CHAPTER 6: **NATURAL TOXINS**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

UNDERSTAND THE POTENTIAL HAZARD

Fish and molluscan shellfish contaminated with natural toxins from the water in which they lived can cause consumer illness. Most of these toxins are produced by naturally occurring marine algae (phytoplankton). Fish or molluscan shellfish consume the algae, or animals that have consumed the algae, which causes the toxins to accumulate in the fish's or molluscan shellfish's flesh. The toxin continues to accumulate in the feeding animal's body at each point of consumption and results in higher levels further up the food chain. Typically, contamination occurs following blooms of the toxic algal species; however, toxin contamination is possible even when algal concentrations are low in certain instances. In addition, there are a few natural toxins and harmful compounds, not produced by algae, that are specific to certain fish species.

There are numerous natural toxins identified worldwide; however, there are currently six recognized natural toxin poisoning syndromes that can occur from consuming contaminated fish and fishery products which are:

- amnesic shellfish poisoning (ASP),
- azaspiracid shellfish poisoning (AZP),
- ciguatera fish poisoning (CFP),
- diarrhetic shellfish poisoning (DSP),
- neurotoxic shellfish poisoning (NSP), and
- paralytic shellfish poisoning (PSP).

All safety levels identified through guidance and regulations for natural toxins may be found in "Appendix 5: FDA and EPA Safety Levels in Regulations and Guidance" of this Guide; however, these levels should not be identified in the HACCP plan as they are utilized for confirming illnesses (i.e. CFP), inform advisories for at risk harvest areas (i.e., CFP) and/or make a determination for harvest area closures (i.e., ASP, AZP, DSP, NSP, and PSP.)

Scombrotoxin fish poisoning, resulting from consumption of certain species of fish that have been time/temperature abused, is caused by spoilage bacteria that form biogenic amines, such as histamine, that are not considered natural toxins. Refer to Chapter 7 for information related to scombrotoxin formation and associated controls.

This chapter has been organized to identify specific information regarding the natural toxins and controls that are specifically associated with "fish other than molluscan shellfish" and "molluscan shellfish." Refer to specific sections appropriately.

- **Specific Information Associated with Recognized Natural Toxins in Fish Other Than Molluscan Shellfish**

This section provides information regarding the implicated finfish, geographic regions, and illness characteristics associated with natural toxins in fish other than molluscan shellfish. It is important to note that additional geographic locations may occur because the distribution of the source algae can vary over time. Processors should always be alert to the potential for emerging hazards in harvest waters and fish sources.

While CFP is the prominent syndrome associated with fish as presented in this section, there are other natural toxins that may occur in fish such as ASP and PSP toxins. Refer to specific toxins in the molluscan shellfish section for information regarding other natural toxins that may occur in fish other than molluscan shellfish.

Ciguatera fish poisoning (from ciguatoxin) is commonly related to the consumption of subtropical and tropical reef fish which have accumulated naturally occurring ciguatoxins through their diet. The highest incidences of ciguatoxins occur between latitudes 35° north and 35° south, and include areas of the Caribbean Sea, Gulf of Mexico, and Atlantic, Pacific, and Indian Oceans. Unsafe ciguatoxin levels have also been detected from fish populations in areas such as the Flower Garden Banks of the Gulf of Mexico, and specific areas of Florida, Hawaii, Puerto Rico, and the U.S. Virgin Islands.

Ciguatoxins originate from marine algae, are transferred through the food web, and accumulate in the flesh of reef dwelling fish with the highest levels of the toxin being observed in long-lived fish-eating predators. These fish may then be harvested by commercial or recreational fishermen for human consumption. Due to differences in life history and diet, not all fish within a given region are equally contaminated. Thus, fish caught side by side may contain widely differing toxin levels. Because ciguatoxic endemic areas are localized, the primary seafood processors should recognize and avoid purchasing fish from known and/or emerging areas of concern.

Many fish species have been associated with CFP including but not limited to: barracuda (Family: Sphyraenidae), grouper (Family: Serranidae), snapper (Family: Lutjanidae), jacks and trevally (Family: Carangidae), wrasse (Family: Labridae), mackerel (Family: Scombridae), tang (Family: Acanthuridae), moray eels (Family: Muraenidae), and parrotfish (*Scarus* spp.). Ciguatoxins have also been found in lionfish (*Pterois volitans* and *Pterois miles*) collected in waters surrounding the U.S. Virgin Islands.

CFP is characterized by gastrointestinal symptoms including: nausea, vomiting, and diarrhea. Neurological symptoms include: numbness and tingling of the lips and extremities; itching of hands and feet; joint pain; muscle pain; muscle weakness; reversal and sensitivity to temperature; dizziness; and vertigo. Cardiovascular symptoms may occur and include irregular heartbeat and low blood pressure. The onset of symptoms typically occurs within 6 hours after consuming toxic fish and may persist from several days to weeks. In severe cases, some neurological symptoms may persist for months and can recur for years. Fatalities do not usually occur from CFP; however, isolated fatalities have been reported.

- **Additional Toxins Found in Fish Other Than Molluscan Shellfish**

There are naturally occurring toxins in some fish species that are either not a result or have not yet been proven conclusively to be a result, of marine algae such as: clupeotoxin, ichthyohemotoxin, gempylotoxin, tetramine, tetrodotoxin, and a possible unidentified toxin that causes seafood-associated rhabdomyolysis (sometimes referred to as Haff disease).

Clupeotoxin poisoning is a rare but severe type of seafood poisoning resulting from the consumption of certain filter-feeding fish such as sardines, herring, and anchovies. The exact cause of clupeotoxin poisoning is unknown but it has been suggested that the marine toxin palytoxin, produced by certain marine algae, contributes to this illness. All illnesses as of August 2019 have been linked to fish harvested from African, Caribbean, and Indo-Pacific waters. No suspected cases of clupeotoxin poisoning have been linked to fish harvested from U.S. waters and no cases of clupeotoxin poisoning have occurred in the U.S. Clupeotoxin poisoning is associated with a high mortality rate.

Gempylotoxin(s) are wax esters naturally found in high concentrations in the meat of escolar (*Lepidocybium flavobrunneum*) and oilfish (*Ruvettus pretiosus*). These particular wax esters are indigestible and may cause diarrhea, abdominal cramps, nausea, headache, and vomiting when consumed in sufficient quantities or consumed in lower quantities by sensitive individuals. The exact quantity required to cause these purgative effects is not known and appears to vary based on individual sensitivities. FDA advises against the importation and interstate marketing of these fish. Additionally, deep sea fish species, such as orange roughy (*Hoplostethus atlanticus*), and oreo dory (*Allocyttus* spp., *Pseudocyttus* spp., *Oreosoma* spp., and *Neocyttus* spp.) are known to contain lesser amounts of the same indigestible wax esters as escolar and oilfish. Sensitive individuals may also experience symptoms from the consumption of these fish. Improperly handled escolar and oilfish also have been associated with scombrotoxin (histamine) poisoning (Refer to Chapter 7).

Ichthyohemotoxin is found in the blood of a variety of different species of eels and considered a rare form of food poisoning. Known implicated species of eels include *Anguilla anguilla*, *Conger conger*, and *Muraena helena*. Very little is known about the nature of the toxin. Ichthyohemotoxin manifests in two different forms: 1. Systemic (caused by the consumption of fresh, uncooked blood); and 2. Topical. Symptoms of the systemic form include: diarrhea, bloody stools, nausea, vomiting, hypersalivation, skin eruptions, cyanosis, apathy, irregular pulse, weakness, paresthesia, paralysis, respiratory distress, and possibly death. Symptoms from the topical form includes a severe inflammatory response when raw eel serum comes in contact with eyes or the mouth. Oral symptoms consist of burning, redness of mucosa and hypersalivation. Ocular contact invokes a severe burning sensation and redness of the conjunctivae, lacrimination, and swelling of the eyelids. Eye irritation may persist for a several days. Recovery is usually spontaneous. Care should be taken when handling eels. Cooking has been known to denature the toxic properties.

Tetramine is a toxin that is found in the salivary glands of whelks (*Neptunia* spp.). This hazard can be controlled through the removal of the glands. Symptoms of tetramine poisoning include: double vision, temporary blindness, difficulty in focusing, tingling of the fingers, prostration, nausea, vomiting, diarrhea, and loss of muscle control. Symptoms usually develop within 1 hour of consumption.

Tetrodotoxin poisoning is usually associated with the consumption of puffer fish from waters of the Indo-Pacific Ocean regions. However, several reported cases of poisonings, including fatalities, involved puffer fish from the Atlantic Ocean, Gulf of Mexico, and Gulf of California. There have been no confirmed cases of poisonings from northern puffer fish (*Sphoeroides maculatus*) as of August 2019, which was once harvested and marketed as "sea squab" on the U.S. east coast.

Puffer fish are also known as fugu, swellfish, bok, blowfish, globefish, toadfish, blaasop, or balloonfish, depending on the country of origin. Other fish species such as xanthid crabs, marine gastropods, and goby fish may contain this toxin and have been implicated in tetrodotoxin illnesses outside of the U.S. Reports of these illnesses have mainly been limited to Asia, and involve species unlikely to be imported into the U.S. Although strictly regulated, it should be noted that there have been several cases of tetrodotoxin illness in the U.S. from the consumption of illegally imported and commercially sold puffer fish products in multiple forms (i.e., frozen and dried).

A restriction exists on the importation of all species of puffer fish and fishery products containing puffer fish. See "The Exchange of Letters between Japan and the U.S. Food and Drug Administration Regarding Puffer Fish" (at website: https://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/ucm107601.htm), Import Alert #16-20 (at website: https://www.accessdata.fda.gov/cms_ia/importalert_37.html), and the Regulatory Food Code for Retail Foods (at website: https://www.fda.gov/food/retail-food-protection/fda-food-code) for further details regarding importation and control of tetrodotoxin. In addition to tetrodotoxin, some puffer fish have also been found to be contaminated with PSP toxins, which are covered elsewhere in this chapter.

Tetrodotoxin poisoning is characterized by symptoms including: numbness of the lips and tongue; tingling sensation in the face and extremities; headache; abdominal pain; nausea; diarrhea; vomiting; difficulty in walking; paralysis; respiratory distress; difficulty in speech; shortness of breath; blue or purplish discoloration of the lips and skin; lowering of blood pressure; convulsions; mental impairment; irregular heartbeat; and death in extreme cases. Symptoms usually develop within 3 hours after consumption of contaminated fish and may last from 24 to 48 hours. Death from this toxin commonly occurs due to muscle paralysis resulting in respiratory failure when ventilatory support is not accessible.

Seafood-associated rhabdomyolysis (sometimes referred to as Haff disease) was first documented in Russia in 1924 with 1,000 cases being reported over a 15-year period at that time from consuming burbot, eel, and pike. Several cases have been reported in the U.S. from the consumption of commercially available domestic buffalo fish. Other isolated cases have been documented from the consumption of crayfish, salmon and imported canned mackerel. Internationally, similar cases have been reported after the consumption of crayfish in China and recently from amberjack and yellow jack from Brazil. The cause(s) of seafood-associated rhabdomyolysis is unknown. Seafood-associated rhabdomyolysis results in the breakdown of skeletal muscle (rhabdomyolysis), with a risk of acute kidney failure that develops within 24 hours after consuming certain fish. FDA is currently collecting meal remnants from patients diagnosed with seafood-associated rhabdomyolysis to confirm the causative species and research the causative agent(s).

FDA makes no recommendations in this guidance document and has no specific expectations with regard to specific controls for clupeotoxin, gempylotoxin, ichthyohemotoxin, tetramine, and seafood-associated rhabdomyolysis for use in a processor's HACCP plan(s).

Note: **Venomous Fish**: Care should be taken when handling venomous fish such as lionfish, scorpion fish and certain species of catfish. The potential for harm from consuming the venom of any venom-producing fish has not been adequately investigated. Currently, FDA makes no recommendations in this guidance and has no specific guidance for food processors with regard to controlling the hazard associated with fish venom. Additional information regarding venomous fish may be found in the "Venomous fish" chapter of the FDA's *Bad Bug Book*, which can be found at the following website: https://www.fda.gov/food/foodborne-pathogens/bad-bug-book-second-edition.

- **Specific Information Associated with Recognized Natural Toxins in Molluscan Shellfish**

This section provides information regarding the implicated molluscan shellfish, geographic regions, and illness characteristics that have been historically associated with natural toxin poisoning syndromes. However, it is important to note that historical precedent may not be an adequate guide for future occurrences regarding geographic locations because the distribution of the source algae may vary over time. Processors should always be alert to the potential for emerging hazards in harvest waters.

ASP, AZP, DSP, NSP, and PSP are not considered a likely food safety hazard for scallops if only the adductor muscle is consumed. However, products such as roe-on scallops and whole scallops do present a potential hazard for natural toxins.

Amnesic shellfish poisoning (from domoic acid) has been associated with molluscan shellfish, crabs, and finfish species. It is most often associated with the consumption of bivalve molluscan shellfish (e.g., mussels, scallops, and razor clams) from the northeast and northwest coasts of North America. Domoic acid has also been identified in the viscera of lobster, Dungeness crab (*Cancer magister*), Tanner crab (*Chionoecetes bairdi*), and Red Rock crab (*Cancer productus*) in these regions. In recent years, levels of domoic acid in Dungeness crab on the west coast have exceeded guidance levels for this toxin and required harvesting closures. Along the west coast of the U.S., domoic acid has also been detected in other fish species including the sardine (*Sardinops sagax*), anchovy (*Engraulis mordax*), Pacific sanddab (*Citharichthys sordidus*), chub mackerel (*Scomber japonicas*), albacore tuna (*Thunnus alalunga*), jack smelt (*Atherinopsis californiensis*), and market squid (*Loligo opalescens*). Domoic acid has also been detected in several finfish species from the U.S. Gulf of Mexico, including plankton-eating fish [e.g., white mullet (*Mugil curema*), menhaden (*Brevoortia partonus*), and predatory species, such as the Florida pompano (*Trachinotus carolinus*), Gulf kingfish (*Menticirrhus littoralis*), and spot (*Leiostomus xanthurus*).]

ASP is characterized by gastrointestinal symptoms including: nausea, vomiting, abdominal cramps, and diarrhea. These symptoms develop within 24 hours of consumption. In severe cases, neurological symptoms may also occur within 48 hours of consumption including: dizziness, headache, seizures, disorientation, short-term memory loss, respiratory difficulty, and coma. In severe cases, ASP should be considered a potentially life-threatening illness. There have been no confirmed cases of ASP in the U.S. since 1987, following the implementation of effective seafood toxin-monitoring programs.

Azaspiracid shellfish poisoning (from azaspiracids) is associated with consumption of bivalve molluscan shellfish. AZP was first recognized following a 1995 outbreak of severe gastroenteritis in the Netherlands which was linked to the consumption of mussels harvested in Ireland. Since then, several outbreaks of AZP have been reported in Europe. In 2008, two cases of AZP were reported in the U.S., and traced to azaspiracid contaminated mussels imported from Ireland. AZP toxins have recently been reported for the first time in Washington State but toxins in excess of guidance levels have not been reported in any commercially harvested shellfish in the U.S. as of August 2019.

AZP is characterized by severe gastrointestinal disorders including: abdominal pain, nausea, vomiting, and diarrhea. Symptoms develop within a few hours following the consumption of contaminated shellfish and can persist for several days. AZP illness is self-limiting and non-fatal.

Diarrhetic shellfish poisoning (from okadaic acid and dinophysistoxins) is generally associated with the consumption of bivalve molluscan shellfish with outbreaks being reported worldwide. In 2008, DSP toxin levels were documented in excess of the guidance level for the first time in several locations along the Texas Gulf Coast during a large algal bloom which led to the first closure of shellfish harvest areas in the U.S.

DSP and DSP-like illnesses have also been associated with shellfish harvested in the Pacific northwest of North America, including Puget Sound and the west coast of Canada. In addition to Texas and Washington State, harvesting closures due to DSP toxins have recently occurred in Maine and Massachusetts. DSP toxins have now been found in shellfish from Alabama, California, Delaware, Maryland, and New York; however, not above guidance levels in commercial growing areas as of August 2019.

DSP is characterized by gastrointestinal symptoms including: nausea, abdominal pain, vomiting, and diarrhea. In addition, headaches and fever may also occur and are usually associated with dehydration. Symptoms typically develop within 3 hours after consuming contaminated shellfish and may persist for several days. DSP is normally considered self-limiting and non-life threatening. However, complications could occur as a result of severe dehydration in compromised individuals. Due to the similarity of symptoms, DSP can be misidentified as a bacterial or viral illness.

Neurotoxic shellfish poisoning (from brevetoxins) in the U.S. is generally associated with the consumption of bivalve molluscs (clams and oysters) from coastal waters of the Gulf of Mexico, and, sporadically, along the southern Atlantic coast. Gastropods (whelk) harvested from the Florida Gulf Coast have also caused NSP. In addition, there have been occurrences of the toxins in New Zealand shellfish and reports of brevetoxin-producing algae in other regions of the world. The largest recorded NSP outbreak occurred in New Zealand from 1992 – 1993; cockles, green shell mussels, and oysters were implicated in the outbreak.

NSP is characterized by gastrointestinal symptoms including diarrhea and vomiting. Neurological symptoms include: tingling and numbness of the lips, tongue, and throat; muscular aches; and dizziness. Symptoms develop within a few hours of consuming contaminated seafood. Treatment consists mainly of supportive care.

Paralytic shellfish poisoning (from saxitoxins) in the U.S. is most often associated with the consumption of bivalve molluscan shellfish (e.g., clams, cockles, mussels, oysters, and scallops) from the northeast and northwest coastal regions. PSP in other parts of the world has been associated with molluscan shellfish from tropical to temperate waters.

Bivalve molluscan shellfish can retain the toxin for different lengths of time. Some species depurate toxins rapidly, whereas others are much slower to depurate the toxins. This lengthens the period of time they pose a human health risk from consumption. For example, most species of bivalves can eliminate the toxin within weeks; however, others such as Washington butter clams, sea scallops, and Atlantic surfclams have been known to retain high levels of toxins for months to more than five years.

Certain predatory gastropods (e.g., conch, snails, and whelk) are also known to accumulate PSP toxins by feeding on toxic bivalve molluscs. In particular, moon snails and whelk from the northeast U.S. are commonly found to contain PSP toxins. Gastropods can accumulate high concentrations of toxin through their predation on toxic bivalves and those concentrations can exceed the levels found in the bivalves. Since gastropods accumulate high concentrations of the toxins, they are a significant risk to humans if consumed when harvested from closed waters or waters where PSP has been found. Gastropods may also retain the toxin for longer periods of time than bivalve molluscan shellfish since they are slow to depurate the toxin.

Abalone from South Africa and Spain have been reported to contain PSP toxins, although there have been no reports of the toxin in abalone from U.S. waters. Similarly, PSP toxins have been reported in echinoderms (e.g., sea cucumbers) and cephalopods (e.g., octopi and squid) harvested for human consumption from Australia and Portugal; however, there have been no reports of PSP toxins in echinoderms or cephalopods from U.S. waters. In the U.S., moon snails and whelks from the northeast U.S. are commonly found to contain PSP toxins. PSP toxins have also been reported in the viscera of mackerel (*Scomber scombrus*), lobster (*Homarus* spp.), Dungeness crab (*Metacarcinus magister*), Tanner crab (*Chionoecetes bairdi*), and Red Rock crab (*Cancer productus*). While the viscera of mackerel are not usually consumed, the viscera of lobsters and crabs may pose a health hazard if harvested from contaminated waters. In 2008, FDA advised against the consumption of American lobster tomalley from New England waters due to unusually high levels of PSP toxins.

In 2002, the first reported case of PSP in the U.S. from the consumption of puffer fish harvested from the central east coast of Florida was identified. PSP toxins were detected in southern (*Sphoeroides nephelus*), checkered (*Sphoeroides testudineus*), and bandtail (*Sphoeroides spengleri*) puffer fish. As a result, Florida Department of State has prohibited the taking of puffer fish (genus Sphoeroides) from the central east coast of Florida per rule 68B-3.007.

PSP symptoms can include: vomiting; abdominal pain; numbness, burning, or tingling of the face and extremities; incoherent speech; loss of coordination and muscle paralysis; shortness of breath; and in severe cases respiratory paralysis. Respiratory paralysis can result in death if ventilator support is not provided in a timely manner. The onset of symptoms can develop within 2 hours post consumption of the PSP toxin contaminated seafood. PSP is an extremely potent toxin with a high mortality rate in cases where medical support is not available.

- **Additional Toxins Found in Molluscan Shellfish**

A number of toxins identified in molluscan shellfish have shown toxicity in mouse studies but have not been linked to human illnesses. These toxins are as follows:

- Cyclic imines have been found in phytoplankton and/or molluscan shellfish in Canada, Denmark, New Zealand, Norway, Scotland, Tunisia, and the U.S.
- Pectenotoxins (PTX) have been detected in phytoplankton and/or molluscan shellfish in Australia, Italy, Japan, New Zealand, Norway, Portugal, Spain, and the U.S.
- Yessotoxins (YTX) have been detected in phytoplankton and/or molluscan shellfish in Australia, Canada, Italy, Japan, New Zealand, Norway, the United Kingdom, and the U.S.

Note: PTX and YTX have been found to co-occur with DSP toxins (okadaic acid and dinophysistoxins) in shellfish.

At this time, FDA makes no recommendations in this guidance document and has no specific expectations with regard to controls for PTX, YTX, and cyclic imines for processors' Hazard Analysis Critical Control Point (HACCP) plans.

- **Natural Toxin Controls**

Natural toxins are odorless, tasteless, colorless, and temperature stable; therefore, they cannot be reliably eliminated through cooking or freezing.

Amnesic shellfish poisoning and paralytic shellfish poisoning in fish other than molluscan shellfish: Where ASP or PSP is a potential hazard in finfish or crustaceans, states have generally closed or restricted fishing areas. Harvesters and processors must rely on public announcements, postings, and advisories by state authorities to avoid harvesting or receiving finfish or crustacean from potential unsafe waters. In addition, removal and destruction of the viscera may eliminate the hazard, and at times is required by state public health authorities. For example, eviscerating fish or harvesting the adductor muscle from the scallop can eliminate the food safety hazards of ASP and/or PSP.

Ciguatera Fish Poisoning: Due to the nature of CFP, a harvest water management system similar to the molluscan shellfish system is not an appropriate control measure. Some states issue advisories identifying endemic areas. For areas without an advisory system, fishermen and processors must rely on their knowledge to avoid harvesting and receiving fish from areas where illnesses have been associated. The state or local department of health and/or associated departments of fisheries would be able to further assist in determining whether harvest areas are free of ciguatoxins.

Guidance levels have been established for Caribbean and Pacific CFP toxins (see Appendix 5) but at this time, these guidance levels are only used to confirm CFP as the cause of illnesses/outbreaks, to establish CFP endemic regions, and to determine potential CFP-causing species based on the analysis of meal remnants involved in cases of CFP.

Molluscan Shellfish: To minimize the risk of molluscan shellfish containing natural toxins from the harvest area, state and foreign government agencies, called shellfish control authorities, manage harvesting activities, based in part on the presence of natural toxins in water and shellfish meats. Shellfish control authorities may also use cell counts of the toxin-forming algae in the harvest waters to manage shellfish harvest areas, and in areas with no previous history of illnesses.

States must have a Biotoxin Contingency Plan that will provide information regarding actions to be taken if toxin-forming algae or natural toxins are likely or have been detected. Shellfish control authorities exercise control over the molluscan shellfish harvesters to ensure that harvesting takes place only when and where shellfish are determined to be safe. In this context, molluscan shellfish include oysters, clams, mussels, and scallops, except where the scallop product contains only the shucked adductor muscle.

Other significant elements of shellfish control authorities' efforts to manage the harvesting of molluscan shellfish include requirements that:

- Molluscan shellfish harvesters be licensed (note that licensing may not be required in all jurisdictions);
- Processors that ship, reship, shuck, or repack molluscan shellfish be certified;
- Containers of molluscan shellfish (shellstock) bear a tag with the harvester's identification number, type and quantity of shellfish, date of harvest, and harvest location;

AND

- Containers of shucked molluscan shellfish bear a label with the processor's name, address, and certification number.

DETERMINE WHETHER THE POTENTIAL HAZARD IS SIGNIFICANT

The following guidance will assist you in determining whether natural toxins are considered a significant hazard at a processing step:

1. Is it reasonably likely that unsafe levels of natural toxins will be introduced at this processing step (e.g., is the natural toxin present in the raw material at an unsafe level)?

Tables 3-2 and 3-3 in Chapter 3 identify the species of vertebrate and non-vertebrate species of fish and molluscan shellfish for which natural toxins are known to be a potential hazard. Under ordinary circumstances, it would be reasonably likely to expect that, without proper controls, natural toxins from the harvest area could enter the process at unsafe levels at the receiving step for those species. There may be other circumstances in a geographic area to conclude that a particular natural toxin is reasonably likely to occur at unsafe levels in those fish or molluscan shellfish. The information provided in this *Guide* and the historical occurrence of a toxin in the fish or molluscan shellfish, where toxin levels exceed established guidance, should be utilized to make a determination whether these fish and molluscan shellfish are harvested and received at the processor. Awareness of emerging geographic areas and additional species of fish should be monitored and acted upon appropriately. Examples of fish species recently identified with the hazard of natural toxins are lobster, specifically the tomalley, containing PSP, anchovies containing ASP, and lionfish have been found with levels of CFP that can cause illness.

The following preventive measures for natural toxins can be applied as appropriate:

- Fish other than molluscan shellfish:
  - Ensuring that incoming fish have not been caught in an area from which harvesting is prohibited, restricted due to the presence of a natural toxin, or where an advisory exists such as for the presence of CFP.
- Molluscan shellfish:
  - Ensuring that incoming molluscan shellfish (shellstock) are from an Approved or Conditionally Approved area in the open status;
  - Ensuring that incoming molluscan shellfish are properly tagged or labeled; and
  - Ensuring that incoming molluscan shellfish are supplied by a licensed harvester (where licensing is required by law) or by a certified dealer.

FDA requires both primary and secondary processors of raw molluscan shellfish to implement steps at receiving to assure that their shellfish originate from safe sources.

2. Can natural toxins that were introduced at unsafe levels at an earlier step be eliminated or reduced to an acceptable level here?

Even though natural toxins should be considered a significant hazard at any processing step, they are usually controlled at receiving by the primary processor who has the ability to directly communicate with the harvester to identify the harvest locations. FDA also requires subsequent processors who receive raw molluscan shellfish to consider natural toxins as a significant hazard. Similarly, the hazard usually may be controlled at receiving where the processor has the ability to assure that the shellfish has originated from certified facilities.

Since, natural toxins are not eliminated through cooking or freezing, subsequent processing steps after receiving the potentially contaminated fish are unlikely to eliminate the hazard. Therefore, if the fish or molluscan shellfish has been identified as potentially containing the hazard of natural toxins, and no measures were taken to prevent its harvest from endemic areas, the processor should not accept the fish or molluscan shellfish.

If a processor chooses to implement controls other than at the receiving step, those controls must provide an equivalent assurance of safety and should be supported by sound scientific evidence. There are limited instances where processing may in fact be able to remove the toxin from the consumed part of the fish or molluscan shellfish. These exceptions are dependent on the type of fish or molluscan shellfish, toxin, and process. Examples include but are not limited to eviscerating the fish, such as lobsters, crabs, and anchovies, or only receiving the adductor muscle of scallops.

- **Intended Use**

In most cases, it is unlikely that the intended use of the product would determine whether the hazard of natural toxin is significant. An exception is with certain products where only the muscle tissue will be consumed. For example, where the finished product is **only** the shucked adductor muscle of the scallop, it is reasonable to assume that the product will not contain natural toxins. In this case, you may not need to identify natural toxins as a significant hazard.

IDENTIFY CRITICAL CONTROL POINTS.

The following guidance will assist you in determining whether a processing step is a critical control point (CCP) for natural toxins.

Where preventive measures during processing, such as those described above, are not feasible, the hazard of natural toxins should be controlled at the receiving step. Two strategies have been identified as controls and are referred to in this chapter as:

- "Control Strategy Example 1 – Source Control for Fish Other Than Molluscan Shellfish" and
- "Control Strategy Example 2 – Harvest Area Control for Molluscan Shellfish."

DEVELOP A CONTROL STRATEGY.

The following guidance provides two control strategy examples for natural toxins. A control strategy different from those suggested is acceptable, provided it complies with requirements of all applicable food safety laws and regulations.

The following are examples of control strategies included in this chapter:

Control Strategy	May apply to primary processor	May apply to secondary processor
Source control for fish other than molluscan shellfish	✓	
Harvest area control for molluscan shellfish	✓	✓

- **CONTROL STRATEGY EXAMPLE 1 – SOURCE COUNTROL FOR FISH OTHER THAN MOLLUSCAN SHELLFISH**

This strategy only applies to primary processors (processors that receive or off-load the fish from the harvest vessel).

Set Critical Limits.

Suspect fish may not be received by the primary processor when harvest locations are:

- Closed to fishing by foreign, federal, state, tribal, territorial, or local authorities (e.g., certain counties in Florida for puffer fish);

  OR

- The subject of a consumption advisory for ASP, AZP, CFP, DSP, NSP, PSP, or other naturally occurring toxins;

  OR

- Known to be contaminated with ciguatoxin.

Establish Monitoring Procedures.

➢ **What Will Be Monitored?**

- The status of the harvest location identified on the harvest vessel records are not restricted, subject of an advisory, or prohibited from harvest based on governmental or other known resources, or through declaration stating that the harvest area are free from natural toxins.

➢ **How Will Monitoring Be Done?**

- Obtain assurances through visual examination of the harvest records for the harvest area location, or declaration identifying the harvest area location is not under a restriction, advisory or prohibition from fishing.

➢ **How Often Will Monitoring Be Done (Frequency)?**

- Every lot of raw fish received from the harvest vessel.

➢ **Who Will Do the Monitoring?**

- Any person with an understanding of the nature of the controls and areas of restricted fishing due to natural toxin hazard.

Establish Corrective Action Procedures.

Take the following corrective action for a product involved in a critical limit deviation:

- Reject the lot.

AND

Take the following corrective action to regain control of the operation after a critical limit deviation:

- Discontinue use of the supplier until evidence is obtained that harvesting practices have changed through record review of harvest locations.

Establish a Recordkeeping System.

- Receiving record(s) that documents the location and status (e.g., prohibited, restricted, or unrestricted) of the harvest area.

Establish Verification Procedures.

- Review monitoring and corrective action records within 1 week of preparation to ensure they are complete and any deviations that occurred were addressed appropriately.

- Periodically monitor governmental and other resources for the most current information regarding harvest restrictions, advisories, and fishing prohibitions due to natural toxins.

TABLE 6-1

Control Strategy Example 1 – SOURCE CONTROL FOR FISH OTHER THAN MOLLUSCAN SHELLFISH

This example table illustrates a hypothetical application of the control strategy just presented in "Control Strategy Example 1 – Source Control for Fish Other Than Molluscan Shellfish." The example illustrates the basic control for natural toxins by a primary processor receiving locally harvested grouper. It is provided for illustrative purposes only.

Natural toxins may be only one of several significant hazards for this product. Refer to Tables 3-2 and 3-4 (Chapter 3) for other potential species or process related hazards.

Example Only: See Text for Full Recommendations

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
			Monitoring						
Critical Control Point	**Significant Hazard(s)**	**Critical Limits**	**What**	**How**	**Frequency**	**Who**	**Corrective Action(s)**	**Records**	**Verification**
Receiving fresh fish - Grouper	Natural toxins - ciguatoxin	Grouper may not be received when a harvest location is under a regulatory or other ciguatoxin advisory, or for which there is information from a valid scientific source that ciguatoxin exists	Harvest vessel records to ensure harvest locations are not identified in a regulatory or other advisory, or locations where ciguatoxin exist.	Visual examination of harvest vessel records for harvest locations and compared with known ciguatoxin locations	Records for every lot of grouper received	Receiving employee with knowledge of harvest locations and hazard	Reject lot Discontinue use of the supplier until evidence is obtained that harvesting practices have changed through examination of harvest records compared to location intel	Receiving record	Review monitoring and corrective action records within 1 week of preparation

- **CONTROL STRATEGY EXAMPLE 2 – HARVEST AREA CONTROL FOR MOLLUSCAN SHELLFISH**

Set Critical Limits.

- All containers of shellstock received from a harvester must bear a tag identifying the:
  - Date and place of harvest (by state and site),
  - Type and quality of shellfish,

    AND
  - By whom they were harvested (i.e., the identification number assigned to the harvester by the shellfish control authority, where applicable or, if such identification numbers are not assigned, the name of the harvester or the name or registration number of the harvester's vessel);

OR

- For bulk shipments of shellstock where the shellstock is not containerized, the shellstock must be accompanied by a bill of lading or similar shipping document that contains the same information;

OR

- All containers of shellstock received from a processor must bear a tag identifying the processor who supplied the shellstock and that discloses the:
  - Date and place of harvest (by state and site),
  - Type and quantity of shellfish,

    AND
  - The certification number of the processor;

OR

- All containers of shucked molluscan shellfish must bear a label identifying the packer or repacker that identifies the:
  - Name,
  - Address,

    AND
  - Certification number of the packer or re-packer of the product;

AND

- All molluscan shellfish must have been harvested from waters authorized for harvesting by a shellfish control authority. For U.S. federal waters, no molluscan shellfish may be harvested from waters that are closed to harvesting by an agency of the federal government;

Note: The National Shellfish Sanitation Program (NSSP) allows for harvest of surf clams and quahogs in federal waters closed due to the risk of PSP utilizing the onboard screening dockside testing protocol. Refer to the NSSP for specific requirements.

AND

- All molluscan shellfish must be from a harvester that is licensed as required (note that licensing may not be required in all jurisdictions) or from a processor that is certified by a shellfish control authority.

Note: Both primary and secondary processors of molluscan shellfish are required to implement source controls in their HACCP plans. Only the primary processor needs to apply controls relative to the identification of the harvester, the harvester's license, or the approval status of the harvest waters. The source controls listed in this critical limit are required under 21 CFR 123.28(c).

Establish Monitoring Procedures.

➢ **What Will Be Monitored?**

- Information listed on tags, or on the bill of lading, or similar shipping document accompanying bulk shipments of shellstock which includes at a minimum;
  - Date of harvest;
  - Location of harvest by state and site;
  - Quantity and type of shellfish;
  - Name of the harvester, name or registration number of the harvester's vessel, or an identification number issued to the harvester by the shellfish control authority (for shellstock received directly from the harvester only);
  - Number and date of expiration of the harvester's license, where applicable;

AND

- Certification number of the shipper, where applicable.

AND

- Receiving information on whether the harvest area is authorized for harvest by a shellfish control authority or information regarding closures of federal harvest waters by an agency of the federal government.

AND

- The harvester's license.

OR

- Information declared on labels on containers of incoming shucked molluscan shellfish such as:
  - Name of the packer or repacker of the product;
  - Address of the packer or repacker of the product;

    AND
  - The certification number of the packer or re-packer of the product.

How Will Monitoring Be Done?

- Visual examination of the harvest area location through harvest records to ensure they are not from areas under a restriction, advisory or prohibition from harvesting;

  AND

- Obtain assurance from shellfish control authorities from the state or country in which your shellstock are harvested that the harvest area is open for harvest.

How Often Will Monitoring Be Done (Frequency)?

- Checking incoming tags:
  - Every container received;

  OR

- Checking the bill of lading or similar shipping document:
  - Every delivery received:

  OR

- Checking incoming labels:
  - At least three containers randomly selected from every lot received;

  AND

- Checking licenses:
  - Every delivery received.

Who Will Do the Monitoring?

- Any person with an understanding of the nature of the controls and closures.

Establish Corrective Action Procedures.

Take the following corrective action for a product involved in a critical limit deviation:

- Reject the lot.

AND

Take the following corrective action to regain control of the operation after a critical limit deviation:

- Discontinue use of the supplier until evidence is obtained that harvesting and/ or tagging practices have changed.

Establish a Recordkeeping System.

For shellstock:

- Receiving record(s) that documents:
  - Date of harvest;
  - Location of harvest by state and site;
  - Quantity and type of shellfish;
  - Name of the harvester, name of registration number of the harvester's vessel, or an identification number issued to the harvester by the shellfish control authority (for shellstock received directly for the harvester only);
  - Number and date of expiration of the harvester's license, where applicable;

    AND
  - Certification number of the shipper, where applicable.

For shucked molluscan shellfish:

- Receiving records that documents:
  - Date of receipt;
  - Quantity and type of shellfish;

AND

- Name and certification number of the packer or re-packer.

Establish Verification Procedures.

- Review monitoring and corrective action records within 1 week of preparation to ensure they are complete and any critical limit deviations that occurred were appropriately addressed.

TABLE 6-2

Control Strategy Example 2 – HARVEST AREA CONTROL FOR MOLLUSCAN SHELLFISH

This example table illustrates a hypothetical application of the control strategy just presented in "Control Strategy Example 2 – Harvest Area Control for Molluscan Shellfish." This example illustrates how a primary processor of shellstock oysters, could control natural toxins in shellstock oysters received directly from a harvester. It is provided for illustrative purposes only.

Natural toxins may be only one of several significant hazards for this product. Refer to Tables 3-2 and 3-4 (Chapter 3) for other potential species or process related hazards.

Example Only: See Text for Full Recommendations

(1)	(2)	(3)	(4)	(5) Monitoring	(6)	(7)	(8)	(9)	(10)
Critical Control Point	**Significant Hazard(s)**	**Critical Limits**	**What**	**How**	**Frequency**	**Who**	**Corrective Action(s)**	**Records**	**Verification**
Receiving shellstock	Natural toxins	All incoming shellstock must be tagged with the date and place of harvest, type and quantity of shellfish, and name or registration number of the harvester's vessel	Information on incoming shellstock tags	Visual checks	Every sack	Receiving employee	Reject untagged sacks; AND Discontinue use of the supplier until evidence is obtained that tagging practices have changed	Receiving record	Review monitoring and corrective action records within 1 week of preparation

(1)	(2)	(3)	(4)	(5) Monitoring	(6)	(7)	(8)	(9)	(10)
Critical Control Point	**Significant Hazard(s)**	**Critical Limits**	**What**	**How**	**Frequency**	**Who**	**Corrective Action(s)**	**Records**	**Verification**
		All shellstock must be harvested from an Approved or Conditionally Approved area	Harvest site on tags	Visual checks; Ask the shellfish control authority from the state or country in which the shellstock are harvested whether the area is authorized for harvest	Every lot	Receiving employee	Reject lots from unapproved waters; AND Discontinue use of the supplier until evidence is obtained that harvesting practices have changed		
		All shellstock must be from a licensed harvester	Harvester's license	Visual check for number and expiration date	Every delivery from harvester	Receiving employee	Reject delivery from unlicensed harvesters; AND Discontinue use of the supplier until evidence is obtained that the harvester has secured a license		

BIBLIOGRAPHY

We have placed the following references on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of June 2018, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after July 2018.

- Abraham, A., E. Jester, H. Granade, S. Plakas, and R. Dickey. 2012. Caribbean ciguatoxin profile in raw and cooked fish implicated in ciguatera. Food Chemistry, 131(1);192-198.

- Arakawa, O., T. Noguchi, and Y. Onoue. 1995. Paralytic shellfish toxin profiles of xanthid crabs *Zosimus aeneus* and *Atergatis floridus* collected on reefs of Ishigaki Island. Fish. Sci. 61(4):659–662.

- Azziz-Baumgartner, E., Luber, G., Conklin, L., Tosteson, T., Granade, H., Dickey, R., & Backer, L. 2012. Assessing the Incidence of Ciguatera Fish Poisoning with Two Surveys Conducted in Culebra, Puerto Rico, during 2005 and 2006. *Environmental Health Perspectives.*

- Bakes, M. J., N. G. Elliott, G. J. Green, and P. D. Nichols. 1995. Variation in lipid composition of some deep-sea fish (Teleostei: Oreosomatidae and Trachichthyidae). Comp. Biochem. Physiol B. 111(4):633–642.

- Braid, H., J. Deeds, S. DeGrasse, J. Wilson, J. Osborne, and R. Hanner. 2011. Preying on commercial fisheries and accumulating paralytic shellfish toxins: a dietary analysis of invasive *Dosidicus gigas* (Cephalopoda Ommastrephidae) stranded in Pacific Canada. Marine Biology. DOI 10.1007/s00227-011-1786-4.

- Braidotti, G. June 2014. Seafood and the food-safety Golden Rules. Fisheries Research & Development Corporation News. Vol 22 Number 2.

- Bravo, I., J. M. Franco, A. Alonzo, R. Dietrich, and P. Molist. 2001. Cytological study and immunohistochemical location of PSP toxins in foot skin of the ormer, *Haliotis tuberculata*, from the Galacian coast (NW Spain). Mar. Biol. 138:709–715.

- Bravo, I., M. I. Reyero, E. Cacho, and J. M. Franco. 1999. Paralytic shellfish poisoning in *Haliotis tuberculata* from the Galician coast: geographical distribution, toxicity by lengths and parts of the mollusc. Aquat. Toxicol. 46:79–85.

- Clifford, M. N., R. Walker, P. Ijomah, J. Wright, C. K. Murray, R. Hardy, E. P. Martlbauer, E. Usleber, and G. Terplan. 1993. Do saxitoxin-like substances have a role in scombrotoxicosis? Food Addit. Contamin. 9(6):657–667.

- Deeds, J., J. Landsberg, S. Etheridge, G. Pitcher, and S. Longan. 2008. Non-Traditional Vectors for Paralytic Shellfish Poisoning. Marine Drugs, ISSN: 1660-3397.

- Deshpande, S. S. 2002. Handbook of Food Toxicology, p 699-700.

- Dickey, R. W. 2008. Ciguatera toxins: chemistry, toxicology, and detection, p. 479–500. *In* L. M. Botana (ed.), Seafood and freshwater toxins: pharmacology, physiology, and detection, 2nd ed. CRC Press/Taylor & Francis.

- Dickey, R.W. and S.M. Plakas. 2010. Ciguatera: A public health perspective. Toxicon 56(2): 123-136.

- Dickey, R.W., S.M. Plakas, E. L. E. Jester, K.R. El Said, J.N. Johannessen, L.J. Flewelling, P. Scott, D.G. Hammond, F.M.V. Dolah, T.A. Leighfield, M-YB Dachraoui, J.S. Ramsdell, R.H. Pierce, M.S. Henry, M.A. Poli, C. Walker, J. Kurtz, J. Naar, D.G. Baden, S.M. Musser, K.D. White, P. Truman, A. Miller, T.P. Hawryluk, M.M. Wekkell, D. Stirling M.A. Quilliam, J.K. Lee. 2004. Multi-laboratory study of five methods for determination of brevetoxins in shellfish tissue extracts. Harmful Algae 2002. St. Petersburg, FL USA: Florida Fish and Wildlife Conservation Commission, Florida Institute of Oceanography, and Intergovernmental Oceanographic Commission of UNESCO. pp. 300-302.

- European Communities. 2002. Commission Decision of 15 March 2002. Laying down rules for the implementation of Council Directive 91/492/EEC as regards the maximum levels and the methods of analysis of certain marine biotoxins in bivalve molluscs, echinoderms, tunicates and marine gastropods. Off. J. Eur. Communities. (2002/225/EC) L 75:62–63.
- Florida Department of State. 2004. *Prohibition on Take of Puffer Fish in Volusia, Brevard, Indian River, St. Lucie, and Martin Counties*. Rule 68B-3.007.
- Food and Agriculture Organization. 2004. In, FAO (ed), FAO Food and Nutrition Paper 80. Risk Assessment of Toxins Associated with PSP, DSP, and ASP in Seafood, pp 56-95. 3. Diarrhoeic Shellfish Poisoning (DSP). Food and Agriculture Organization of the United Nations, Rome.
- Food and Drug Administration: Guidance for Industry: "Purchasing Reef Fish Species Associated with the Hazard of Ciguatera Fish Poisoning", March 2013.
- Food and Drug Administration: Bad Bug Book, Foodborne Pathogenic Microorganisms and Natural Toxins. Second Edition. 2012.
- Food Safety Authority of Ireland. August 2006. Risk assessment of azaspiracids (AZAs) in shellfish. Food Safety Authority of Ireland, Dublin, Ireland.
- Friedman, M. A., L. E. Fleming, M. Fernandez, P. Bienfang, K. Schrank, R. Dickey, M. Y. Bottein, L. Backer, R. Ayyar, R. Weisman, S. Watkins, R. Granade, and A. Reich. 2008. Ciguatera fish poisoning: treatment, prevention, and management. Mar. Drugs 6:456–479.
- Friedman, M.A., M. Fernandez, L. Backer, R. Dickey, J. Bernstein, K. Schrank, S. Kibler, W. Stephan, M.O. Gribble, P. Bienfang, R. Bowen, S. Degrasse, H. Flores-Quintana, C. Loeffler, R. Weisman, D. Blythe, E. Berdalet, D. Ayyare, D. Clarkson-Towsend, K. Swajian, R. Benner, T. Brewer, and L.E. Flemming. 2017. An Updated Review of Ciguatera Fish Poisoning: Clinical, Epidemiological, Environmental, and Public Health Management. Mar. Drugs 15:1-41.
- Hall, S. and G. Strichartz (ed.). 1990. Marine toxins: origin, structure, and molecular pharmacology. ACS Symposium Series 418. American Chemical Society, Washington, DC.
- Halstead, B. W. 1967. Poisonous and venomous marine animals of the world, vol. 2 - invertebrates. U.S. Government Printing Office, Washington, DC.
- Halstead, B. W. 1988. Poisonous and venomous marine animals of the world, 2nd rev. ed. The Darwin Press, Inc., Princeton, NJ.
- Hess, P., L. Nguyen, J. Aasen, M. Keogh, N. Keogh, J. Kilcoyne, P. McCarron, and T. Aune. 2005. Tissue distribution, effects on cooking, and parameters affecting the extraction of azaspiracids from mussels, *Mytilus edulis*, prior to analysis by liquid chromatography coupled to mass spectrometry. Toxicon. 46:62–71.
- Hwang, D-F., and Y-H. Tsai. 1999. Toxins in toxic Taiwanese crabs. Food. Rev. 15(2):145–162.
- Hwang, D-F., Y-H. Tsai, T-J. Chai, and S-S Jeng. 1996. Occurrence of tetrodotoxin and paralytic shellfish poison in Taiwan crab *Zosimus aeneus*. Fish. Sci. 62(3):500–501.
- James, K. A. C. and B. P. Treloar. 1984. Comparative effects of orange roughy (*Hoplostethus atlanticus*) and snapper (*Chrysophrys auratus*) in the diets of growing rats. New Zealand J. Sci. 27:295–305.

- James, K. A. C., D. R. Body, and W. C. Smith. 1986. A nutritional evaluation of orange roughy (*Hoplostethus atlanticus*) using growing pigs. New Zealand J. Tech. 2:219–223.
- James, K. J., A. Furey, M. Lehane, H. Ramstad, T. Aune, P. Hovgaard, S. Morris, W. Higman, M. Satake, and T. Yasumoto. 2002. First evidence of an extensive northern European distribution of azaspiracid poisoning (AZP) toxins in shellfish. Toxicon. 40:909–915.
- Kawai, N., Y. Nakayama, S. Matsuoka, and T. Mori. 1985. Lipid composition of various tissues of *Lepidocybium flavobrunneum*. Yukagaku 34:25–31.
- Kim, J., U. Tillmann, N. Adams, B. Krock, W. Stutts, J. Deeds, M. Han, and V. Trainer. 2017. Identification of *Azadinuim* species and a new azaspiracid from *Azadinium poporum* in Puget Sound, Washington State, USA. Harmful Algae. 68: 152-167.
- Krishna, N, and J Wood. 2001. It looked like a myocardial infarction after eating crawfish.... Ever heard of Haff disease? Louisiana Morbidity Report. May-June2001 Volume 12 Number 3.
- Lawrence, J. F., M. Maher, and W. Watson-Wright. 1994. Effect of cooking on the concentration of toxins associated with paralytic shellfish poison in lobster hepatopancreas. Toxicon. 33(12):1669–1673.
- Lehane, L. 2000. Paralytic shellfish poisoning: a review. National Office of Animal and Plant Health Agriculture, Fisheries and Forestry, Canberra, Australia.
- Lehane, L. and R. J. Lewis. 2000. Ciguatera: recent advances but the risk remains. Int. J. Food Microbiol. 61:91–125.
- Ling, K. H., C. W. Cheung, S. W. Cheng, L. Cheng, S-L. Li, P. D. Nichols, R. D. Ward, A. Graham, and P. P-H. But. 2008. Rapid detection of oilfish and escolar in fish steaks: a tool to prevent keriorrhea episodes. Food Chem. 110:538–546.
- Lopes, V., A. Lopes, P. Costa, and R. Rosa. 2013. Cephalopods as Vectors of Harmful Algal Bloom Toxins in Marine Food Webs. Marine Drugs.
- Martinez, A., J. M. Franco, I. Bravo, M. Mazoy, and E. Cacho. 1993. PSP toxicity in *Haliotis tuberculata* from NW Spain, p. 419–423. *In* T. J. Smayda and Y. Shimizu (ed.), Toxic phytoplankton blooms in the sea. Elsevier, Amsterdam, Netherlands.
- National Shellfish Sanitation Program (NSSP): Guide for the Control of Molluscan Shellfish 2013 Revision.
- Nichols, P. D., B. D. Mooney, and N. G. Elliott. 2001. Unusually high levels of non-saponifiable lipids in the fishes escolar and rudderfish. Identification by gas chromatography and thin-layer chromatography. J. Chromatogr A 936:183–191.
- Noguchi, T. and Y. Hashimoto. 1973. Isolation of tetrodotoxin from a goby *Gobius criniger.* Toxicon. 11:305–307.
- Ochiai, Y., S. Watabe, K. Hashimoto, H. Narita, Y. Ukishima, and M. Nara. 1984. Biochemical identification of two gempylid fish causative of a food poisoning. Bull. Japan. Soc. Sci. Fish. 50:721–725.
- Olsen, D., D. Nellis, and R. Wood. 1984. Ciguatera in the Eastern Caribbean. *Marine Fisheries Review*.
- Perez-Zarza, M. C., V. Ruiz-Gutierrez, and L. Bravo. 1993. Lipid composition of two purgative fish: *Ruvettus pretiosus* and *Lepidocybium flavobrunneum*. Grasas y Aceites 44:47–52.
- Pitcher, G. C., M. Franco, G. J. Doucette, C. L. Powell, and A. Mouton. 2001. Paralytic shellfish poisoning in abalone *Haliotis midae* on the west coast of South Africa. J. Shellfish Res. 20(2):895–904.

- Poli, M., S. Musser, R. Dickey, P. Eilers, and S. Hall. 2000. Neurotoxic shellfish poisoning and brevetoxin metabolites: a case study from Florida. Toxicon. 38:981–993.

- Robertson, A., D. Stirling, C. Robillot, L. Llewellyn and A. Negri. 2004. First report of saxitoxin in octopi. Toxicon 44 (2004) 765-771.

- Saito, T., T. Kohama, K. Ui, and S. Watabe. 2006. Distribution of tetrodotoxin in the xanthid crab (*Atergatis floridus*) collected in the coastal waters of Kanagawa and Wakayama prefectures. Comp. Biochem. Physiol. D: Genomics and Proteomics 1(1):158–162.

- Satake, M., K. Ofuji, H. Naoki, K. James, A. Furey, T. McMahon, J. Silke, and T. Yasumoto. 1998. Azaspiracid, a new toxin having unique spiro ring assemblies, isolated from Irish mussels, *Mytilus edulis*. J. Am. Chem. Soc. 120: 9967–9968.

- Shui, L. M., K. Chen, K., J. Y. Wang, H. Z. Mei, A. Z. Wang, Y.-H. Lu, and D.-F. Hwang. 2003. Tetrodotoxin-associated snail poisoning in Zhoushan: a 25-year retrospective analysis. J. of Food Prot. 66(1):110–114.

- Sobel, J. and J. Painter. November 1, 2005. Illnesses caused by marine toxins. Food Safety Invited Article. Clin. Infect. Dis. 41:1290–1296.

- Spark, A. A. and A. A. deWit. 1980. Wax esters in edible fish. Identification of wax esters, p. 45–47. *In* Annual Report of the Fishing Industry Research Institute of South Africa, no. 34.

- Torgersen, T., J. Aasen, and T. Aune. 2005. Diarrhetic Shellfish Poisoning by okadaic acid esters from Brown crabs (*Cancer pagurus*) in Norway. Toxicon 46 572-578.

- Toyofuku, H. 2006. FAO/WHO/IOC activities to provide scientific advice on marine biotoxins (research report). Mar. Pollut. Bull. 52:1735–1745.

- Tsai, Y-H., D-F. Hwang, T-J. Chai, and S. S. Jeng. 1995. Occurrence of tetrodotoxin and paralytic shellfish poison in the Taiwanese crab *Lophozozymus pictor*. Toxicon. 33(12):1669–1673.

- Tsai, Y-H., D-F. Hwang, T-J. Chai, and S. S. Jeng. 1996. Occurrence of paralytic shellfish toxin in Taiwanese crab *Atergatopsis germaini*. Toxicon. 34(4):467–474.

- Twiner, M. J., N. Rehmann, P. Hess, G. J. Doucette. 2008. Azaspiracid shellfish poisoning: a review on the chemistry, ecology, and toxicology with an emphasis on human health impacts. 6:39–72.

- Van Egmond, H. P., T. Aune, P. Lassus, G. Speijers, and M. Waldock. 1993. Paralytic and diarrhoeic shellfish poisons: occurrence in Europe, toxicity, analysis and regulation. J. Nat. Toxins 2:41–83.

- Witers, N. 1988. Marine toxins and venoms. *In* A. T. Tu (ed.), Handbook of natural toxins, vol. 3. Marcel Dekker, New York, NY.

- Yasumoto, T., and M. Murata. 1993. Marine toxins. Chem. Rev. 93:1897–1909.

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