Proposal for Task Force Consideration at the ISSC 2019 Biennial Meeting	1. a. ☒ Growing Area b. ☐ Harvesting/Handling/Distribution c. ☐ Administrative

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10. Proposal Subject	Marine Biotoxin Control - Public Health Reasons
11. Specific NSSP Guide Reference	Section III. Public Health Reasons and Explanations, Model Ordinance Chapter IV. Shellstock Growing Areas, @.04
12. Text of Proposal/ Requested Action	**. @.04 Marine Biotoxin Control** ***Marine Biotoxins*** Unlike human pathogens, marine biotoxins occur naturally in aquatic environments. Toxins are produced by certain micro-algae (also called phytoplankton), including dinoflagellates and others. Shellfish are filter feeders and may ingest and concentrate toxic phytoplankton from the water column when present in shellfish growing waters. Toxins are accumulated in the viscera and/or other tissues of shellfish and are transferred to humans when the shellfish are eaten (Gordon et al., 1973). Marine biotoxins are a public health concern for many reasons; for example, marine biotoxins: • May build up in shellfish in concentrations up to 100 times greater than in surrounding waters; • Are not normally destroyed by cooking or processing; • Cannot be detected by taste; and • Can cause illness and death if consumed in sufficient concentrations. In most cases, the toxin has no effect on the shellfish itself, and how long each shellfish vector remains toxic depends on the individual species in question. Additionally, there are non-traditional and emerging vectors of these toxins that also are potentially toxic foods. One example is that pufferfish, typically associated with tetrodotoxin, may also contain saxitoxin (e.g., puffers from coastal waters of Florida). Toxic dinoflagellates or diatoms are single-cell marine plants that are indigenous to most coastal and estuarine waters on the Atlantic, Gulf, and Pacific coasts of America, as well as in many other parts of the world. Dinoflagellates and diatoms in their vegetative stage flourish (“bloom”) seasonally when water conditions are favorable. Blooms of these organisms can occur unexpectedly and rapidly, or may follow predictable patterns. Because dinoflagellates occur naturally, their presence in the water column does not necessarily constitute a health risk. In fact, traces of their toxin in shellfish

meat does not necessarily mean they are hazardous. Toxicity depends on concentration (dose) in the shellfish.

Red tide refers to the discoloration of seawater caused by blooms of marine algae. Red tides are not always red. They occur in many colors, including amber, brown, purple, red, and pink. The relationship between red tides and biotoxin poisoning is widely misunderstood, and many people mistakenly believe that shellfish are safe to eat if no red tide is visible. While red tide can be related to harmful algae, it is helpful to remember that:

- Toxic blooms may be other colors, such as blue-green;
- Marine biotoxin poisoning can happen when there is no discoloration of the water; and
- Several marine algae that pose no public health risk to humans can turn the water red.

Diseases and Outbreaks

All humans are susceptible to shellfish poisoning. A disproportionate number of shellfish-poisoning cases occur among tourists or others who are not native to the location where the toxic shellfish are harvested, and fishermen and recreational harvesters. This may be due to disregard for either official quarantines or traditions of safe consumption.

Diagnosis of shellfish poisoning is based entirely on observed symptomatology and recent dietary history. Human ingestion of contaminated shellfish results in a wide variety of symptoms, depending on the toxin(s) present, their concentrations in the shellfish, and the amount of contaminated shellfish consumed.

Marine Biotoxin Plans – Management & Contingency

The suitability of some growing areas for shellfish harvesting is periodically influenced by the presence of marine biotoxins, such as those responsible for PSP, NSP, ASP, DSP and AZP. The occurrence of these toxins is often unpredictable, and the potential for them to occur exists along most coastlines of the United States and other countries having shellfish sanitation Memoranda of Understanding (MOU) agreements with the United States.

For this reason, even when the authority has no history or reason to expect toxin-producing phytoplankton in their growing areas, every shellfish-producing authority must have a contingency plan that defines administrative procedures, laboratory support, sample collection procedures, and patrol procedures to be implemented on an emergency basis in the event of the occurrence of shellfish toxins. For producing authorities where there is historic occurrence of toxin-producing phytoplankton and toxicity in shellfish from their growing areas, the authority must develop a management plan.

Most authorities will have a combination of management and contingency plans - management plans to address those growing areas with historic occurrence of certain toxin-producing phytoplankton, and contingency plans to address toxin-producing phytoplankton in growing areas in the event of such emergence. As an example, an authority may have statewide historical occurrence of PSP toxin-

producing phytoplankton, for which it develops a management plan; however, because of a lack of illness outbreak or historical evidence of phytoplankton that produce ASP, NSP, DSP, and AZP toxins, the authority also develops a contingency plan that addresses how the authority will manage the emergence of those particular toxins.

Guidance for the development of contingency and management plans is found at Ch IV @.04.

Shellfish Meat Analyses

Laboratory methods to detect marine biotoxins in shellfish include:

- Animal bioassay;
- Biochemical;
- Rapid test kits; and
- Chemical analytical methods.

The mouse bioassay historically has been the most universally applied technique for examining shellfish toxins. Other bioassay procedures have been developed and are becoming more generally applied. In recent years, considerable effort has been appli to development of chemical analyses to replace or provide alternatives to in-vivo (liv animal) bioassays.

Marine biotoxin testing methods fall into two categories in the NSSP:

1. **Approved** (Section IV. Guidance Documents Chapter II Growing Areas .14 Table 2.)
   Approved methods are those methods that have undergone ISSC evaluation and have been adopted into the NSSP (for certain species) for regulatory decisions, including reopening a growing area after a closure.

2. **Approved Limited Use** (Section IV. Guidance Documents Chapter II Grow Areas .14 Table 4.)
   Approved limited use methods (sometimes referred to as rapid or screening methods) are testing methods that have been evaluated by the ISSC and foun fit for purpose for the NSSP, thereby providing confidence in those methods specific screening purposes. **Most limited use methods may be used for specific screening purposes, the results of which an authority may use to close a growing area; however, an approved method must be utilized to reopen an area following a closure.**

For analyses of toxins for which no method has been adopted into the NSSP, best available science is employed.

Toxin Profiles (PSP, DSP, NSP, ASP, AZP)

Paralytic Shellfish Poisoning (PSP) Toxin	
Cause	Saxitoxins are produced by the dinoflagellates of the genus *Alexandrium* (formerly *Gonyaulax*). The dinoflagellate *Pyrodinium bahamense* is also a producer of saxitoxins.
Analogs	Water-soluble alkaloid neurotoxins that are collectively referred to as saxitoxins or paralytic shellfish toxins (PSTs). To date 57 analogs have been identified, although not all are

		always present, and they vary greatly in overall toxicity. In addition to saxitoxin (the parent compound), monitoring laboratories typically analyze for approximately 12 other analogs that may contribute measurably to toxicity.
	Occurrences	Historically, *Alexandrium* blooms have occurred between April and October along the Pacific coasts from Alaska to California and in the Northeast from the Canadian Provinces to Long Island Sound (US Public Health Service, 1958); but these patterns may be changing. The blooms, which may or may not result in discoloration of seawater, generally last only a few weeks and most shellfish (with the exceptions of some species of clams and scallops, which retain the toxin for longer periods) clear themselves rapidly of the toxin once the bloom dissipates.
	Predictability	Toxic blooms of these dinoflagellates can occur unexpectedly or follow predictable patterns.
	Action Level	0.8 ppm (80 µg/100 g) saxitoxin equivalents. Selective species closures are allowed under the NSSP. In shellfish growing areas where low levels of PSP routinely occur, harvesting for thermal processing purposes is allowed. Thermal processing is defined by FDA regulation 21 CFR 113. Thermal processing will not entirely destroy PSP content of the shellfish; therefore, the Authority must develop and implement procedures to control harvesting and transportation of shellfish intended to be processed.
	Action Level Origin	The regulatory limit was set in the 1930s (Wekell, 2004). The minimum concentration of PSP toxin that will cause intoxication in susceptible persons is not known. Epidemiological investigations of PSP in Canada, however, have indicated 200 to 600 micrograms of PSP toxin will produce symptoms in susceptible persons. A death has been attributed to the ingestion of a probable 480 micrograms of PSP toxin. Investigations indicate that lesser amounts of the toxin have no deleterious effects on humans.
	Monitoring	Monitoring programs for analysis of PSP toxins include: • Samples submitted by industry with a MOU. • Samples collected by shellfish authority personnel. • Sentinel species monitoring.
	Shellfish Lab Methods	The mouse bioassay is still the most widely accepted detection method for the saxitoxins around the world and has been shown to adequately protect the public's health. In 2009, the Interstate Shellfish Sanitation Conference approved a post-column oxidation HPLC-PCOX method, making it the newest regulatory method available for PSP toxins in the U.S. The receptor binding assay, a competition assay whereby radiolabeled saxitoxin competes with unlabeled saxitoxin for a finite number of available receptor sites as a measure of native saxitoxin concentrations in a sample, was also approved as an official AOAC method in

	2011.
Disease	Paralytic Shellfish Poisoning
Mortality	Death has been reported to occur as soon as 3 to 4 hours after consumption.
Onset	Symptoms can generally occur within 30 minutes of consuming contaminated seafood, although reports have indicated that symptoms can even ensue within a few minutes, if high enough toxin concentrations are present.
Symptoms, Illness Course	Predominantly neurologic and include tingling of the lips, mouth, and tongue; numbness of extremities; paresthesias; weakness; ataxia; floating/dissociative feelings; nausea; shortness of breath; dizziness; vomiting; headache; and respiratory paralysis. Medical treatment consists of providing respiratory support, and fluid therapy can be used to facilitate toxin excretion. For patients surviving 24 hours, with or without respiratory support, the prognosis is considered good, with no lasting side effects. In fatal cases, death is typically due to asphyxiation. In unusual cases, death may occur from cardiovascular collapse, despite respiratory support, because of the weak hypotensive action of the toxin.
General Food Associations	Mussels, clams, cockles, oysters, and scallops (excluding the scallop adductor muscle).
Outbreak Examples	In New England in 1972, shellfish suddenly became toxic in a previously unaffected portion of the coastline, which resulted in many illnesses (Schwalm, 1973). Despite widespread PSP closures, poisoning events still occur and are generally associated with recreational harvest. For example, in July 2007, a lobster fisherman harvested mussels from a floating barrel off Jonesport, Maine (an area that was currently open to shellfish harvesting), and he and his family ate them for dinner. All four consumers became ill with PSP symptoms, and three of them were admitted to the hospital. It was apparent that the barrel of mussels had originated further up the coast in an area that had been banned to commercial harvest (DeGrasse, 2014).
Diarrhetic Shellfish Poisoning (DSP) Toxin	
Cause	Certain *Dinophysis spp*. and *Prorocentrum spp*. produce okadaic acid and dinophysis toxins that cause DSP.
Analogs	A group of lipid-soluble polyether toxins that includes okadaic acid, the dinophysistoxins, and a series of fatty acid esters of okadaic acid and the dinophysistoxins (collectively known as DSTs) (Uchida, 2018).
Occurrence	DSP toxin-producing phytoplankton have been documented to occur off the coasts of Washington (Trainer et al., 2013) and Texas (Deeds et al., 2010) as well as off the coast in the northeast (e.g., Massachusetts [Tong et al., 2014], Maine, and Connecticut). Known global distribution of DSTs also

	includes Japan, Europe, Asia, Chile, Canada, Tasmania, and New Zealand (Trainer, 2013). In 2008, a large portion of the Texas Gulf Coast was closed to the harvesting of oysters due to the presence of okadaic acid in excess of the FDA guidance level. Although no illnesses were reported in 2008, these were the first closures in the U.S. due to confirmed toxins.
Predictability	Dinoflagellates are known to thrive in stratified systems and Dinophysis has particular adaptive strategies to cope with freshwater plumes (Trainer, 2013).
Action Level	0.16 ppm total okadaic acid equivalents (i.e., combined free okadaic acid, dinophysistoxins, acyl-esters of okadaic acid and dinophysistoxins)
Action Level Origin	Established by FDA in 2011 for total (esterified plus non-esterified OA + DTXs (with no guidance for PTXs and YTXs) (Trainer, 2013).
Monitoring	Production of DSTs has been confirmed in several *Dinophysis* species, including *D. fortii*, *D. acuminata*, *D. acuta*, *D. norvegica*, *D. mitra*, *D. rotundata*, *D. ovum*, *D. sacculus*, *D. caudate, and D. tripos*, and in the benthic dinoflagellates *Prorocentrum lima*, *P. concavum* (or *P. maculosum*), *P. micans*, *P. minimum*, and *P. redfieldii*. One other *Dinophysis* species, *D. hastate*, is also suspected to produce toxins (Trainer, 2013). Precautionary closures initiated based on cell abundance are not useful, but observations show promise in providing early warning to DSP events (Trainer, 2013).
Shellfish Lab Methods	Until recently, DSP was managed by mouse bioassay and/or monitoring shellfish growing waters for the presence of *Dinophysis* organisms. Unfortunately, the dose-survival times for the DSP toxins in the mouse assay vary considerably, and fatty acids interfere with the assay, giving false-positive results. A suckling mouse assay has been developed and used for control of DSP. This assay measures fluid accumulation after injection of the shellfish extract. In 2017 an LCMS/MS method for quantifying DTXs in clams was approved in the NSSP. For other species, the best available science is recommended.
Disease	Diarrhetic Shellfish Poisoning
Mortality	This disease generally is not life-threatening.
Onset	Onset of the disease, depending on the dose of toxin ingested, may be as little as 30 minutes to 3 hours.
Symptoms, Illness Course	DSP is primarily observed as a generally mild gastrointestinal disorder; i.e., nausea, vomiting, diarrhea, and abdominal pain, accompanied by chills, headache, and fever. Symptoms may last as long as 2 to 3 days, with no chronic effects.
General Food Associations	Mussels, clams, cockles, oysters, and scallops (excluding the scallop adductor muscle).
Outbreak Examples	Although there have been numerous outbreaks of diarrhetic shellfish poisoning around the world, until recently there were

	no confirmed cases of DSP in the U.S. that were due to domestically harvested shellfish (Trainer, 2013). In 2011, approximately 60 illnesses occurred in British Columbia, Canada, and 3 illnesses occurred in Washington State due to consumption of DSP-contaminated mussels. Subsequent harvesting closures and product recalls were issued (Lloyd, 2013).
Neurotoxic Shellfish Poisoning (NSP) Toxin	
Cause	NSP is caused by brevetoxins produced by the dinoflagellates of the genus *Karenia* (formerly *Gymnodinium*).
Analogs	Comprised of more than 10 lipid-soluble cyclic polyethers. A number of analogs and metabolites have been identified. NSP-causing toxins in shellfish include intact algal brevetoxins and their metabolites (collectively known as NSTs). In addition to brevitoxins, numerous other *Karenia spp*. Found in the Gulf of Mexico and around the world regularly associated with blooms produce hymnodimine, karlotoxins, and other potent toxins (Watkins, 2008).
Occurrence	In Gulf coast areas, toxicity in shellfish has been associated with red tide outbreaks caused by massive blooms of the toxic dinoflagellate, *Karenia brevis* (formerly *Ptychodiscus brevis*). Naturally occurs in Gulf of Mexico, Caribbean Sea, and along New Zealand coasts; it regularly produces blooms along the coasts of Florida and Texas. Blooms may cause ocean to appear red, brown, or simply darkened and are usually accompanied by massive fish kills and mortalities in marine mammals and sea birds (Watkins, 2008). Dupuration time of brevetoxins in shellfish varies, but is typically within two to eight weeks, although reports of much longer retention (nearly one year post bloom) have been documented (Watkins, 2008).
Predictability	*Karenia* blooms show no indication of regular recurrence and shellfish generally take longer to eliminate the toxin. Blooms were once considered to be sporadic and seasonal, but historical records demonstrate these blooms have occurred in Florida almost annually in the years since the 1940s. Although more frequent in late summer and early fall, Florida blooms have been documented in almost every month of the year and may disperse in a matter of weeks, or may be present for many months at a time; in 2006, a bloom off the coast of Sarasota lasted over 12 months. Occurrence and magnitude of blooms are unpredictable.
Action Level	0.8 ppm (20 mouse units/100 g tissue or 80 µg/100 g tissue) brevetoxin-2 equivalents The cell count of members of *Karenia brevis* in the water column exceeds 5,000 cells per liter of water.
Action Level Origin	Uncooked clams from a batch eaten by a patient in Florida with NSP symptoms were found to contain 118 mouse units per 100 grams of shellfish meat. However, consumption of

	even a few contaminated shellfish may result in poisoning and the severity of the disease may be dependent on many factors, including dose, bodyweight, underlying medical conditions, and the age of the victim as well as possibly the toxin mixture of the particular bloom (Watkins, 2008).
Monitoring	Water cell counts and tissue samples.
Shellfish Lab Methods	Toxicity of shellfish exposed to the dinoflagellate *Karenia brevis* has been historically assessed by mouse bioassay in the U.S.; however, mouse bioassay is not very specific for NSP toxins (Watkins, 2008). Efforts are underway to validate *in-vitro* methods for detection of brevetoxins in shellfish. For example, rapid, sensitive ELISA test kits already are commercially available for this purpose. Biomarkers of brevetoxin contamination in shellfish have been identified by using LC/MS. Structural confirmation of these metabolites and brevetoxins in shellfish can be made by LC/MS, a method that offers high sensitivity and specificity. A method for detection, identification, and quantification of brevetoxins is HPLC-MS. Radioimmunoassay (RIA) and Receptor Binding Assay (RBA) are also under current use (Watkins, 2008). Available detection methods are not equal in their ability to measure naturally-produced brevetoxins, and most methods are hampered by the absence of specific reference standards for brevetoxin congeners (Watkins, 2008).
Disease	Neurotoxic Shellfish Poisoning
Mortality	No fatalities have been reported, but hospitalizations occur.
Onset	Onset of this disease occurs within a few minutes to a few hours. A mean time to onset of 3-4 hours has been reported in the few documented outbreaks (Watkins, 2008).
Symptoms, Illness Course	Both gastrointestinal and neurological symptoms characterize NSP, including tingling and numbness of lips, tongue, and throat; muscular aches; dizziness; diarrhea; and vomiting. Respiratory distress has been recorded. Duration is fairly short, from a few hours to several days. Recovery is complete, with few after-effects.
General Food Associations	Oysters and clams.
Outbreak Examples	The most common public health problem associated with *Karenia* blooms is respiratory irritation; however, neurotoxic shellfish poisonings associated with *Karenia brevis* blooms have been reported in Florida (US Center for Disease Control, 1973). Until NSP toxins were implicated in more than 180 human illnesses in New Zealand in 1992/1993 due to consumption of cockles and green shell mussels, NSP was considered to be an issue only in the U.S. Outbreaks of NSP are rare where programs for monitoring *K. brevis* blooms and shellfish toxicity are implemented. An NSP outbreak involving 48 individuals occurred in North Carolina in 1987

	(Morris, 1991). A series of NSP cases occurred along the southwest coast of Florida, in 2006, after people consumed recreationally-harvested clams from waters unapproved for shellfish harvesting (Watkins, 2008).
Amnesic Shellfish Poisoning (ASP) Toxin	
Cause	ASP is caused by domoic acid that is produced by diatoms of the genus *Pseudonitzchia*.
Analogs	The neurotoxin domoic acid is a water-soluble, non-protein, excitatory amino acid. Isomers of domoic acid have been reported, but are less toxic than domoic acid itself. Excitatory amino acid (EAA) analogues of glutamate.
Occurrence	During a 1991-1992 incident in Washington and a 2015 event on the west coast from Washington to California, high toxin levels persisted for several months (Liston, 1994; McCabe et al. 2016). There was also an extensive event in the Northeast from Maine to Rhode Island in 2016, with different regions showing varying toxicity and species dominance within the bloom. The event started in late September in eastern Maine and ended in October; however, Rhode Island experienced another bloom in February of 2017. During 1991 and 1992, there was a spread of domoic acid producing organisms throughout the world including the detection of high numbers of the diatom *Pseudonitzschia pseudodelcatissima* in Australia and *Pseudonitzschia pseudoseratia* in California. Domoic acid has also been recovered from shellfish in Washington and Oregon.
Predictability	Blooms of *Pseudonitzschia* are of varying intensity, duration and extent. Environmental factors associated with ASP in shellfish are currently unknown.
Action Level	20 ppm domoic acid
Action Level Origin	In 1987 in eastern Canada, DA poisonings sickened individuals, leading to Health Canada's establishment of the regulatory limit. (Wekell, 2004)
Monitoring	Monitoring programs for ASP toxin are designed around the shellfish species of interest.
Shellfish Lab Methods	The mouse bioassay for domoic acid is not sufficiently sensitive and does not provide a reliable estimate of potency. The NSSP approved regulatory method for detecting domoic acid in seafood is a reversed-phase HPLC method with ultraviolet (UV) detection. There is also an AOAC approved ELISA for the detection of domoic acid.
Disease	Amnesic Shellfish Poisoning
Mortality	All fatalities, to date, have involved elderly patients.
Onset	The toxicosis is characterized by onset of gastrointestinal symptoms within 24 hours; neurologic symptoms occur within 48 hours.
Symptoms, Illness	ASP is characterized by gastrointestinal disorders (vomiting, diarrhea, abdominal pain) and neurological problems

Course	(confusion, short-term memory loss, disorientation, seizure, coma). Human clinical signs of domoic acid toxicity are reported as mild gastrointestinal symptoms, from an oral dose of 0.9-2.0 mg domoic acid (DA)/kg body weight. Neurologic effects, such as seizure and disorientation, are reported from an oral dose of 1.9-4.2 mg DA/kg body weight. The toxicosis is particularly serious in elderly patients, and includes symptoms reminiscent of Alzheimer's disease.
General Food Associations	Mussels, clams, cockles, oysters, and scallops (excluding the scallop adductor muscle).
Outbreak Examples	The first human domoic acid poisoning events were reported in 1987, in Canada (Perl, 1990). While domoic acid exposure still exists, there have been no documented ASP cases since 1987, following implementation of effective seafood toxin-monitoring programs (Pulido, 2008).
Azaspiracid Shellfish Poisoning (AZP) Toxin	
Cause	*Azadinium spp*. is the producer of azaspiracids, which cause AZP.
Analogs	The lipid-soluble toxin azaspiracid and several derivatives (AZAs). More than 30 AZA analogs have been identified, with three analogs routinely monitored in shellfish (AZA1, AZA2, and AZA3).
Occurrence	Coastal regions of western Europe, as well as NW Africa and eastern Canada.
Predictability	Detected between mid-summer and mid-winter from northern/western European waters, but in certain cases, the presence of AZAs in phytoplankton does correspond to the timing of shellfish contamination, yet toxin levels in bivalves can remain elevated for 8 – 12 months following initial exposure.
Action Level	160 µ/kg shellfish meat
Action Level Origin	Estimation of consumption of a single portion of shellfish and through estimate of an Acute Reference Dose. Derived from epidemiological observations caused by a mixture of naturally occurring analogs (AZA 1, 2, and 3). Based on methods available in 2001.
Monitoring	Range of species in which AZAs have been detected includes mussels (*M. edulis; M. galloprovincialis*), oysters (*Crossostrea gigas*, *Ostrea edulis*), scallops (*Pecten maximus*), clams (*Tapes philipinarum*, *Ensis siliqua*, *Donax* spp.), and cockles (*Cerastroderma edule*). AZAs have also been found in crustaceans. Monitoring programs will benefit from major research efforts to identify the causative organism(s) because there is often, but not always, a correlation between the presence of potentially toxigenic phytoplankton species and the subsequent accumulation of toxins in shellfish.
Shellfish Lab Methods	AZAs are not routinely monitored in shellfish harvested in the U.S., but, in the EU, the mouse bioassay has been used. As

	for many of the lipophilic toxins, the mouse assay is not adequately sensitive or specific for public- health purposes. *In-vitro* assays and analytical methods are now available to assess the toxicity of AZA-contaminated shellfish and to confirm the presence of AZA analogs in shellfish. These methods are in various stages of validation for regulatory use around the world. LC/MS is used as a confirmatory method for AZA, providing unambiguous structural confirmation of AZA analogs in shellfish samples.
Disease	Azaspiracid Shellfish Poisoning
Mortality	No known fatalities to date.
Onset	Symptoms appear in humans within hours of eating AZA-contaminated shellfish.
Symptoms, Illness Course	Symptoms are predominantly gastrointestinal disturbances resembling those of diarrhetic shellfish poisoning and include nausea, vomiting, stomach cramps, and diarrhea. Illness is self-limiting, with symptoms lasting 2 or 3 days.
General Food Associations	Detected in mussels, oysters, scallops, clams, cockles, and crabs.
Outbreak Examples	The first case of AZP was detected in the Netherlands in 1995, where 8 people became ill after consuming mussels. From 1997 – 2000, approximately 80 individuals reported illnesses from mussels and scallops harvested from Ireland, Italy, France, and United Kingdom (Twiner, 2008). There have been no confirmed cases of AZP in the U.S. from domestically-harvested product. In 2008, the first recognized outbreak of AZP in the U.S. was reported, but was associated with a mussel product imported from Ireland (Klontz et al. 2009).

Resources

The 2012 version of FDA's Bad Bug Book, Foodborne Pathogenic Microorganisms and Natural Toxins, is a comprehensive resource from which a great deal of information has been used for the toxin profiles in the table above. It is accessible at https://www.fda.gov/media/83271/download

For more discussion of chemical structures and properties, methods of analysis, source organisms and habitat, occurrence and accumulation in shellfish, toxicity of toxins, prevention of intoxication, cases and outbreaks, and regulations and monitoring, see the FAO Paper 80: Marine Toxins. This may be accessed as follows:

Paralytic Shellfish Poisoning	http://www.fao.org/3/y5486e/y5486e05.htm
Diarrhetic Shellfish Poisoning	http://www.fao.org/3/y5486e/y5486e0e.htm
Neurotoxic Shellfish Poisoning	http://www.fao.org/3/y5486e/y5486e0o.htm
Amnesic Shellfish Poisoning	http://www.fao.org/3/y5486e/y5486e0n.htm
Azaspiracid Shellfish Poisoning	http://www.fao.org/3/y5486e/y5486e0p.htm
References	http://www.fao.org/3/y5486e/y5486e0t.htm

The FDA online course, Shellfish Growing Areas, introduces participants to requirements and procedures under the NSSP to ensure that shellfish are harvested from safe waters. The course contains a significant section addressing marine biotoxins. The course may be accessed at https://www.accessdata.fda.gov/ORAU/ShellfishGrowingAreas/SGA_summary.htm.

Additional information from the Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report (MMWR) contains illness reports related to these toxins. This may be accessed at https://www.cdc.gov/mmwr/index.html.

NIH/PubMed: Various Shellfish-Associated Toxins provides a list of research abstracts in the National Library of Medicine's MEDLINE database.

The specific seafood with which each toxin generally is associated is included in the profiles above to help readers link symptoms to potential sources. However, all shellfish (filter-feeding mollusks, as well as the carnivorous grazers that feed on these mollusks (such as whelk, snails, and, in some cases, even lobster and octopus), may become toxic in areas where the source algae are present.

References

Deeds, J.R., & Landsberg, J.H., Etheridge, S.M., Pitcher, G.C., Longan, S.W. (2008). Non-traditional vectors for paralytic shellfish poisoning. *Marine Drugs, 6(2)*, 308-348. Retrieved from https://doi.org/10.3390/md6020308.

Degrasse, S., & Rivera, V., Roach, J., White, K., Callahan, J., Couture, D., Simone K., Peredy, T., Poli, M. (2014). Paralytic shellfish toxins in clinical matrice extension of AOAC official method 2005.06 to human urine and serum and application to a 2007 case study in Maine. *Deep Sea Research Part II: Topical Studies in Oceanography*, 103, 368-375. Retrieved from https://doi.org/10.1016/j.dsr2.2012.08.001.

Food and Agriculture Organization of the United Nations. (2015) Codex Alimentar Standard for Live and Raw Bivalve Molluscs Codex Stan 292-2008. Retrie from http://www.fao.org/fao-who-codexalimentarius/codex-texts/all-standards/en/

Food and Agriculture Organization of the United Nations. (2004). FAO Food and Nutrition Papers, 80 - Marine Biotoxins. Retrieved from http://www.fao.org/3/y5486e/y5486e00.htm

Joint Sanitation Seminar on North Pacific Clams Juneau, A., Felsing, W. A. (Willi August)., United States. Public Health Service., Alaska. Dept. of Health an Welfare. (1966). *Proceedings of Joint Sanitation Seminar on North Pacific Clams.* Washington, D.C.: For sale by the Supt. of Docs., G.P.O.. Retrieve from https://babel.hathitrust.org/cgi/pt?id=pur1.32754081175147&view=1up&se

Klontz, K.C., & Abraham, A., Plakas, S., Dickey, R. (2009). Mussel-associated azaspiracid intoxication in the United States. *Annals of Internal Medicine*, 150(5), 361. Retrieved from https://www.researchgate.net/publication/24174858_Mussel-

Associated_Azaspiracid_Intoxication_in_the_United_States

Liston, J. (1994). Association of *Vibrionaceae*, natural toxins, and parasites with fe indicators, p. 215-216. In Hackney, C.R. and M.D. Pierson (eds.). *Environmental Indicators and Shellfish Safety*. Chapman and Hall, New Yo NY.

Lloyd, J.K., & Duchin, J., Borchert, J., Quintana, H.F., Robertson, A. (2013). Diarrh Shellfish Poisoning, Washington, USA, 2011. Emerging Infectious Diseases 19(8), 1314-1316. Retrieved from https://doi.org/10.3201/eid1908.121824.

Marsden I.D., & Contreras, A.M., MacKenzie, L., Munro, M.H.G. (2015). A comparison of the physiological responses, behaviour and biotransformatic of paralytic shellfish poisoning toxins in a surf-clam (*Paphies donacina*) a the green-lipped mussel (*Perna canaliculus*). *Marine and Freshwater Research*, 67, 1163-1174. Retrieved from http://www.publish.csiro.au/mf/MF14374

McCabe, R.M., & Hickey, B.M., Kudela, R.M., Lefebvre, K.A., Adams, N.G., Bill B.D., Gulland, F.M.D., Thomson, R.E., Cochlan, W.P., Trainer, V.L. (201 An unprecedented coastwide toxic algal bloom linked to anomalous ocean conditions. *Geophysical Research Letters*, 43(19), 10,366–10,376. Retriev from https://DOI.org/10.1002/2016GL070023.

Morris, P.D., & Campbell, D.S., Taylor, T.J., Freeman, J.I. (1991). Clinical and epidemiological features of neurotoxic shellfish poisoning in North Carolir *American Journal of Public Health*, 81(4), 471-474. Retrieved from: https://DOI.org/10.2105/ajph.81.4.471.

National Shellfish Sanitation Workshop., United States. Shellfish Sanitation Branch. (1964). *Proceedings - National Shellfish Sanitation Workshop.* [Washington]: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Food and Drug Administration, Shellfish Sanitation Branch. Retrieved from https://catalog.hathitrust.org/Record/006685147

Perl, T.M., & Bedard, L., Kosatsky, T., Hockin, J.C., Todd, E.C.D., NcNutt, L.A., Remis, R.S. (1990). Amnesic shellfish poisoning: a new clinical syndrome due to domoic acid. In: Hynie, I., Todd, E.C.D., editors. Proceedings of a symposium, domoic acid toxicity. Canada Disease Weekly Report; Ottawa, Ontario. Pp. 7-8.

Prakash, A., & Medcof, J.C., Tennant, A.D. (1971). Paralytic shellfish poisoning i eastern Canada. Bulletin 177, Fisheries Research Board of Canada. Ottawa, Canada. Retrieved from http://dfo-mpo.gc.ca/library/1498.pdf.

Pulido, O.M. (2008). Domoic acid toxicologic pathology: a review. *Marine Drugs, 6(2)*, 180-219. Retrieved from https://doi.org/10.3390/md20080010.

Quayle, D.B. (1969). Paralytic shellfish poisoning in British Columbia. Bulletin 168, Fisheries Research Board of Canada. Ottawa, Canada.

Schwalm, D.J. (1973). The 1972 PSP outbreak in New England. FDA Report, Boston, MA. U.S. Food and Drug Administration, Washington, D.C.

Tong, M., & Smith, J.L., Richlen, M.L., Steidinger, K., Kulis, D., Fux, E., Anderson, D.M. (2014) Characterization and comparison of toxin-producing isolates of *Dinophysis acuminata* from New England and

Canada. *Journal of Phycology*, 51(1), 66-81. Retrieved from https://www.researchgate.net/publication/267340694_Characterization_and_comparison_of_toxin-producing_isolates_of_Dinophysis_acuminata_from_New_England_and_Canada .

Trainer, V.L., & Moore, L., Bill, B.D., Adams, N.G., Harrington, N., Borchert, J., da Silva, D.A.M., Eberhard, B.T.L. (2013). Diarrhetic shellfish toxins and other lipophilic toxins of human health concern in Washington State. *Marine Drugs*, 11, 1815–1835. Retrieved from https://doi.org/10.3390/md11061815.

Twiner, M.J., & Bottein Dechraoui, M.Y., Wang, Z., Mikulski, C.M., Henry, M.S., Pierce, R.H., Doucette, G.J. (2007). Extraction and analysis of lipophilic brevetoxins from the red tide dinoflagellate *Karenia brevis*. *Analytical Biochemistry*, 369(1), 128-135. Retrieved from https://DOI.org/10.1016/j.ab.2007.06.031.

Twiner, M.J., & Rehmann, N., Hess, P., Doucette G.J. (2008). Azaspiracid shellfish poisoning: a review on the chemistry, ecology, and toxicology with an emphasis on human health impacts. *Marine Drugs*, *6(2)*, 39-72. Retrieved from https://doi.org/10.3390/md6020039.

Uchida, H., & Watanabe, R., Matsushima, R., Oikawa, H., Nagai, S., Kamiyama, T., Baba, K., Miyazono, A., Kosada, Y., Kaga, S., Matsuyama, Y., Suzuki, T. (2018). Toxin profiles of okadaic acid analogues and other lipophilic toxins in Dinophysis from Japanese Coastal Waters. Toxins (Basel). 10(11), 457. Retrieved from https://doi.org/10.3390/toxins10110457 .

US Center for Disease Control. (1973). Shellfish poisoning - Florida. *Morbidity Mortality Weekly Report*, 22(48), 397-398. Retrieved from https://stacks.cdc.gov/view/cdc/1843

US Food and Drug Administration. (1997). Poisonous or Deleterious Substances Food. *Federal Register*, 42(190), 52814-52819.

US Food and Drug Administration. (2000). Guidance for Industry: Action Levels for Poisonous or Deleterious Substances in Human Food and Animal Feed. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-action-levels-poisonous-or-deleterio substances-human-food-and-animal-feed.

US Food and Drug Administration. (2011). Fish and Fishery Products Hazards and Controls Guidance 4th Edition. Retrieved from https://www.fda.gov/food/seafood-guidance-documents-regulatory-information/fish-and-fishery-products-hazards-and-controls-guidance-4th-edition

US Public Health Service (PHS). (1958). Proceedings: 1957 Conference on Shellfish Poison. U.S. PHS, Washington, D.C. 125 pages. Retrieved from https://babel.hathitrust.org/cgi/pt?id=uc1.31822005678131&view=1up&seq

Watkins, S.M., & Reich, A., Fleming, L.E., Hammond, R. (2008). Neurotoxic shellfish poisoning. *Marine Drugs*, *6(3)*, 431-455. Retrieved from: https://doi.org/10.3390/md6030431.

Wekell, J.C., & Hurst, J., Lefebvre, K.A. (2004). The origin of the regulatory limits f PSP and ASP toxins in shellfish. *Journal of Shellfish Research*, 23(3), 927-9 Retrieved from: https://www.researchgate.net/publication/285809374_The_origin_of_the_re atory_limits_for_PSP_and_ASP_toxins_in_shellfish

Wiese, M., & D'Agostino, P.M., Mihali, T.K., Moffitt, M.C., Neilan, B.A. (2010). Neurotoxic alkaloids: saxitoxin and its analogs. *Marine Drugs*, *8(7)*, 2185-2211. Retrieved from https://doi.org/10.3390/md8072185.

~~Marine biotoxins may be ingested by molluscan shellfish feeding on toxic dinoflagellates. Dinoflagellates in their vegetative stage flourish seasonally when water conditions are favorable. Toxic blooms of dinoflagellates or diatoms can occur unexpectedly or may follow predictable patterns. PSP, NSP and Domoic Acid poisoning, also known as ASP are the three (3) types of poisonings most commonly associated with oysters, clams, mussels and scallops in the United States.~~

~~Cases of paralytic shellfish poisoning, including several fatalities resulting from poisonous shellfish, have been reported from both the Atlantic and Pacific coasts. The minimum quantity of poison, which will cause intoxication in the susceptible person, is not known. Epidemiological investigations of paralytic shellfish poisoning in Canada have indicated 200 to 600 micrograms of poison will produce symptoms in susceptible persons. A death has been attributed to the ingestion of a probable 480 micrograms of poison. Investigations indicate that lesser amounts of the poison have no deleterious effects on humans. Growing areas should be closed at a level to provide an adequate margin of safety, since in many instances, toxicity levels will change rapidly.~~

~~A review of the literature and research dealing with the source of the poison, the occurrences, and distribution of poisonous shellfish physiology and toxicology, characteristics of the poison, and prevention and control of poisoning has been prepared.~~

~~In Gulf coast areas, toxicity in shellfish has been associated with red tide outbreaks caused by massive blooms of the toxic dinoflagellate, *Karenia brevis* (formerly *Ptychodiscus brevis*). Toxic symptoms in mice suggest a type of NSP rather than symptoms of PSP. The most common public health problem associated with *Karenia brevis* blooms is respiratory irritation; however, NSP associated with *Karenia brevis* blooms have been reported in Florida. Uncooked clams from a batch eaten by a patient with neurotoxic symptoms were found to contain 118 mouse units per 100 grams of shellfish meat.~~

~~Toxic dinoflagellates or diatoms are indigenous to most coastal and estuarine waters on the Atlantic, Gulf, and Pacific coasts of America, as well as in many other parts of the world. Blooms of these organisms can occur unexpectedly and rapidly. This phenomenon occurred in New England in 1972 when shellfish suddenly became toxic in a previously unaffected portion of the coastline and resulted in many illnesses. During 1991 and 1992, there was a spread of domoic acid producing organisms throughout the world including the detection of high~~

	~~numbers of the diatom *Pseudo-nitzschia pseudo-delcatissima* in Australia and *Pseudo-nitzschia pseudo-seratia* in California. Domoic acid was also recovered from shellfish in Washington and Oregon. All shellfish producing States or MOU countries must have a contingency plan that defines administrative procedures, laboratory support, sample collection procedures, and patrol procedures to be implemented on an emergency basis in the event of the occurrence of shellfish toxins. A model State contingency plan for control of marine biotoxins is provided in the NSSP Model Ordinance Guidance Documents, *Guidance for Developing Marine Biotoxin Contingency Plans* (ISSC/FDA, 2017).~~ ~~All States or MOU countries must monitor toxin levels to establish a baseline historical reference. Thereafter, States or MOU countries where shellfish toxins are likely to occur must monitor toxin levels on a routine basis to meet the approved area requirements for direct market harvesting. Experience with monitoring for shellfish toxins suggests that an effective program should include the following:~~ ~~Sampling stations should be located at sites where past experience has shown toxin is most likely to appear first.~~ ~~Samples should be collected of shellfish species which are most likely to reveal the early presence of toxin and which are most likely to show the highest toxin levels. For example, mussels have been found to be useful for early PSP detection.~~ ~~The frequency and period for collection of samples should be based upon historical patterns. This assumes several years of baseline data in order to establish stations and sampling plans.~~ ~~An information network should be established between the health and marine resource communities and the Authority. Any toxin-like illnesses related to shellfish and environmental phenomena such as algal blooms, fish kills, or bird kills, which might indicate the early stages of an increase in toxin levels, should be rapidly communicated over the network.~~ ~~Sampling stations and frequency of sampling should be increased when monitoring data or other information suggests that toxin levels are increasing.~~ ~~Sample collection, sample transportation, and sample analysis procedures should be developed so that in an emergency sample results will be known within twelve (12) hours.~~ ~~When monitoring data or other information indicates that toxin levels have increased to the quarantine levels, growing area closures must be immediately implemented. The determination of which growing areas should be closed should include consideration of the rapidity with which toxin levels can increase to excessive levels and the inherent delays in the State sample collection procedures. It may be appropriate to close growing areas adjacent to known toxic areas until increased sampling can establish which areas are toxin-free and that toxin levels have stabilized.~~

~~Shellfish growing areas closed because marine biotoxins have exceeded quarantine levels may be reopened for growing after a sufficient number of samples and other environmental indices, if used, have established that the level of toxin will remain below quarantine levels for an extended period. For example, experience has shown that appropriate reopening criteria include a minimum of three (3) samples collected over a period of at least fourteen (14) days. These samples should show the absence of PSP or levels below 80 micrograms per 100 grams.~~

~~**A.** Contingency Plan.~~

~~The suitability of some areas for harvesting shellstock is periodically influenced by the presence of toxigenic micro-algae. Recent increases in toxigenic micro-algae distribution dictate that a more comprehensive series of public health controls be adopted. The need exists to make contingency plans to address the contamination of a growing area by toxigenic micro-algae or a disease outbreak caused by marine biotoxin. This contingency plan must describe administrative procedures, laboratory support, sample collection procedures, and patrol procedures to be implemented on an emergency basis in the event of the occurrence of marine biotoxin in shellstock. The primary goal of this planning should be to ensure that maximum public health protection is provided in growing areas subject to marine biotoxin contamination. For a discussion of marine biotoxin disease and its management in shellfish growing areas, see the NSSP Model Ordinance Guidance Documents: *Guidance for Developing Marine Biotoxin Contingency Plan* (ISSC/FDA, 2017).~~

~~**B.** Marine Biotoxin Monitoring.~~

~~The primary purpose of a marine biotoxin monitoring program is to prevent illness or death among the shellfish consuming public. The monitoring program should use the "indicator station" and "critical species" concepts to develop an early warning system to prevent harvest of biotoxin contaminated shellstock. For a full discussion, see the NSSP Model Ordinance Guidance Documents: *Guidance for Developing Marine Biotoxin Contingency Plan* (ISSC/FDA, 2017).~~

~~**C.** Closed Status of Growing Areas.~~

~~In the event of a toxigenic micro-algae bloom, shellstock growing areas shall be placed in the closed status for harvesting to prevent human consumption of biotoxin contaminated shellfish. The biotoxin level governing the need to place the growing area in the closed status will vary depending on the species of toxigenic micro-algae and the species of bivalve shellfish. Since the ability to concentrate biotoxins varies among species, it is possible for one (1) species in a growing area to have safe levels of biotoxin while another species in the same growing area will have dangerous biotoxin concentrations. In this situation, the Authority may permit the harvesting of one (1) species with no adverse public health consequences while prohibiting the harvest of another species. In these situations, the Authority must closely monitor the growing area and develop a sufficient database for use in making this determination.~~

	~~The Authority must develop criteria, which must be met before a growing area can be returned to the open status for harvesting. These criteria should integrate public health, conservation, and economic considerations. The criteria should also employ a sufficient number of samples and other environmental indices, if used, to establish that the level of toxin will remain, for an extended period of time, at levels safe for human consumption. For additional discussion concerning biotoxin contamination of shellstock, see the NSSP Model Ordinance Guidance Documents: *Guidance for Developing Marine Biotoxin Contingency Plan* (ISSC/FDA, 2017).~~ ~~**D.** Heat Processing.~~ ~~Heat treatment can reduce the toxicity of some biotoxins. When heat treatment is used, the Authority must require that the processor provide adequate demonstration of the destruction of the biotoxin and adequate controls to assure that the end product is safe for human consumption.~~ ~~**E.** Records.~~ ~~Good record keeping is essential to the successful management of a Marine Biotoxin Contingency Plan. Appropriate records of monitoring data, evaluation reports, and closure and reopening notices should be compiled and maintained by the Authority. This information is important in defining the severity of the problem, as well as for a retrospective evaluation of the adequacy of the entire control program.~~
13. Public Health Significance	Marine biotoxins can cause injury, illness, or death. More clearly presented information will assist NSSP participants in understanding the public health reasons for marine biotoxin contingency and management plans.
14. Cost Information	None