

Amnesic Shellfish Poisoning (ASP)

Todd (1989) [91] proposed the term "amnesic shellfish poisoning" to describe the syndrome caused by domoic acid. This syndrome was identified during a series of outbreaks in Canada in November and December 1988, affecting 103 individuals. Domoic acid, produced by the diatom Nitzschia pungens, was found to be present in certain types of mussels and clams in Atlantic Canada during a period of diatom blooms. Symptoms of the illness included vomiting, abdominal cramps, diarrhea, disorientation, and memory loss (Perl *et al*., 1988; Teitelbaum *et al*., 1990) [72, 89]. Of these symptoms, short-term memory loss was the most persistent and, in some cases, lasted for over a year. Necrosis of the hippocampus was observed during autopsies of three fatal cases. Older individuals were particularly vulnerable to this severe disease, and some deaths were reported during the Canadian outbreaks.

It is evident that this toxin should be included in the testing protocols of the United States, and there should be strong collaboration between U.S. and Canadian regulatory agencies regarding the importation of Canadian shellfish into the United States. *Nitzschia pungens* and *N. pseudodelicatissima* have been reported in waters of northern U.S. and Canada, raising the possibility of shellfish in these regions becoming toxic. Currently, states in the northeastern United States are conducting tests on mussels to detect the presence of domoic acid.

Specific intoxications

Ciguatera toxin: Ciguatera is a clinical condition that arises from consuming the flesh of toxic fish found in tropical reef and island waters. The toxin is believed to originate from a microscopic dinoflagellate alga called Gambierdiscus toxicus, which grows on reefs (Bagnis *et al*., 1980) [5]. However, other benthic algae have also been linked to this syndrome. When fish consume these algae, they become toxic, and the toxicity is amplified as it moves up the food chain, making larger predatory fish the most toxic. The presence of toxic fish tends to be localized, although the specific locations are inconsistent, and toxic fish may appear sporadically in any reef or island area (Engleberg *et al*., 1983) [23]. Ciguatera poisoning has been associated with over 400 species of fish (Randall, 1980) [74], with common culprits including amberjack, snapper, grouper, barracuda, goatfish, and reef fish from the Carrangidae family. In the United States, ciguatera is primarily found in Hawaii, Puerto Rico, the Virgin Islands, Guam, and Florida (CDC, 1989) [18]. Guam has reported a particularly high incidence of cases (Haddock, 1989), and a few instances have been reported in other states due to fish shipments from Florida. Cases often occur in individuals who have traveled to regions where ciguatera is endemic, such as Hawaii and the Virgin Islands, and there is concern that many cases go unrecognized by mainland U.S. physicians.

The disease affects both the gastrointestinal and neurological systems (Bagnis *et al*., 1979; Morris *et al*., 1982a) [6, 63]. Gastrointestinal symptoms, such as diarrhea, nausea, vomiting, and abdominal pain, typically manifest within 3-5 hours after consuming the fish and are of short duration. Neurological symptoms emerge 12-18 hours after ingestion and can range from moderate to severe. They usually persist for 1-82 days but can extend for several months. In rare instances, symptoms may last for years, with flare-ups triggered by fish consumption or possibly alcohol (Halstead, 1967) [34]. Common neurological symptoms include sensory abnormalities such as hot-cold inversion (perceiving hot things as cold and cold things as hot), muscular aches, tingling and numbness in the lips, tongue, and surrounding areas, a metallic taste, dry mouth, anxiety, weakness, dizziness, chills, sweating, dilated pupils, blurred vision, and temporary blindness. In extreme cases, paralysis and death can occur. The symptoms can be severely debilitating, leading to prolonged periods of disability. Acute symptoms can be alleviated with intravenous mannitol.

A variety of harmful substances have been identified in ciguatoxic fish and Gambierdiscus, with the main toxin referred to as "ciguatoxin." Ciguatoxin is a small polyether

compound that can dissolve in lipids, weighing approximately 1, 112 atomic mass units (Scheuer *et al*., 1967) [80]. Extensive purification and structural analysis conducted by Murata *et al*. (1990) [66] have provided insight into the composition of this toxin. Ciguatoxin, also known as CTX, has a molecular formula of C60H88O19 and belongs to the brevitoxin type of polyethers. It exhibits a potency around 100 times greater than that of tetrodotoxin. The action of ciguatoxin involves the activation of voltage-dependent sodium channels in cellular membranes (Bidard, 1984) [8]. Experimental investigations using tissue preparations indicate that the toxin induces a blockade of nerve conduction after the initial stimulation of neural activity. When administered in animals, low doses of ciguatoxin lead to mild hypotension and bradycardia. Higher doses elicit a biphasic response, initially causing bradycardia and hypotension, followed by tachycardia and hypertension. Very high doses can result in the impairment of the phrenic nerve, leading to respiratory arrest (Gillespie *et al*., 1986) [29]. Another lipid-soluble neurotoxin identified in ciguateric fish is called "scaritoxin." Studies have shown that this toxin inhibits oxidative metabolic processes in the brain of rats and exerts a depolarizing effect on excitable membranes.

According to Legrand and Bagnis (1984) [59], the pharmacological effects of other toxins are similar to those of ciguatoxin, suggesting a potential relationship between these compounds. One such toxin is maitotoxin, which is soluble in water and may interfere with or alter the movement and conductance of calcium in tissues. Additional lipid-soluble toxins have been reported, but their structures and specific pharmacological roles remain unclear (Ragelis, 1984) [73]. Based on data from the Centers for Disease Control and Prevention (CDC), the documented incidence of ciguatera poisoning indicates approximately 15-20 outbreaks per year, involving 50 to 100 cases. The majority of cases reported to the CDC are concentrated in Hawaii, Puerto Rico, the Virgin Islands, and Florida.

In regions where reef fish are commonly consumed, particularly among local residents or tourists who engage in recreational or small-boat fishing, it is challenging to completely prevent cases of ciguatera poisoning. The inability to detect toxic fish through sensory examination and the sporadic nature of its occurrence impose limitations on control measures. The situation could be significantly improved with the availability of a simple and reliable test. Currently, the Tokyo Central Wholesale Fish Market in Japan is the only entity that implements a ciguatera screening program. Inspectors in charge of hygiene assess incoming shipments of fish originating from tropical island regions. If any specimens raise suspicion, they are removed for testing. Muscle extracts from the fish are prepared and evaluated for ciguatoxicity using cats and mice as test subjects (Halstead, 1970) [35]. However, this screening technique is time-consuming and expensive, making it impractical for handling large numbers of samples. A radioimmunoassay (RIA) was initially developed by Hokama and colleagues in Hawaii (Hokama *et al*., 1977) [47] and later simplified to an enzyme immunoassay (Hokama, 1985) [45]. Subsequently, the method was further streamlined into a "stick" test, which has shown promise as a practical approach for screening fish landed in Hawaii and potentially serving as a control measure (Hokama *et al*., 1989b) [49].

Scombroid (Histamine) Fish Poisoning: Scombroid intoxication occurs when people consume fish that contain elevated amounts of histamine. Originally, this condition was linked to the consumption of scombroid fish like tuna, mackerel, bonito, and saury. However, additional fish species have been identified as culprits of this intoxication, including mahimahi, bluefish, jack, mackerel, amberjack, herring, sardine, and anchovy. In the United States, scombroid fish poisoning has mainly been attributed to mahimahi, tuna, and bluefish, according to the CDC in 1989 [18].

Scombroid food poisoning is more widespread across the United States compared to ciguatera, with incidents reported in 45 states between 1978 and 1988. While Hawaii had the highest number of outbreaks (45) and cases (171), mainland states collectively reported 111 outbreaks and 582 cases. This indicates that the illness, although associated with warm temperatures, is not limited to tropical or subtropical fish species alone. Consequently, the risk of scombroid poisoning is present among consumers who eat fish regardless of their location. Fortunately, the disease is generally mild, of short duration, and resolves on its own without any long-term effects in the majority of cases. Furthermore, since improper handling or storage of fish is the cause of the toxic condition and effective testing methods exist to identify toxic fish, control and prevention measures are feasible. The mild and temporary nature of scombroid poisoning likely leads to underreporting of the disease.

The United States has identified fish imported from warmwater countries, especially mahimahi, as a potential source of scombroid poisoning. This connection is attributed to the combination of high ambient water and air temperatures in the fish's origin region, as well as inadequate handling practices on boats and in markets. These suboptimal conditions promote the growth of bacteria that convert histidine to histamine, leading to the occurrence of scombroid poisoning.

The correct term for the disease is histamine poisoning, as stated by Taylor in 1986 [86]. It manifests with various symptoms affecting the gastrointestinal, neurological, hemodynamic, and cutaneous systems. These symptoms include nausea, vomiting, diarrhea, cramping, headache, palpitations, flushing, tingling, burning, itching, hypotension, rash, urticaria, edema, and localized inflammation. The most commonly observed symptoms are tingling and burning sensations around the mouth, gastrointestinal complaints, and a rash accompanied by itching. Generally, the illness is mild and resolves on its own, with symptoms appearing rapidly and lasting only a few hours. Treatment is typically unnecessary, but relief can be obtained with antihistamine drugs.

Histamine is generated in fish flesh through the decarboxylation process of free histidine, which naturally exists in high amounts in fish species linked to scombroid fish poisoning (Lukton and Olcott, 1958) [60]. Bacteria present on the fish produce an enzyme called histidine decarboxylase, which is responsible for histamine production. Histidine decarboxylase production is not widespread among bacteria and is primarily found in species such as Enterobacteriaceae, Clostridium, Lactobacillus (Taylor, 1986) [86], and potentially Vibrio (Van Spreekens, 1987) [92]. Morganella morganii, Klebsiella pneumoniae, and Hafnia alvei, which are enteric bacteria, have been isolated and identified in fish associated with histamine poisoning (Havelka, 1967; Kawabata *et al*., 1956; Taylor *et al*., 1979) [88, 52]. Although other enteric bacteria like Clostridium perfringens and halophilic vibrios

have been reported, *M. morganii* and *K. pneumoniae* are the most commonly implicated ones. These organisms are not typically found in live fish and are likely introduced during the catching and handling process (Taylor, 1986) [86].

For histamine production to be significant, bacteria need to reach a sufficiently large population. These bacteria are mesophilic, meaning they thrive at temperatures above 15°C. In tropical regions, fish captured often have temperatures exceeding 20 °C, and on small vessels, it is not uncommon for fish to be kept on deck at even higher temperatures for several hours. The ideal temperature for histamine production is around 30 °C (Arnold *et al*., 1980) [2]. Even at refrigeration temperatures (0-5 °C), where bacterial growth ceases, there is still residual enzyme activity that allows for slow histamine production. Therefore, the production of histamine in fish is a result of mishandling and improper storage practices after the fish is caught. In fact, the level of histamine can serve as an indicator of fish spoilage in certain cases. The Food and Drug Administration (FDA) considers a histamine level of 20 milligrams (mg) per 100 grams (g) of fish flesh, or 200 parts per million (ppm), as an indication of spoilage in tuna. A level of 50 mg/100 g (500 ppm) is considered a hazard (Federal Register, 1982). This is close to the estimated toxic dose of 60 mg/100 g proposed by Simidu and Hibiku (1955) [82]. However, there is some uncertainty regarding the exact toxic dose threshold due to the presence of substances in fish that enhance toxicity, thereby lowering the effective dosage compared to pure histamine.

According to reports from the CDC, there have been approximately 12 to 20 outbreaks of scombroid fish poisoning each year, involving fewer than 100 cases. It should be noted that these numbers are likely an underestimate because the illness is typically mild, short-lived, and does not usually get reported to health authorities. Reliable chemical tests for detecting histamine in fish flesh are available (Taylor, 1986) [86], which has enabled the FDA to establish a threshold of 50 mg/100 g of flesh as the action level for histamine in tuna. If the histamine level exceeds this threshold, the fish is considered hazardous.

Preventing fish histamine poisoning can be achieved by adopting proper handling practices at the time of capture and throughout subsequent storage, processing, and distribution stages. Fish should be rapidly chilled after being caught using methods such as ice, refrigerated seawater or brine, or mechanical refrigeration. The temperature of the fish flesh should be lowered to below 15 °C, preferably below 10 °C, within four hours. This should be a standard practice in commercial systems. Routine monitoring of histamine levels should be conducted by the industry for susceptible species where proper handling prior to capture cannot be guaranteed. The specific level at which testing is performed will depend on the species and the form of the product (e.g., tuna for canning, hot smoked mackerel).

In the United States, the highest-risk fish commercially is likely to be imported fresh or frozen fish from tropical regions. Such fish may contain elevated histamine levels even when there are no obvious signs of spoilage, such as a foul odor or discoloration. Imported fish should be subject to stringent controls. Domestically caught species in regular commercial channels are probably less problematic due to the widespread use of ice and refrigeration. However, controlling histamine levels in bluefish and tuna or mackerel caught by sports fishermen presents a more challenging situation. These fish are often caught by individuals and may not enter traditional commercial channels. Implementing local or state regulations could be considered for licensed charter fishing boats, potentially requiring adequate facilities for rapid fish chilling and ensuring that fish are stored in a chilled state until landed. In the absence of a simple litmus test, education is crucial for controlling histamine levels among most sports fishermen and their families. States should provide advisory bulletins to inform sports fishermen about proper handling practices. It is important to emphasize that scombroid fish poisoning is a mild illness that is not long-lasting or life-threatening. Symptoms can be quickly relieved with antihistamines.

Puffer Fish Poisoning (PFP)

Puffer fish poisoning occurs when certain types of fish from the Tetraodontidae family are consumed. The toxin responsible for this poisoning is called tetrodotoxin, which was initially believed to be a toxin produced by the fish itself. The toxicity levels in poisonous puffer fish vary significantly. The idea that cultured puffer fish are toxic supports the theory that the toxin originates from the food chain, although this has yet to be confirmed. Recent research has revealed that specific marine vibrios, commonly found in the microflora of puffer fish, can produce a variant of the toxin. This finding suggests that these vibrios may play a role in the development of toxicity.

In recent years, there have been no reported cases of puffer fish poisoning in mainland United States, although there were incidents in the past. Between 1951 and 1974, seven cases were reported in Florida, three of which resulted in fatalities. These cases were attributed to the consumption of locally caught Sphoeroides species of puffer fish. In Hawaii, the common puffer fish, Arothron hispidus, has been associated with at least seven deaths. In Japan, where various species of puffer fish are consumed as a delicacy, there are an estimated 20 to 100 deaths from fugu poisoning each year. Despite strict controls imposed by Japanese authorities on the marketing and preparation of the dish in restaurants, these fatalities continue to occur (Ogura, 1971) [70].

The symptoms of puffer fish poisoning resemble those associated with paralytic shellfish poisoning. These symptoms include initial tingling and numbness of the lips, tongue, and fingers, which can progress to paralysis of the limbs. Other symptoms may include ataxia, difficulty in speaking, and ultimately, death due to respiratory paralysis. Nausea and vomiting are common early signs of poisoning. The similarity in symptoms is expected because tetrodotoxin, although chemically distinct from saxitoxins, also blocks sodium channels. Currently, there is no known antidote for tetrodotoxin, and treatment mainly focuses on providing supportive care. The toxicity of tetrodotoxin is comparable to that of saxitoxin, with a lethal dose for humans ranging from 1 to 4 mg.

Despite rigorous public health regulations and trained, certified puffer cooks in Japan, the wholesale, preparation, and sale of puffer fish as food have not eliminated the risk of intoxication. Fugu (puffer fish) remains a significant cause of fatal food poisoning in Japan. In summary, consuming poisonous puffer fish is akin to playing Russian roulette, as all U.S. puffers have the potential to be toxic. Due to numerous variables involved in the puffer fish industry, the sale of these fish should be prohibited in the United States Halstead (1967,

1988) [37].

Considering the aforementioned findings, it would be wise to refrain from including puffer fish, whether domestic or imported, in the commercial distribution within the United States until a thorough evaluation of the potential risks they pose is conducted. The Food and Drug Administration (FDA) has recently granted approval for the importation of Japanese puffer fish to be used in fugu restaurants across the United States. Despite the implementation of stringent regulations to guarantee the non-toxicity of these fish, the ongoing experiences in Japan raise concerns about the safety of this practice for the American population (Halstead, 1988) [37].

References

1. Anderson BS, Sims JK, Wiebenga N, Sugi M. The epidemiology of ciguatera fish poisoning in Hawaii 1975-1982. Haw. Med. J. 1983;42:326-334.
2. Arnold SH, Price RJ, Brown WD. Histamine formation by bacteria isolated from skipjack tuna, *Katsuwonas pelamis*. Bull. Jpn. Soc. Sci. Fish. 1980;46:991-995.
3. AOAC (Association of Official Analytical Chemists). 1984. P. 344 in S. Williams, editor., ed. Official Methods of Analysis of the Association of Official Analytical Chemists, 14th ed. AOAC, Arlington, Va.
4. Baden DG, Mende TJ, Poli MA, Block RE. Toxins from Florida's red tide dinoflagellate *Ptychodiscus brevis*. Pp. 359-367 in E.P. Ragelis, editor., ed. Seafood Toxins. American Chemical Society, Washington, D.C. 1984.
5. Bagnis R, Kuberski T, Laugier S. Clinical observations on 3009 cases of ciguatera (fish poisoning) in the South Pacific. Am. J Trop. Med. Hyg. 1979;28:1067-1073.
6. Bagnis R, Chanteau S, Chungue E, Hurtel JM, Yasumoto T, Inoue A. Origins of ciguatera fish poisoning: A new dinoflagellate *Gambierdiscus toxicus* Adachi and Fukuyo, definitely involved as a causal agent. Toxicon. 1980;18:199-208.
7. Benson J. Tetradon (blowfish) poisoning. A report of two fatalities. J Forensic Sci. 1956;1:119-126.
8. Bidard JN, Vijuerbert HPM, Frelin C, Chungue E, Legrand AM, Bagnis R, *et al*. Ciguatoxin is a novel type of Na^+ channel toxin. J Biol. Chem. 1984;359:8353-8357.
9. Bowman PB. Amitriptyline and ciguatera. Med. J. Australia. 1984;140:802.
10. Boyer GE, Schantz J, Schnoes HK. Characterization of 11-hydroxysaxitoxin sulfate. J Chem. Soc. London Chem. Comm. 1978;20:889-893.
11. CDC (Centers for Disease Control). *Salmonella* Surveillance, Annual Summary, 1978. HHS Publ. No. (CDC) 81-8219. Public Health Service, U.S. Department of Health and Human Services, Atlanta, Ga. 1981a. p. 25.
12. CDC (Centers for Disease Control). Annual Summary of Foodborne Disease, 1978. HHS Publ. No. (CDC) 81-8185. U.S. Department of Health and Human Services, Atlanta, Ga. 1981b. p. 53.
13. CDC (Centers for Disease Control). Annual Summary of Foodborne Disease, 1979. HHS Publ. No. (CDC) 8185. U.S. Department of Health and Human Services, Atlanta, Ga. 1981c. p. 40.
14. CDC (Centers for Disease Control). Food-Borne Disease Outbreaks, Annual Summary, 1980. HHS Publ. No. (CDC) 83-8185. Public Health Service, U.S. Department of Health and Human Services, Atlanta, Ga. 1983a. p. 32.
15. CDC (Centers for Disease Control). Food-Borne Disease Outbreaks, Annual Summary, 1981. HHS Publ. No. (CDC) 83-8185. Public Health Service, U.S. Department of Health and Human Services, Atlanta, Ga. 1983b. p. 41.
16. CDC (Centers for Disease Control). Food-Borne Disease Outbreaks, Annual Summary 1983: Reported morbidity and mortality in the United States. Morbid. Mortal. Weekly Rep. (annual suppl.). 1984. p. 32.
17. CDC (Centers for Disease Control). Food-Borne Disease Outbreaks, Annual Summary 1982. HHS Publ. No. (CDC) 85-8185. Public Health Service, U.S. Department of Health and Human Services, Atlanta, Ga. 1985. p. 38.
18. CDC (Centers for Disease Control). Annual Summary of Foodborne Disease, unpublished dates from 1983 to 1986. U.S. Department of Health and Human Services, Atlanta, Ga. 1989.
19. Chu FS, Fan TSL. Indirect enzyme-linked immunosorbent assay for saxitoxin in shellfish. J. Assoc. Off. Anal. Chem. 1985;68:13-16.
20. Cooper MJ. Ciguatera and other marine poisonings in the Gilbert Islands. Pacific Sci. 1964;18:411-440.
21. DNR (Department of Natural Resources, Florida). Pp. 1-10 in Contingency Plan for Control of Shellfish Potentially Contaminated by Marine Biotoxins. Bureau of Marine Research, St. Petersburg, Fla. 1985.
22. Edler L, Hageltorn M. Identification of the causative organism of a DSP outbreak on the Swedish west coast. Pp. 345-349 in E. Graneli, editor;, B. Sundström, editor;, L. Edler, editor;, and D.M. Anderson, editor., eds. Toxic Marine Phytoplankton. Elsevier, Amsterdam, The Netherlands. 1990.
23. Engleberg NC, Morris JG Jr., Lewis J, McMillan JP, Pollard RA, Blake PA. Ciguatera fish poisoning: A major common source outbreak in the U.S. Virgin Islands. Ann. Intern. Med. 1983;98:336-337.
24. FDA (Food and Drug Administration). Revision. Sanitation of shellfish growing areas. National Shellfish Sanitation Program Manual of Operations Part I. Center for Food Safety and Applied Nutrition, Division of Cooperative Programs, Shellfish Sanitation Branch, Washington, D.C. 1989.
25. Federal Register. Department of Health and Human Services. Food and Drug Administration. Defect action levels for histamine in tuna: Availability of a guide. Fed. Reg. 470:40487-40488. 1982.
26. Freudenthal AR. Public health aspect of ciguatera poisoning contracted on tropical vacations by North American tourists. Pp. 463-468 in E. Graneli, editor;, B. Sundström, editor;, L. Edler, editor;, and D.M. Anderson, editor., eds. Proceedings of the 4th International Conference on Toxic Marine Phytoplankton. Elsevier, Amsterdam, The Netherlands. 1990.
27. Freudenthal AR, Jijina JL. Potential hazards of *Dinophysis* to consumers and shellfisheries. J. Shellfish Res. 1988;7:695-701.
28. Gilgan MW, Burns BG, Landry GJ. Distribution and magnitude of domoic acid contamination of shellfish in Atlantic Canada during 1988. Pp. 469-474 in Proceedings of the 4th International Conference on Toxic Marine Phytoplankton. Elsevier, Amsterdam, The Netherlands. 1989.
29. Gillespie NC, Lewis RJ, Pearn JH, Bourke ATC, Holmes MJ, Bourke JB, *et al*. Ciguatera in Australia: Occurrence,

clinical features, pathophysiology and management. Med. J Aust. 1986;145:584-590.
30. Goe DR, Halstead BR. A preliminary report of the toxicity of the Gulf puffer, *Sphoeroides annulatus*. Calif. Fish and Game. 1953;39:229-232.
31. Gollop JH, Pon EW. Ciguatera fish poisoning: Review of pathogenesis, clinical manifestations and epidemiology in Hawaii 1984-1988. Hawaii Med. J. (in press). 1991.
32. Haddock RL. Letter report on food-borne disease incidence, dated September 8, 1989, from Dr. Robert L. Haddock, Territorial Epidemiologist, Department of Public Health and Social Services, Government of Guam to Dr. Farid E. Ahmed, Project Director, Committee on Evaluation of the Safety of Fishery Products, Institute of Medicine, National Academy of Sciences, Washington, D.C. 1989.
33. Hall S, Reichardt PB. Cryptic paralytic shellfish toxins. Pp. 113-124 in Ragelis, E.P., editor. ed. Seafood Toxins. American Chemical Society, Washington, D.C. 1984.
34. Halstead BW. Dangerous Marine Animals. Cornell Maritime Press, Cambridge. 1959. p. 146.
35. Halstead BW. Poisonous and Venomous Marine Animals of the World, U.S. Government Printing Office, Washington, D.C. 1967;1(83-87):679-844.
36. Halstead BW. Poisonous and Venomous Marine Animals of the World. U.S. Government Printing Office, Washington, D.C. 1970. p. 1006.
37. Halstead BW. Poisonous and Venomous Marine Animals of the World, 2nd rev. ed. Darwin Press, Princeton, N.J. 1988. p. 1168.
38. Halstead BW. Dangerous Aquatic Animals of the World: A Color Guide. Darwin Press, Princeton, N.J. 1990. p. 288.
39. Halstead BW, Lively WM. Poisonous fishes and ichthyosarcotoxism. Their relationship to the Armed Forces. U.S. Armed Forces Med. J. 1954;5:157-175. [PubMed]
40. Halstead BW, Schantz EJ. Paralytic shellfish poisoning. WHO Offset Publication No. 79:1-60. Geneva, Switzerland. 1984. [PubMed]
41. Halstead BW, Auerbach PS, Campbell D. A Colour Atlas of Dangerous Marine Animals. Wolfe Medical Publications, Ipswich, England. 1990. p. 192.
42. Havelka B. Role of *Hafnia* bacteria in the rise of histamine in tuna fish meat. Cesk. Hyg. 1967;12:343.
43. HDH (Hawaii Department of Health). Fish Poisoning in Hawaii. Advisory Leaflet. Honolulu, Hawaii. 1988.
44. Hemmert CD. Tetraodon (puffer fish) poisoning. Memorandum of Florida Department of Health, Tallahassee, Fla. 1974.
45. Hokama Y. A rapid simplified enzyme immunoassay stick test for the detection of ciguatoxin and related polyethers from fish tissue. Toxicon. 1985;23:939-946. [PubMed]
46. Hokama Y. Simplified solid-phase immunobead assay for detection of ciguatoxin and related polyethers. J. Clin. Lab. Anal. 1990;4:213-217. [PubMed]
47. Hokama Y, Banner AH, Boyland D. A radioimmunoassay for the detection of ciguatoxin. Toxicon. 1977;15:317-325. [PubMed]
48. Hokama Y, Honda SAA, Asahina AY, Fong JML, Matsumoto CM, Gallacher TS. Cross-reactivity of ciguatoxin, okadaic acid, and polyethers with monoclonal antibodies. Food Agric. Immunol. 1989a;1:29-35.
49. Hokama Y, Honda SAA, Kobayashi MN, Nakagawa LK, Asahina AY, Miyahara JT. Monoclonal antibody (MAb) in detection of ciguatoxin (CTX) and related polyethers by the stick-enzyme immunoassay (S-EIA) in fish tissues associated with ciguatera poisoning. 1989b. p. 303-310 in S. Natori, editor; K. Hashimoto, editor; and Y. Ueno, editor., eds. Mycotoxins and Phycotoxins '88. Elsevier Science Publishers, Amsterdam, The Netherlands.
50. Holt RJ, Miro G, Del Valle A. An analysis of poison control center reports of ciguatera toxicity in Puerto Rico for one year. Clin. Toxicol. 1984;22:177-185. [PubMed]
51. Hughes JM, Merson MH. Fish and shellfish poisoning. N. Engl. J Med. 1976;295:1117-1120. [PubMed]
52. Kawabata T, Ishizaka K, Miura T, Sasaki T. Studies on the food poisoning associated with putrefaction of marine products. VII. An outbreak of allergy-like food poisoning caused by sashimi of *Parathunnus mebachi* and the isolation of the causative bacteria. Bull. Jpn. Soc. Sci. Fish. 1956;22:41-47.
53. Kodama AM, Hokama Y, Yasumoto T, Fukui M, Manea SJ, Sutherland N. Clinical and laboratory findings implicating palytoxin as cause of ciguatera poisoning due to *Decapterus macrosoma* (mackerel). Toxicon. 1989;27:1051-1053.
54. Lalone RC, DeVillez ED, Larson E. An assay of the toxicity of the Atlantic puffer fish *Sphoeroides maculatus*. Toxicon. 1963;1:159-164.
55. Lange WR, Kreider SD, Hattwick M, Hobbs J. Potential benefit of tocainide in the treatment of ciguatera: Report of three cases. Am. J Med. 1988;84:1087-1088.
56. Larson E, Rivas LR, Lalone RC, Coward S. Toxicology of the Western Atlantic Puffer Fish of the Genus *Sphoeroides*. The Pharmacologists. 1959;1:70. (Abstract).
57. Larson E, Lalone RC, Rivas L. Comparative toxicity of the Atlantic pufferfishes of the genera *Sphoeroides*, *Lactophrys*, *Lagocelhalus* and *Chilomycterus*. Fed. Proc. 1960;19:388. (Abstract).
58. Lawrence DN, Enriquez MB, Lumish RM, Maceo A. Ciguatera fish poisoning in Miami. J. Am. Med. Assoc. 1980;244:254-258.
59. Legrand AM, Bagnis R. Mode of action of ciguatera toxins. Pp. 217 in E.P. Ragelis, editor., ed. Seafood Toxins. American Chemical Society, Washington, D.C. 1984.
60. Lukton A, Olcott HS. Content of free imidazole compounds in the muscle tissue of aquatic animals. Food Res. 1958;23:611-618.
61. Miller MD. Ciguatera Seafood Toxins. CRC Press, Boca Raton, Fla. 1991. p. 176.
62. Mills AR, Passmore R. Pelagic paralysis. Lancet. 1988;1:161-164.
63. Morris JG Jr., Lewin P, Hargrett NT, Smith CW, Blake PA, Schneider R. Clinical features of ciguatera fish poisoning: A study of the disease in the U.S. Virgin Islands. Arch. Intern. Med. 1982a;142:1090-1092.
64. Morris JG Jr., Lewin P, Smith CW, Blake PA, Schneider R. Ciguatera fish poisoning: Epidemiology of the disease on St. Thomas, U.S. Virgin Islands. Am. J Trop. Med. Hyg. 1982b;31:574-578.
65. Mosher H, Fuhrman FA. Occurrence and origin of

tetrodotoxin. Pp. 333-334 in E.P. Ragelis, editor., ed. Seafood Toxins. American Chemical Society, Washington, D.C. 1984.
66. Murata M, Legrand AM, Ishibashi Y, Fukui M, Yasumoto T. Structures and configurations of ciguatoxin from the moray eel *Gymnothorax javanicus* and its likely precursor from the dinoflagellate *Gambierdiscus toxicus.* J Am. Chem. Soc. 1990;112:4380-4386.
67. Narita H, Matsubara S, Miwa N, Akahane S, Murakami M, Goto T, *et al*. *Vibrio alginolyticus* a TTX-producing bacterium isolated from the starfish *Astropecten polyacanthus.* Nippon Suisan Gakk. 1987;53:617-621.
68. Nishitani L, Chew K. PSP toxins in the Pacific Coast states: Monitoring programs and effects on bivalve industries. J Shellfish Res. 1988;1:653-669.
69. NOAA (National Oceanic and Atmospheric Administration). Japan's "Fugu" (Puffer Fish) Market Advisory. Doc/NOAA/NMFS, Washington, D.C. 1988. p. 1.
70. Ogura Y. Fugu (puffer fish) poisoning and the pharmacology of crystalline tetrodotoxin in poisoning. Pp. 139-159 in L.L. Simpson, editor., ed. Neuropoisons, Vol. I. Plenum Press, New York. 1971.
71. Palafox NA, Jain LG, Pinano AZ, Gulick TM, Williams RK, Schatz IJ. Successful treatment of ciguatera fish poisoning with intravenous mannitol. J. Am. Med. Assoc. 1988;259:2740-2742.
72. Perl TM, Bédard L, Kosatsky T, Hockin JC, Todd ECD, Remis RS. An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. N. Engl. J Med. 1988;322:1775-1780.
73. Ragelis EP. Ciguatera seafood poisoning: An overview. Pp. 25-36 in E.P. Ragelis, editor, ed. Seafood Toxins. American Chemical Society, Washington, D.C. 1984.
74. Randall JE. A survey of ciguatera at Eniwetok and Bikini Marshall Islands, with notes on the systematics and food habits of ciguatoxic fish. Fish Bull. 1980;78:201-249.
75. Ruff TA. Ciguatera in the Pacific: A link with military activities. Lancet. 1989;1:201-205.
76. Schantz E. Seafood toxicants. Pp. 424-447 in Toxicants Occurring Naturally in Foods, 2nd ed. National Academy Press, Washington, D.C. 1973.
77. Schantz E. Chemistry and biology of saxitoxins and related toxins. Ann. N.Y. Acad. Sci. 1986;479:15-23.
78. Schantz EJ, McFarren EF, Schafer ML, Lewis KH. Purified shellfish poison for bioassay standardization. J Off. Agric. Chem. 1958;41:160-170.
79. Schantz EJ, Ghazarossian VE, Schnoes HK, Strong FM, Springer JP, Pezzanite JD, *et al*. The structure of saxitoxin. J Am. Chem. Soc. 1975;97:1238-1239.
80. Scheuer PJ, Takahashi W, Tsutsumi J, Yoshida T. Ciguatoxin: Isolation and chemical nature. Science. 1967;155:1267-1268.
81. Shimizu Y, Hsu C. Confirmation of the structure of gonyautoxins I-IV by correlation with saxitoxin. J. Chem. Soc. Chem. Comm. 1981. p. 314-315.
82. Simidu W, Hibiku S. Studies on putrefaction of aquatic products. XXIII. On the critical concentration of poisoning for histamine. Bull. Jpn. Soc. Sci. Fish. 1955;21:365-367.
83. Sugita H, Iwata J, Miyajima C, Kubo T, Noguchi T, Hashimoto K, *et al*. Changes in microflora of a puffer fish *Fugu niphobles* with different water temperatures. Marine Biology. 1989;101:299-304.
84. Sullivan JJ, Iwaoka WT. High pressure liquid chromatographic determination of toxins associated with paralytic shellfish poisoning. J Assoc. Off. Anal. Chem. 1983;66:297-303.
85. Sullivan JJ, Iwaoka WT, Liston J. Enzymatic transformation of PSP toxins in the littleneck clam (*Protothacis staminea*). Biochem. Biophys. Res. Commun. 1983;114:465-472.
86. Taylor SL. Histamine food poisoning: Toxicology and clinical aspects. C.R.C. Crit. Rev. Toxicol. 1986;17:91-128.
87. Taylor SL. Marine toxins of microbial origin. Food Tech. 1988;42:94-98.
88. Taylor SL, Guthertz LS, Leatherwood M, Lieber ER. Histamine production by *Klebsiella pneumoniae* and an incident of scombroid fish poisoning. Appl. Environ. Microbiol. 1979;37:274-278.
89. Teitelbaum JS, Zatorre RJ, Carpenter S, Gendron D. Evans AC, Gjedde A, *et al*. Cashman. Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. N. Engl. J Med. 1990;322:1781-1787.
90. Tester PA, Fowler PK. Brevetoxin contamination of *Mercenaria mercenaria* and *Crassostrea virginica*: A management issue. Pp. 499-503 in E. Graneli, editor;, B. Sundström, editor;, L. Edler, editor;, and D.M. Anderson, editor., eds. Proceedings of the 4th International Conference on Toxic Marine Phytoplankton. Elsevier, Amsterdam, The Netherlands. 1990.
91. Todd ECD. Amnesic shellfish poisoning–A new seafood toxin syndrome. Pp. 504-508 in E. Graneli, editor;, B. Sundström, editor;, L. Edler, editor;, and D.M. Anderson, editor., eds. Proceedings of the 4th International Conference on Toxic Marine Phytoplankton. Elsevier, Amsterdam, The Netherlands. 1989.
92. Van Spreekens K. Histamine production by the psychrophilic flora. Pp. 309-318 in D.E. Kramer, editor; and J. Liston, editor., eds. Seafood Quality Determination. Elsevier Science Publishers, Amsterdam, The Netherlands. 1987.
93. Wekell J, Liston J. Pp. 111-155 in P. Newberne, editor., ed. Seafood Biotoxicants in Trace Substances and Health: A Handbook Part II. Marcel Dekker, New York. 1982.
94. Yasumoto T, Murata M. Polyether toxins involved in seafood poisoning. Pp. 120-132 in S. Hall, editor; and G. Stricharty, editor., eds. Marine Toxins. Origin, Structure and Molecular Pharmacology. American Chemical Society, Washington, D.C. 1990.
95. Yasumoto T, Murata M, Oshima Y, Matsumoto GK, Clardy J. Diarrhetic shellfish poisoning. in E.P. Ragelis, editor., ed. Seafood Toxins. American Chemical Society, Washington, D.C 1984, p. 207-216.