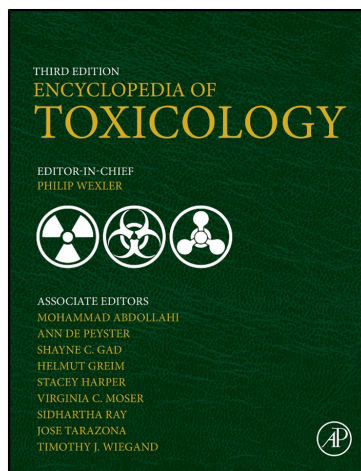


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Algae

KD Hambright and RM Zamor, Plankton Ecology and Limnology Laboratory, University of Oklahoma Biological Station, and Program in Ecology and Evolutionary Biology, University of Oklahoma, Norman, OK, USA

JD Easton and B Allison, Plankton Ecology and Limnology Laboratory, University of Oklahoma Biological Station, University of Oklahoma, Kingston, OK, USA

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Toxins discussed in this article are produced by microscopic, aquatic organisms commonly known as harmful algae, including unicellular, coenobial, and colonial species of Bacteria (Cyanobacteria) and Eukarya. Algae are generally autotrophic and rely on photosynthesis for their energy, but many species can also obtain energy heterotrophically from external dissolved and particulate organic sources via osmotrophy (direct absorption and uptake of organic molecules from the surrounding water), phagotrophy (ingestion of prey or other food particles), dasmotrophy (cell membranes of prey are perforated by extracellular toxins, inducing osmosis and leakage of organic compounds available for uptake or incorporation), and a variety of other heterotrophic strategies. Algae that are capable of both auto- and heterotrophy are known as mixotrophs. Included in algae are organisms also commonly referred to as phytoplankton, dinoflagellates, red and brown tides, diatoms, cyanobacteria, blue-green algae, and golden algae, of which some produce very potent toxins. This article focuses on the following algal toxins that are fairly well characterized in terms of adverse effects known to occur in humans and laboratory animals: azaspiracids, brevetoxins, ciguatoxins, maitotoxins, domoic acid (DA), okadaic (or okadeic) acid, saxitoxins, aplysiatoxins, anatoxins, microcystins, nodularins, and cylindrospermopsins. Azaspiracids, brevetoxins, ciguatoxins, maitotoxins, and okadaic acid are all classified chemically as polyether toxins. Domoic acid is a cyclic amino acid and saxitoxin is a purine alkaloid. A secondary focus is provided at the end of this article in which other less-studied, primarily ichthyotoxic, algal and cyanobacterial toxins with suspected human health concerns are mentioned briefly.

Commonly used synonyms for these sources and types of toxicity include azaspiracid shellfish poisoning (AZP) caused by at least 12 azaspiracid analogs; neurotoxic shellfish poisoning (NSP) caused by at least 10 known brevetoxins; ciguatera fish poisoning (CFP or Ciguatera) caused by more than 20 ciguatoxin congeners, gambiertoxins, and maitotoxins; amnesic shellfish poisoning (ASP) caused by one or more of three DA derivatives; paralytic shellfish poisoning (PSP) caused by at least 24 derivatives of saxitoxins; diarrhetic shellfish poisoning (DSP) caused by okadaic acid and dinophysistoxins; plus many other less-characterized toxins too numerous for detail in this brief overview (e.g., cyclic imines, golden algal toxins, karlotoxins, *Pfiesteria* toxins, pectenotoxins, and yessotoxins); and finally, red tides; harmful algal blooms (HAB), dinoflagellate blooms, cyanotoxins, and phycotoxins.

Exposure Routes and Pathways

A major route of human exposure to algal toxins is through the consumption of contaminated seafood products. The consumption of contaminated clams, mussels, scallops, oysters, and other shellfish causes shellfish-associated diseases (ASP, AZP, DSP, NSP, and PSP). Consuming contaminated large reef fish, like barracuda and grouper, causes ciguatera. Consumption of puffer fish with saxitoxin through shellfish feeding has resulted in cases of PSP.

Inhalation exposure of airborne toxins is also known to occur. For example, *Karenia brevis* which produces brevetoxin is relatively fragile and easily broken apart, particularly in wave action along beaches, thus releasing the toxin. During an active near-shore bloom (a.k.a., red tide), the water and aerosols of salt spray can contain toxins and cellular fragments, both in the droplets and attached to salt particles. These airborne particulates can cause respiratory irritation in humans on or near beach areas and can be carried inland under certain wind and other environmental conditions. The use of particle filter masks or retreat from the beach to indoors may provide protection from such airborne toxins. Similar airborne exposure in scientific laboratories that study toxigenic algae has been implicated in human toxicity.

Ciguatera, caused by ingested ciguatoxins and maitotoxins, can reportedly be sexually transmitted. There are also reports of acute health effects of ciguatera toxin in the fetus and newborn child exposed through placental and breast milk transmission from the mother. Domoic acid (ASP) has been shown to enter the placenta, accumulate in the amniotic fluid, enter the brain tissue of prenatals, and can be transferred to milk in mammals.

Humans can also be exposed to cyanobacteria and their toxins through direct skin contact or by drinking contaminated water. Other possible routes of exposure include inhalation of contaminated aerosols, consumption of contaminated food, and even through dialysis. Therefore, occupational exposures for fisherman, watermen, and scientists, as well as recreational exposures for the general public, are all possible.

Toxicokinetics

The fate and metabolism of algal toxins is unclear and understudied; however, it is known that the absorption of both lipophilic and hydrophilic algal toxins occurs rapidly from the gastrointestinal and respiratory tracts. For example, to evaluate brevetoxin toxicokinetics from acute inhalation exposure up to

7 days, 12-week-old male F344/Crl BR rats were exposed to a single dose of 6.6 mg kg^{-1} of the brevetoxin PbTx-3 through intratracheal instillation. More than 80% of the PbTx-3 was rapidly cleared from the lung and distributed by the blood throughout the body, particularly the skeletal muscle, intestines, and liver with low but constant amounts present in blood, brain, and fat. Approximately 20% of the toxin was retained in the lung, liver, and kidneys for up to 7 days.

Domoic acid can be absorbed orally at 5–10% of the administered dose. Domoic acid is distributed to the blood, but penetration of the blood–brain barrier is poor. Domoic acid is excreted unchanged in the urine with no evidence of metabolism. Impaired renal function can result in increased blood serum concentrations, residence time, and risk. Elimination half-life ranges from 20 min in rodents to 114 min in monkeys.

Postmortem examinations of patients that have died from PSP via saxitoxin found toxins in blood, urine, bile, cerebrospinal fluid, liver, lung, kidney, stomach, spleen, heart, brain, adrenal glands, pancreas, and thyroid glands with evidence of conversion of saxitoxin to neosaxitoxin and of gonyautoxin 2–3 to gonyautoxin 1–4. There is some evidence for human metabolism of saxitoxin through glucuronidation, a detoxification pathway in humans for metabolically converting xenobiotics to water-soluble metabolites, with excretion occurring in urine and feces.

Absorption of many of the cyanobacterial toxins occurs rapidly from the gastrointestinal tract. Microcystins are selectively transported from the gut and blood into the liver, where they can become concentrated. Microcystins in the liver can persist for up to 6 days; others found in the kidney can remain detectable for up to 24 h.

Acute and Chronic Toxicity and Mechanisms of Action: Algal Toxins

In general terms, people suffering from signs and symptoms of illnesses associated with eating seafood (invertebrates and fish) contaminated with algal toxins typically present the acute onset of gastrointestinal symptoms within minutes to 24 h. Victims may also exhibit a wide range of signs and symptoms involving many organ systems, including respiratory (difficulty breathing), peripheral nervous system (numbness and tingling), central nervous system (hallucinations and memory loss), and cardiovascular system (fluctuating blood pressure and cardiac arrhythmia). These signs and symptoms, depending on the particular disease, may last from hours to months. There are no records of human illnesses from consumption of invertebrates or fish contaminated with freshwater algal or bacterial toxins, although there is evidence of bioaccumulation of bacterial toxins in fish.

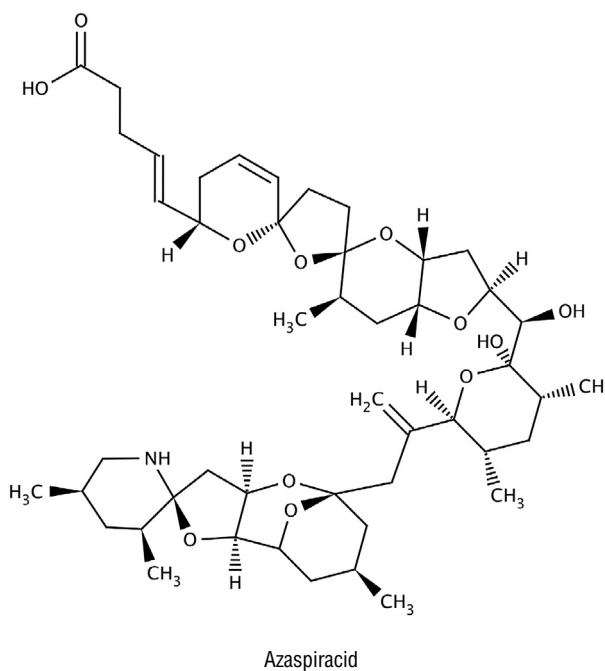
In addition to consumption of contaminated seafood, humans can be exposed to both marine and freshwater algal and bacterial toxins through airborne aerosols and with direct contact with water containing toxins and toxin-producing algae and bacteria, including drinking contaminated water.

Chronic algal toxin exposure remains mostly unstudied, although some limited information about specific toxins is included in the descriptions that follow. On the other hand, exactly how some of these toxins affect cells and tissues

(mechanism of action) have received considerable attention from researchers.

Azaspiracids

Azaspiracid 1 (AZA1, Chemical Abstracts Service (CAS) Registry Number 214899-21-5, $\text{C}_{47}\text{H}_{71}\text{NO}_{12}$) and its 11 analogues, AZA2–AZA12, are polyether, lipophilic toxins produced by the dinoflagellate *Azadinium spinosum*. AZA1–AZA3 tend to be the dominant compounds found in shellfish, followed by AZA4 and AZA5. AZA6–AZA11 are typically minor components and believed to be bioconversion products of the main AZA analogues. Chromatographic studies suggest as many as 32 different analogues, but these are yet to be properly characterized. AZA, first detected in 1995 when consumers of blue mussels (*Mytilus edulis*) imported to the Netherlands from Ireland became ill, accumulates in various bivalve shellfish species, including clams, cockles, scallops, and oysters, and also in crabs. Cases of AZP have since been reported from numerous European countries, including Norway, Sweden, Ireland, England, France, Spain, and Portugal, and Morocco and eastern Canada.



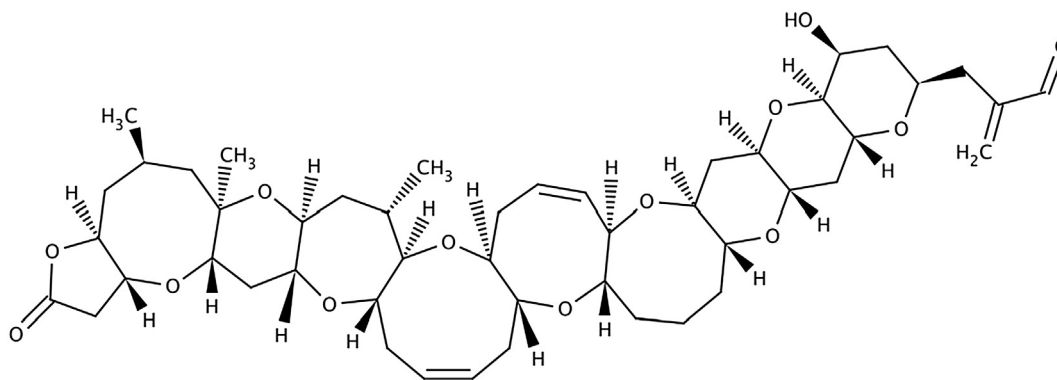
In general, AZA poisoning is rare. Symptom manifestation of acute AZP occurs within hours of ingestion of contaminated shellfish and includes nausea, vomiting, severe diarrhea, and stomach cramps, which are similar to the symptoms associated with DSP. Illness may persist for several days, and full recovery was established for the 1997 Arranmore Island incident. No long-term effects or illnesses have been reported.

Intraperitoneal (IP) minimum lethal dose of partially purified AZA in mice was $150 \text{ } \mu\text{g kg}^{-1}$ and of purified AZA1, AZA2, and AZA3, the minimum lethal doses were 200, 110, and $140 \text{ } \mu\text{g kg}^{-1}$, respectively. The oral minimum lethal dose of

AZA varies between 250 and 450 $\mu\text{g kg}^{-1}$, depending on mouse age. Toxicological studies conducted using mice revealed that AZA targets the liver, lung, pancreas, thymus, spleen (T and B lymphocytes) and digestive tract. AZA1 has been shown to be cytotoxic to a range of cell types, particularly neurons, and a potent teratogen to finfish. AZA4 inhibits plasma membrane Ca^{2+} channels. Chronic effects observed in mice after oral administration of AZA were interstitial pneumonia, shortened villi in the stomach and small intestine, fatty changes in the liver, and necrosis of lymphocytes in the thymus and spleen.

Brevetoxins

Brevetoxin A (PbTx-1, CAS 98225-48-0, $\text{C}_{49}\text{H}_{70}\text{O}_{13}$) and its analogues, PbTx-2, PbTx-3, PbTx-4, PbTx-5, PbTx-6, PbTx-7, PbTx-8, and PbTx-9, are cyclic polyether, lipophilic toxins produced by *K. brevis*, formerly known as *Gymnodinium breve*, and *Ptychodiscus brevis*. PbTx-1 and PbTx-1 are believed to be the parent algal toxins from which PbTx-3 through PbTx-9 are derived. PbTx-2 is the most common form, while PbTx-1 is the most potent of the brevetoxins. Brevetoxins are known to accumulate in various shellfish species, such as oysters, clams, and mussels. They are not toxic to shellfish but are toxic to fish, marine mammals, birds, and humans, in which consumption of brevetoxin-contaminated shellfish causes NSP. Most cases of NSP have occurred in the coastal waters of New Zealand and in the Gulf of Mexico during 'red tide' events, but NSP intoxication has been identified worldwide.



Brevetoxin A

Brevetoxins are neurotoxins which activate voltage-sensitive sodium channels causing sodium influx and nerve membrane depolarization. Brevetoxins cause biphasic cardiovascular response with hypotension and bradycardia followed by hypertension and tachycardia. The respiratory arrest induced by a lethal dose results mainly from depression of the central respiratory center. Although evidence suggests that brevetoxins affect mammalian cortical synaptosomes and neuromuscular preparations, the majority of toxic effects associated with brevetoxins predominantly appear to result from the substantial and persistent depolarization of nerve membranes. In the lung, brevetoxin appears to be a potent respiratory toxin involving both cholinergic and histamine-related mechanisms.

The two forms of brevetoxin-associated clinical effects first characterized in Florida are (1) an acute gastroenteritis with

neurologic symptoms following ingestion of contaminated shellfish (a.k.a., NSP) and (2) an apparently reversible upper respiratory syndrome (conjunctival irritation, copious catarrhal exudates, rhinorrhea, nonproductive cough, and bronchoconstriction) following inhalation of contaminated aerosols. Recovery is reportedly complete in a few days, although persons with chronic pulmonary disease such as asthma may experience more severe and prolonged respiratory effects. In addition, skin and eye irritation by environmental exposures among people living or visiting Florida during *K. brevis* bloom has been reported. NSP and the respiratory irritation associated with aerosolized brevetoxins have both been reported along the Gulf of Mexico as well as far north as North Carolina; similar brevetoxin-associated syndromes have been reported in New Zealand.

After oral ingestion, brevetoxin poisoning (or NSP) is characterized by a combination of gastrointestinal and neurologic signs and symptoms. The incubation period ranges from 15 min to 18 h. Gastrointestinal symptoms include abdominal pain, vomiting, and diarrhea. Neurological symptoms include paresthesias, reversal of hot and cold temperature sensation, vertigo, and ataxia. Inhalational exposure to brevetoxin results in cough, dyspnea, and bronchospasm. Persons exposed to aerosolized brevetoxins may suffer shortness of breath, sneezing, and other allergy and asthma-like symptoms. Those with preexisting airway disease appear most likely to be affected. During swimming, direct contact with the toxic blooms may take place and eye and

nasal membrane irritation can occur. No fatalities have been reported but there are a number of cases, which led to hospitalization.

Fish, birds, and mammals are all susceptible to brevetoxins. In Japanese medaka fish (*Oryzias latipes*), brevetoxins induce embryonic toxicity and developmental abnormalities. The fish are killed apparently through lack of muscle coordination and paralysis, convulsions, and death by respiratory failure. In the mosquito fish (*Gambusia affinis*) bioassay, the lethal dose (LD_{50}) is reported at 0.011 mg l^{-1} . Exposed birds die acutely with neurologic and hematologic effects. Brevetoxins were implicated in the deaths of manatees in Florida during a widespread bloom of *G. breve*. At necropsy, the animals did not appear to be unhealthy, and they had recently fed. High levels of brevetoxin were found by

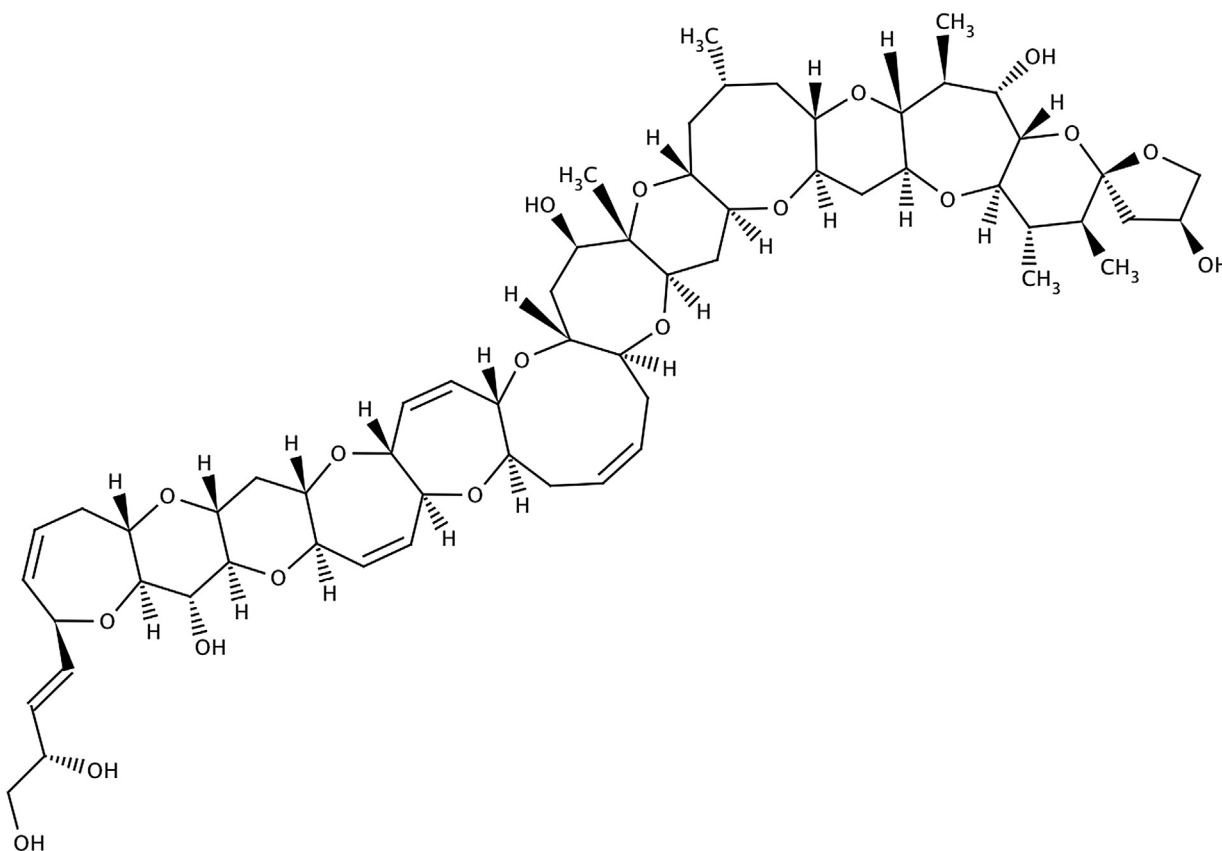
histochemical stain in cells throughout the body, particularly macrophages.

The mouse LD₅₀ of brevetoxins ranges 170–400 µg kg⁻¹ body weight (bw) IP, 94 µg kg⁻¹ bw intravenously, and 520–6600 µg kg⁻¹ bw orally.

Ciguatoxins

Ciguatoxin 1 (CTX-1, CAS 11050-21-8, C₆₀H₈₆O₁₉) and its analogues (more than 20 identified to date) are lipid-soluble

America and Northern Europe. Ciguatoxins accumulate in benthic-feeding organisms and pass up the food chain, bioconcentrating in top-predator (apex, piscivorous) reef fishes, especially in fatty tissues, liver, viscera, and eggs. Ciguatoxins are relatively heat stable, remaining toxic after cooking and following exposure to mild acids and bases. Ciguatoxins arise from biotransformation in the fish of precursor gambiertoxins and less polar ciguatoxin. The primary Pacific ciguatoxin is Pacific ciguatoxin 1 (P-CTX-1) and the primary Caribbean form is C-CTX-1.



Ciguatoxin-1

polyether compounds produced by members of the dinoflagellate genus *Gambierdiscus*, not only including *Gambierdiscus toxicus* but also many other 'cryptic' *Gambierdiscus* species. Unlike open-water red tides, *Gambierdiscus* spp. tend to be benthic or epiphytic, often associated with the quiet waters of mangrove systems, leeward sides of coral reefs, and even man-made structures including petroleum platforms and artificial reefs that serve as benthic habitat within the euphotic (lighted) zone and fish aggregation areas. The most commonly reported marine toxin disease in the world is CFP or ciguatera. CFP outbreaks typically occur in a circumglobal belt extending approximately from latitude 35° N to 34° S, which includes Hawaii, the South Pacific including Australia, the Caribbean, and the Indo-Pacific, although the transport of contaminated fish and tourism have led to cases of CFP in both North

Ciguatera presents primarily as an acute neurologic disease manifested by multiple gastrointestinal (diarrhea, abdominal cramps, and vomiting) and cardiovascular (arrhythmias and heart block) signs and symptoms within a few hours of contaminated fish ingestion, followed by neurologic manifestations (paresthesias, pain in the teeth, pain on urination, blurred vision, and temperature reversal) within hours to days. Neurologic symptoms may precede the gastrointestinal symptoms in Pacific CFP. Acute fatality usually due to respiratory failure, circulatory collapse, or arrhythmias is reported. Lethality is usually seen with ingestion of the most toxic parts of fish (liver, viscera, roe). The minimal lethal dose for a person weighing 165 lbs is less than 1 µg kg⁻¹. Those surviving ciguatera intoxication, especially in the Caribbean, suffer for weeks to months with debilitating neurologic symptoms,

including profound weakness, temperature sensation changes, pain, and numbness in the extremities. Affected mothers have been reported to transmit ciguatoxins through breast milk, and some evidence suggests that the disease may also be transmitted through semen.

Chronic ciguatera can present as a psychiatric disorder of general malaise, depression, headaches, muscular aches, and peculiar feelings in extremities for several weeks to months. This may be due to prolonged debilitating paresthesias ranging from extreme fatigue to pain in the joints and changes in temperature sensation that can last from weeks to months and possibly to years. It is reported anecdotally that those with chronic symptoms seem to have recurrences of their symptoms with the ingestion of fish (regardless of type), ethanol, caffeine, and nuts up to 3–6 months from initial ingestion of ciguatera. Ciguatoxins are reported to induce developmental toxicity in Japanese medaka fish (*O. latipes*).

Lipid-soluble ciguatoxins and brevetoxins have immunologic cross-reactivity and thus have similar epitopic sites and mechanisms of action, as described in the previous section. Ciguatoxins activate voltage-sensitive sodium ion channels in nerve and muscle tissues, leading to cell membrane instability. P-CTX-1 is the most polar and toxic form of ciguatoxins, causing CFP in humans ingesting fish with levels at or above $0.1 \mu\text{g kg}^{-1}$ fish flesh. The LD_{50} in mice for ciguatoxin P-CTX-1, P-CTX-2, and P-CTX-3 is 0.25, 2.3, and $0.9 \mu\text{g kg}^{-1}$ bw when injected IP. The minimal lethal dose for a person weighing 165 lbs is less than $1 \mu\text{g kg}^{-1}$. C-CTX-1 is less polar and 10 times less toxic than P-CTX-1.

Maitotoxins

Maitotoxin (MTX-1, CAS 59392-53-9, $\text{C}_{164}\text{H}_{256}\text{O}_{68}\text{S}_2\text{Na}_2$) and its analogues (MTX-2 and MTX-3) are water-soluble polyether compounds produced by the dinoflagellate *G. toxicus*. Maitotoxin precursors are also produced by *Prorocentrum* spp., *Ostereopsis* spp., *Coolia monotis*, *Thecadinium* spp., and *Amphidinium carterae*. Maitotoxins, named from the ciguateric fish *Ctenochaetus striatus* called 'Maito' in Tahiti from which maitotoxin was first isolated, are biotransformed to ciguatoxins by herbivorous fishes and invertebrates that graze on *G. toxicus*.

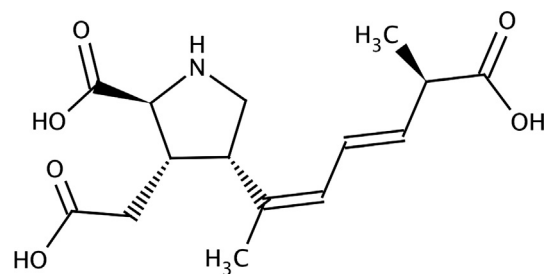
Like ciguatoxins, maitotoxins bioaccumulate as they move up the food chain into higher trophic levels.

Maitotoxin is yet another toxin which is believed to cause ciguatera but with different symptoms than those caused by ciguatoxins. In smooth muscle and skeletal muscle exposed *in vitro*, maitotoxins cause calcium ion-dependent contraction. Maitotoxins increase the calcium ion influx through excitable membranes, causing cell depolarization, hormone and neurotransmitter secretion, and breakdown of phosphoinositides (important in regulating the function of integral cell membrane proteins). The calcium-dependent action of maitotoxins occurs in the absence of sodium ions and in the presence of tetrodotoxin, precluding the participation of sodium channels.

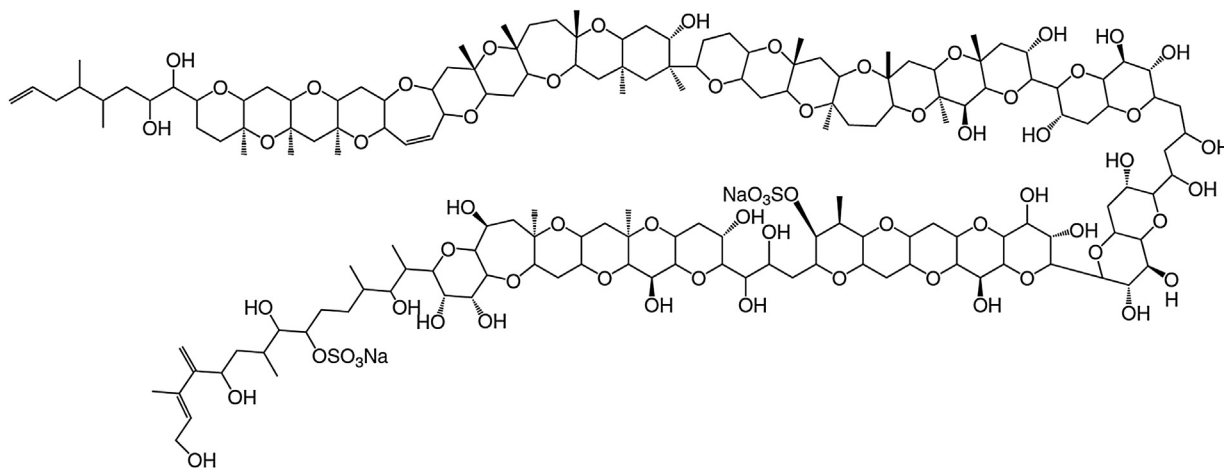
MTX is considered one of the most potent toxins (by weight) known with a mouse LD_{50} of $0.13 \mu\text{g kg}^{-1}$ IP.

Domoic Acid

Domoic acid (DA, CAS 14277-97-5, $\text{C}_{15}\text{H}_{21}\text{NO}_6$), identified as the causative agent of ASP, is primarily produced by diatoms of the genus *Pseudo-nitzschia* but is also produced by members within the diatom genera *Amphora* and *Nitzschia* and some members within the red algae genera *Alsidium*, *Amansia*, *Chondria*, *Digenea*, and *Vidalia*. It was first isolated from the red alga *Chondria armata*, commonly known as 'Domoï', in 1959 and was used as an effective anthelmintic. Domoic acid consists of a proline ring, three carboxyl groups, and an imino group that can appear in five charged states depending on pH. It is



Domoic acid

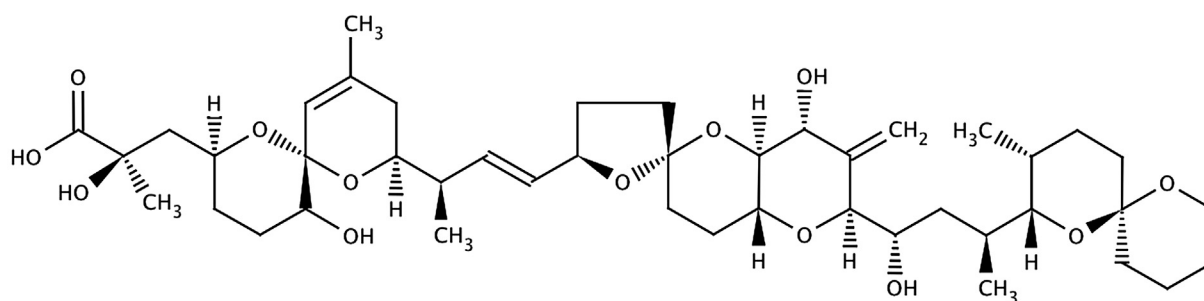


Maitotoxin

a water-soluble amino acid (nonprotein) and is structurally similar to kainic acid, glutamic acid, and aspartic acid.

The toxin accumulates in the hepatopancreas of mussels, scallops, and other filter-feeding shellfish. Heat-stable neurotoxic DA is similar in structure to the excitatory dicarboxylic amino acid, kainic acid, and has an antagonistic effect at the glutamate receptor. Domoic acid interacts with glutamate receptors on nerve cell terminals, causing excitotoxicity that can lead to neuronal cell damage or death from an excessive influx of Ca^{2+} . This is caused by coactivation of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and especially kainate receptors for which DA has a high affinity. For the kainate receptors, the efficacy with which DA binds is thought to be the result of a nondesensitization of the channel.

In 1998, DA toxicity was reported in California sea lions. Predominantly neurological signs were observed, which included severe seizures that resulted in opisthotonus (spasm in which the head, neck, and back are arched backward), then death. Domoic acid has also been implicated in the deaths of marine mammals and birds in the Pacific Northwest of the US coast.



Okadaic acid

DA exposure studies have been conducted on monkeys, mice, rats, birds, and fish including IP injections, direct brain injections, and intravenous, intraarterial, intrauterine, and oral dosing. Symptoms include vomiting, seizures, and memory loss in humans, vomiting in monkeys, scratching and seizures in mice, tremors in birds, and spiral swimming in fish.

Human toxicity results primarily from consuming contaminated shellfish and one of the most prominent features of human toxicity is memory loss, hence the name 'amnesic shellfish poisoning.' ASP was first described from an outbreak in Canada in 1987 during which 143 people became affected and 4 died from eating contaminated shellfish cultivated from Prince Edward Island. Since that time, DA contamination of shellfish stocks and the associated ASP has become a global problem coming to the attention of numerous monitoring programs and food safety regulatory agencies (including the World Health Organization) in affected coastal regions of Europe, Australia, and New Zealand, the east coast of Asia and Japan, and the west coast of North America.

The acute symptoms of ASP caused by DA include vomiting, abdominal cramps, diarrhea, severe headache, and loss of

short-term memory. In some cases, confusion, memory loss, disorientation, and even coma are reported. In addition, seizures and myoclonus are observed acutely. Permanent neurologic sequelae, especially cognitive dysfunction, were reportedly most likely in persons who developed neurologic illness within 48 h, males, in older patients (>60 years) and in younger persons with preexisting illnesses such as diabetes, chronic renal disease, and hypertension with a history of transient ischemic attacks.

The mouse LD_{50} of DA is 3.6 mg kg^{-1} when injected IP.

Okadaic Acid

Okadaic acid (okadeic acid, okadaic acid, OA, CAS 78111-17-18, $\text{C}_{44}\text{H}_{68}\text{O}_{13}$) and its analogues dinophysistoxin-1 (DTX-1, CAS 81720-10-7, $\text{C}_{45}\text{H}_{70}\text{O}_{13}$) and dinophysistoxin-2 (DTX-2, CAS 139933-46-3 $\text{C}_{44}\text{H}_{68}\text{O}_{13}$) are lipophilic, polyether toxins produced by various dinoflagellates in the genera *Prorocentrum* (e.g., *P. lima*, *P. arenarium*, *P. hoffmannianum*, *P. maculosum*, *P. faustiae*, *P. levis*, and *P. belizeanum*) and *Dinophysis* (e.g., *D. acuta*, *D. acuminata*, *D. caudata*, *D. fortii*, *D. miles*, *D. norvegica*, *D. rapa*, and *D. sacculus*).

Toxins within the OA group are responsible for provoking DSP in humans after the consumption of shellfish that have accumulated these toxins in their digestive gland. OA was originally isolated from marine sponges of the genus *Halichondria* and DTX-1 and -2 were first isolated from mussels. OA and DTXs are polyketide compounds containing furane- and pyrane-type ether rings and an α -hydroxycarboxyl function differing only in the number or position of the methyl groups. Many derivatives of these parent toxins have been described after being found in shellfish and algae, including OA esters, okadaates, OA-diol-esters (e.g., acylated derivatives with fatty acids in the DTX-3 group, primarily with hexadecanoic acid, diol-esters formed in the unsaturated diols, and esterification of the diol-esters with sulfated chains with or without and amide function in the DTX-4 and DTX-5a-c groups) and other compounds that comprise changes to the OA backbone (e.g., norokadanone, 19-epi-OA, and belizeanic acid). Prorocentrin is another compound that shows similarity with OA that is produced by *P. lima*. Of particular interest is the fact that significant portions of the toxins found in bivalves are the acylated derivatives. These derivatives may be a product of animal metabolism not produced directly by the algae and they show increased liposolubility when compared to their parent toxins.

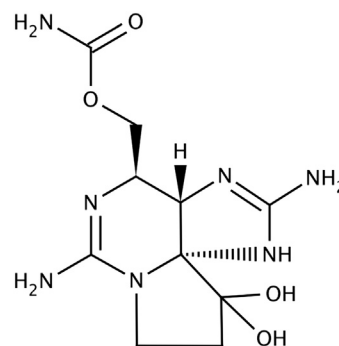
DSP was first identified in 1978 after a series of food poisonings resulting from eating contaminated mussels and scallops in the Tohoku district of Japan affected 164 individuals. DSP outbreaks have been predominantly reported in Japan, Europe, and Australia, but cultures of *P. lima* isolated from the gulf of California and Mexico are capable of producing toxin. Thus the problem is generally considered to be a worldwide phenomenon. Toxins within the OA group can withstand mildly acidic to strongly basic pH but degrade rapidly in strong mineral acids. However, without acid, OA group compounds are largely stable to heat and are not degraded with normal cooking procedures and contaminated foods may serve to buffer against degradation of the toxins by the gastric juices. Compounds within the OA group produce toxic effects on hydrolysis within the human digestive tract. They are inhibitors of the serine/threonine protein phosphatases 1 (PP1) and 2A (PP2A), enzymes responsible for dephosphorylation of proteins, which are essential to metabolic processes in eukaryotic cells. Symptoms of DSP poisoning are nausea, diarrhea, vomiting, and abdominal pain starting within 3–12 h of initial consumption. Although originally the cause of the symptoms of diarrhea were thought to be caused by sodium secretion of intestinal cells, an increase in the paracellular permeability of intestinal cells by the toxins is now thought to be the likely cause of diarrhea. The Report of the Joint Food and Agriculture Organization of the United Nations, Intergovernmental Oceanographic Commission of United Nations Educational, Scientific, and Cultural Organization (UNESCO), and World Health Organization ad hoc Expert Consultation on Biotoxins in Bivalve Molluscs established a lowest observed adverse effect level (LOAEL) of $1 \mu\text{g OA kg}^{-1}$ bw. They established a provisional acute reference dose of $0.33 \mu\text{g OA kg}^{-1}$ bw. Most individuals recover within 3 days, and there have been no reported long-term effects or deaths reported due to acute DSP poisoning. However, these toxins have been shown to be tumor promoters and ancillary evidence has associated these toxins with digestive cancer. Additionally, there is evidence for cytotoxicity and potentially genotoxicity including formation of unspecific DNA adducts.

The LD_{50} for mouse injected IP for OA is $0.2\text{--}0.225 \text{ mg kg}^{-1}$ bw, for DTX-1 is 0.16 mg kg^{-1} bw, for DTX-2 is 0.35 mg kg^{-1} bw, and for DTX-3 is $0.2\text{--}0.5 \text{ mg kg}^{-1}$ bw. However, IP doses have been shown to have little effect on the digestive tract, primarily affecting the liver. Lethal oral doses have been reported for mouse from 2 to 10 times higher than the IP dose.

Saxitoxins

Saxitoxins (STXs, PSTs, CAS 35523-89-8, $\text{C}_{10}\text{H}_{17}\text{N}_7\text{O}_4$) are a group of neurotoxic purine alkaloids that are responsible for causing PSP in humans after consumption of contaminated shellfish or other seafood, particularly lobster and puffer fish (not to be confused with poisonings caused by tetrodotoxin). STXs responsible for most reports of PSP are primarily produced by dinoflagellates of the genera *Alexandrium* (*A. fundyense*, *A. catenella*, *A. tamarensis*, *A. hiranoi*, *A. monilatum*, *A. minutum*, *A. lusitanicum*, *A. tamiyavanichii*, *A. taylori*, and *A. peruvianum*), *Gymnodinium* (*G. catenatum*), and *Pyrodinium* (*P. bahamense*) but can also be produced by some species of cyanobacteria (see below) in the genera *Anabaena* (*A. circinalis* and

A. lemmermannii), *Aphanizomenon* (*A. gracile* and *A. issatschenkoi*), *Cylindrospermopsis* (*C. raciborskii*), *Lyngbya* (*L. wollei*), *Planktothrix*, and *Rivularia*. There are suggestions that saxitoxins may actually have a bacterial origin, but the evidence is inconclusive at this point.



Saxitoxin

Substitutions with different hydroxyl, carbamyl, and sulfate functional groups at four sites along the backbone structure have resulted in the identification of at least 24 saxitoxin-like compounds that can vary by more than three orders of magnitude in toxicity. The most toxic of these are the carbamate toxins (saxitoxin (STX), neosaxitoxin (NEO), and gonyautoxins 1–4 (GTX)) followed by the decarbamoyl toxins (dcSTX, dcNEO, dcGTX 1–4, not common) and the *N*-sulfo-carbamoyl toxins (B1 [GTX5], B2 [GTX6], and C1–C4), respectively. A fourth group of toxins, the hydroxybenzoate toxins, are produced by *G. catenatum* (GC 1–3), but more research needs to be conducted to determine the extent of their toxicity. Saxitoxin is the most well-studied member of this group.

The first PSP event on record occurred in 1927 in San Francisco, USA, coinciding with a bloom of the *A. catenella*, affecting 102 people and causing 6 deaths. However, saxitoxin was first isolated from butter clams, *Saxidomus giganteus*. The problem is now known to be a worldwide, having been reported in 27 locations by 1990. STXs are heat and acid stable, thus cooking the seafood does not denature the toxins. Saxitoxin acts by specifically and selectively binding to voltage-gated sodium channels on excitable cells functionally blocking sodium conductance and preventing impulse generation in peripheral nerves and skeletal muscles. STX exposure studies have been conducted on cats, chickens, dogs, guinea pigs, monkeys, mice, rats, birds, and rabbits including IP injections, intravenous injections, inhalation, and oral dosing. Saxitoxin can also block action potentials directly in skeletal muscles. Symptoms of poisoning generally occur within 30 min of consuming contaminated seafood including tingling sensations of the lips, mouth, and tongue, numbness of extremities, paresthesias, weakness, ataxia, floating/dissociative feelings, nausea, shortness of breath, dizziness, vomiting, headache, dysphagia, dysarthria, diastolic and systolic hypertension, and death. Death is caused by asphyxiation. Onset of symptoms has been reported as starting within a few minutes of seafood consumption, and death has been reported within 3–4 h of consumption. Medical treatment consists of providing

respiratory support and fluid therapy. Humans typically start to recover within 12–24 h with no long-lasting effects; however, little if anything is known about the chronic effects of these toxins. Currently, STX is strictly regulated by the Organization for the Prohibition of Chemical Weapons listed as a schedule 1 chemical intoxicant.

The Report of the Joint Food and Agriculture Organization of the United Nations, Intergovernmental Oceanographic Commission of UNESCO, and World Health Organization ad hoc Expert Consultation on Biotoxins in Bivalve Molluscs established an LOAEL of $2 \mu\text{g STX kg}^{-1} \text{ bw}$ and a provisional acute reference dose of $0.7 \mu\text{g STX kg}^{-1} \text{ bw}$. Generally, the action limit for STX for most seafood and shellfish is $0.8 \text{ mg STX equivalents per kilogram of tissue}$ that has been accepted by many regulatory agencies worldwide. This standard has been in place for approximately 50–60 years. Recently, the European Food Safety Authority suggested a level of $75 \mu\text{g STX equivalents per kilogram of tissue}$. The mouse bioassay is the primary determinant of PSP toxins in shellfish for most regulatory agencies. The LD_{50} for mice injected peritoneally for STX is $0.008 \text{ mg kg}^{-1} \text{ bw}$, injected intravenously is $8.5 \text{ mg kg}^{-1} \text{ bw}$, and administered orally is $263 \text{ mg kg}^{-1} \text{ bw}$.

Acute and Chronic Toxicity and Mechanisms of Action: Cyanobacterial Toxins

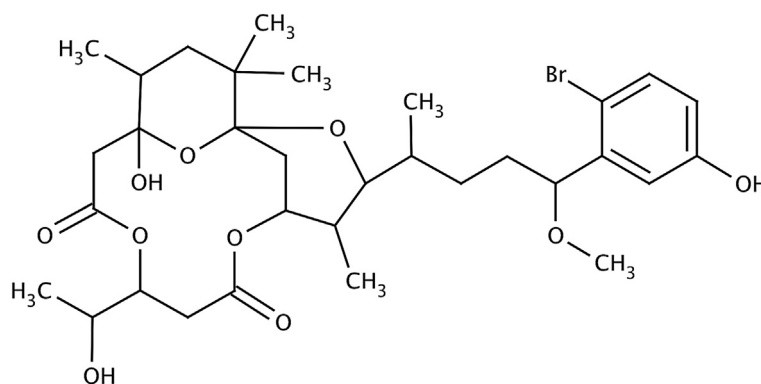
There are at least 13 different genera of cyanobacteria that have been shown to produce toxins, often several different toxins per species. The main toxin-producing genera include *Anabaena*, *Aphanizomenon*, *Cylindrospermopsis*, *Gloeotrichia*, *Hapalosiphon*, *Lyngbya*, *Microcystis*, *Nodularia*, *Nostoc*, *Oscillatoria*, *Schizothrix*, *Spirulina*, and *Synechocystis*. Toxic blooms of cyanobacteria with associated animal poisonings have been reported in all continents except Antarctica. There have been frequent reports of thirsty domestic animals and wildlife consuming fresh water contaminated with toxic cyanobacterial algal blooms and dying within minutes to days from acute neurotoxicity and/or

morbidity and mortality have been reported in animals exposed to cyanobacterial algae in the wild.

There are individual case reports of persons exposed through swimming to cyanobacterial algal blooms with skin irritation and allergic reactions (both dermatologic and respiratory) with continued positive reaction on skin testing. In particular, urticaria (hives), blistering, and even deep desquamation of skin in sensitive areas like the lips and under swimsuits have been reported, especially with *Lyngbya majuscula* in tropical areas. Consumption of or swimming in cyanobacterial toxin-contaminated waters has also yielded increased case reports of gastrointestinal symptoms, especially diarrhea. One severe outbreak in Brazil was associated with lethality from hepatotoxicity in dialysis patients exposed to water contaminated with microcystins; another outbreak in Australia was also associated with lethality from hepatorenal syndrome in children and adults exposed to contaminated drinking water. In addition to gastrointestinal and dermatologic symptoms, eye irritation, asthma, and 'hay fever symptoms' have been reported repeatedly with exposure to contaminated recreational water exposure in the United States, Canada, the United Kingdom, and Australia. The chronic effects of exposure to small quantities of cyanobacterial algal toxins are still under study. In the mid-1980s, studies were done in China, where people were drinking untreated water contaminated with cyanobacterial algal toxins. It was found that drinking contaminated pond and ditch water was associated with high rates of liver cancer. When the quality of drinking water sources was improved in these areas, the rate of liver cancer decreased. The incidence of liver cancer attributable to cyanobacterial algal toxins in the United States is unknown.

Aplysiatoxins

Aplysiatoxins (CAS 52659-57-1, $\text{C}_{32}\text{H}_{47}\text{BrO}_{10}$) and debromoaplysiatoxins are alkyl phenols produced by *Lyngbya gracilis*, *L. majuscula*, *Calothrix crustacean*, *Nostoc muscorum*, *Schizothrix calcicola*, and *S. muscurom*.



Aplysiatoxin

hepatotoxicity. Mammals and birds appear to be more susceptible to cyanobacterial algal toxins than aquatic invertebrates and fish, with some species variability. Prolonged

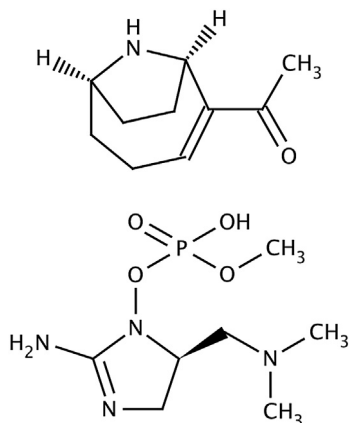
Aplysiatoxins can cause severe skin dermatitis and are potent tumor promoters and protein kinase C activators. Aplysiatoxins and debromoaplysiatoxins from blue-green

algae attached to seaweed (*Gracilaria coronopifolia*) are suspected of causing gastrointestinal symptoms, including diarrhea, nausea, and vomiting in a poisoning case in Hawaii in 1994. Mouse studies have shown small intestinal bleeding and large intestinal edema following toxic injections of aplysiatoxin.

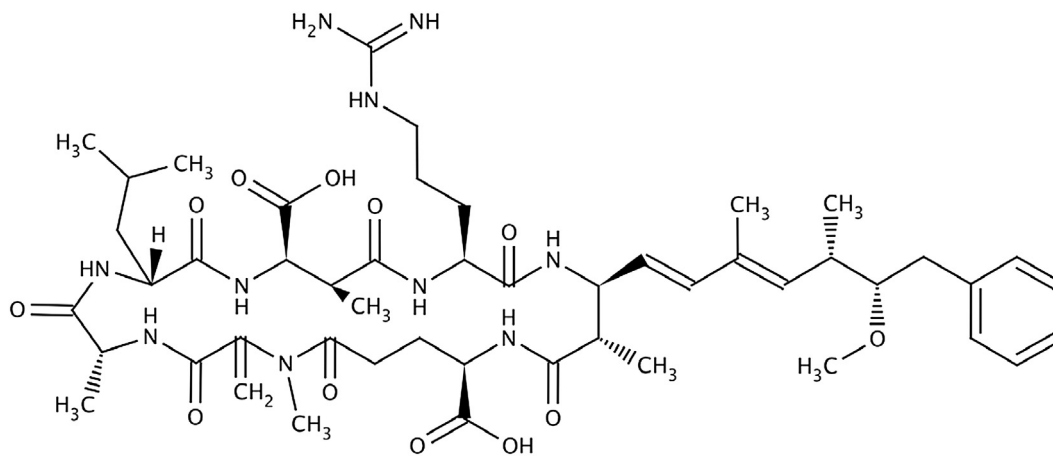
The mouse LC_{50} of aplysiatoxin is $118 \mu\text{g kg}^{-1}$, IP.

Anatoxins

Anatoxins, are alkaloid neurotoxins, represented here by anatoxin-A (CAS 64285-06-9, $C_{10}H_{15}NO$) and anatoxin-A (S) (CAS 103170-78-1, $C_7H_{17}N_4O_4P$), produced by species of the genera *Anabaena*, *Planktothrix*, *Cylindrospermum*, *Aphanizomenon*, and *Phormidium*.



Anatoxin-A and Anatoxin-A (S)



Microcystin-LR

To date, only cattle, dog, and bird poisonings have been documented. Anatoxin-A acts like the neurotransmitter acetylcholine, except that it cannot be degraded by acetylcholinesterase. Anatoxin-A (S) is a natural organophosphate that binds to acetylcholinesterase enzymes, resulting in uncontrolled muscle hyperstimulation. Hypersalivation, lacrimation, and

urinary incontinence, signs of parasympathetic stimulation, characterize anatoxin-A (S) poisoning.

Anatoxin-A and Anatoxin-A (S) have mouse LC_{50} of 250 and $40 \mu\text{g kg}^{-1}$, IP.

Saxitoxins

Saxitoxin and neosaxitoxin are both neurotoxins that may also be classified as cyanobacterial toxins. See above for details.

Microcystins

Microcystins, of which there are at least 80 variants, are based on a cyclic heptapeptide structure. Toxic variants contain the unique hydrophobic amino acid, 3-amino-9-methoxy-10-phenyl-2,6,8-trimethyl-deca-4(E),6(E)-dienoic acid (ADDA), and are represented by the prototype compound microcystin-LR or cyanoginosin LR; CAS 101043-37-2, $C_{49}H_{74}N_{10}O_{12}$. Microcystins are produced by a wide variety of planktonic cyanobacteria, including *Microcystis aeruginosa*, *M. viridis*, *M. ichthyoblabe*, *M. botrys*, *Planktothrix agardhii*, *P. rubescens*, *P. mougeotii*, *Anabaena flos-aquae*, *A. cirinalis*, *A. lemmermannii*, *Nostoc* spp., and *Snowella lacustris*, as well as the benthic cyanobacteria *Hapalosiphon hibernicus* and *Oscillatoria limosa*.

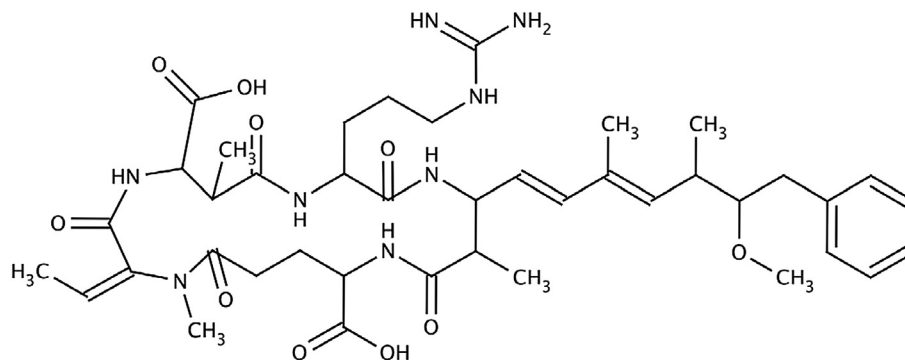
Experimentally, acute high-dose administration of microcystin can lead to death from hepatoencephalopathy within hours. Chronic administration of sublethal amounts of *Microcystis* (a cyanobacterial algae which produces microcystin) extracts in drinking water to mice resulted in increased mortality with chronic active liver disease, even at fairly low

doses and in relatively short time periods in the laboratory. Studies in mice have also shown that some cyanobacterial algal toxins cause precancerous damage to both the liver and the bowel. In the laboratory experimental animals, teratogenic activity has been demonstrated with oral administration of *Microcystis* extracts; ~10% of otherwise normal neonatal mice had small brains with extensive hippocampal neuronal damage.

Poisoning by microcystins can lead to visual disturbances, nausea, and vomiting. Acute exposure can lead to liver failure and death within hours to days. Microcystins inhibit protein phosphatases, particularly PP1 and PP2A, resulting in hyperphosphorylation of many cellular proteins, including the hepatocellular cytoskeleton, causing loss of cell-to-cell contact and intrahepatic hemorrhaging. Other effects include altered mitochondrial membrane permeability, generation of reactive oxygen species, and initiation of programmed cell death (apoptosis). Microcystins are also believed to cause damage to cell DNA by the activation of endonucleases and have been linked to human liver and colon cancer. Microcystin-LR has an LC_{50} of $60 \mu\text{g kg}^{-1}$ IP in mice.

Nodularins

Nodularin (CAS 118399-22-7, $C_{41}H_{60}N_8O_{10}$), a cyclic pentapeptide toxin similar to microcystin, was first isolated from *Nodularia spumigena*. Because this species tends to inhabit brackish waters, humans generally are at low risk to exposure through drinking waters.



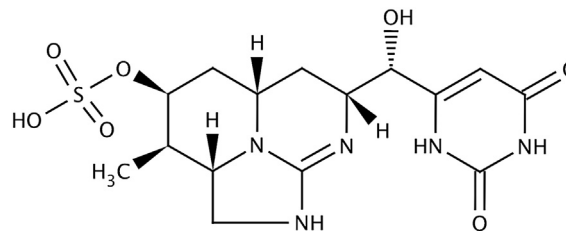
Nodularin

ADDA is present in nodularins, as in microcystins, but other amino acids are different. For example, dehydroalanine is replaced by *N*-methyl-dehydrobutyrine. The presence of ADDA results in similar phosphatase inhibition and the many subsequent effects as seen in microcystins. The smaller size of nodularins prevents the molecule from binding covalently to active sites (as seen in microcystins), allowing nodularins to affect other sites in cells, and possibly explaining observed carcinogenic effects. Nodularin has a mouse LC_{50} of $60 \mu\text{g kg}^{-1}$, IP.

Cylindrospermopsin

Cylindrospermopsin (CAS 143545-90-8, $C_{15}H_{21}N_5O_7S$), a cyclic guanidine alkaloid, with at least three variants, is

produced by *Cylindrospermopsis raciborskii*, *Aphanizomenon ovalisporum*, *Anabaena bergii*, *Umezakia natans*, *Raphidiopsis curvata*, and other unidentified species.



Cylindrospermopsin

Cylindrospermopsins are included in the cyanobacterial hepatotoxin group which blocks protein synthesis. Acute exposure to cylindrospermopsin results in lipid accumulation in the liver followed by hepatocellular necrosis. Other organs are also affected with widespread necrosis of the tissues of the kidneys, bladder, ureter, and spleen. Cylindrospermopsin has a delayed toxicity, with an LC_{50} of $2100 \mu\text{g kg}^{-1}$ IP in mice at 24 h, but $200 \mu\text{g kg}^{-1}$ after 5 days.

Other Cyanobacterial Toxins

A large variety of other toxins are produced by cyanobacteria but are not as well documented. These include lyngbyatoxin (dermatotoxic), endotoxins, and other substances as yet undescribed, including additional tumor promoters.

Acute and Chronic Toxicity and Mechanisms of Action: Other Toxins

Numerous other algal toxins have been described. Many are believed to play important roles in prey capture and predator avoidance. These compounds tend to be ichthyotoxic, but their toxicity to humans is less certain than the toxins described above.

Cyclic Imines

Cyclic imines, including gymnodimine (GYM), spirolides (SPX), pinnatoxins (PnTx), procochlorolide, and spirocentrimine, are fast-acting toxins. The presence of this group of compounds in shellfish was discovered because of their very high acute toxicity in mice upon IP injections of lipophilic extracts. All the cyclic

imines for which data are available are toxic to mice after IP administration. Mouse LC_{50} values for GYMs range 6.5–100 $\mu\text{g kg}^{-1}$, for SPX, 6.5–8 $\mu\text{g kg}^{-1}$, and for PnTx, 16–45 $\mu\text{g kg}^{-1}$. There is no evidence that any of the cyclic imines have been responsible for toxic effects in humans.

Dinophysistoxin

See OA.

Golden Algal Toxins

Blooms of algal genera within the Prymnesiophyceae, notably species of *Prymnesium*, *Chrysochromulina*, and *Phaeocystis*, and the Raphidophyceae, primarily species of *Chattonella*, *Heterosigma*, and *Fibrocapsa*, are well known for massive fish kills that have led to great economic losses, but no cases of human toxicity have been reported. Four species of *Prymnesium* are reported to be toxic to vertebrates or invertebrates and toxicity in two other species is suspected. Several hemolytic compounds termed 'prymnesins' have been described in *P. parvum*, but have yet to be fully characterized. These include several galactolipids and two polyoxy-polyene-polyethers (prymnesin-1 and -2). Mouse LC_{99} values for prymnesins-1 and prymnesins-2 were 50 and 80 $\mu\text{g kg}^{-1}$; LC_{50} values for the fish *Tanichthys albonubes* were 8 and 9 nM.

A different assemblage of ichthyotoxic polyunsaturated fatty acids and their conjugated galactoglycerolipid progenitors, consisting primarily of stearidonic acid ($LC_{50} = 21.9 \mu\text{M}$, 10- to 14-day-old fry of the fish *Pimephales promelas*), and including docosahexanoic acid ($LC_{50} = 4.7 \mu\text{M}$), arachidonic acid ($LC_{50} = 9.2 \mu\text{M}$), pinolenic acid ($LC_{50} = 18.2 \mu\text{M}$), and eicosapentaenoic acid ($LC_{50} = 23.6 \mu\text{M}$), was identified in laboratory cultures of *P. parvum*. Some of these toxins were present in bloom and fish kill sites, but below toxic concentrations. Instead a different, yet-characterized, ichthyotoxic fatty acid was detected. Cytotoxicity to a human (MDA-MB-435) cancer cell line was observed for one of the fatty acids isolated from *P. parvum* in cultures (GAT 512A, $IC_{50} = 24.2 \mu\text{M}$).

Chrysochromulina polylepis produces two compounds, one hemolytic and one ichthyotoxic. The hemolytic compound was characterized as a galactolipid, 1-acyl-3-digalacto-glycerol. Small amounts of a polyunsaturated fatty acid, octadecapentaenoic acid, were also detected.

Karlotoxins

Karlotoxins are water-soluble hemolytic, cytotoxic, and ichthyotoxic compounds produced by the dinoflagellate *Karlodinium veneficum*.

Pfiesteria Toxins

The dinoflagellate *Pfiesteria* spp. is believed to produce and release into the environment potent extracellular toxins, or exotoxins, referred to generally as *Pfiesteria* toxins (PFTx) that have been linked to mass fish mortalities and human disease in mid-Atlantic estuaries. Learning impairments have been seen as long as 10 weeks after a single acute exposure to *Pfiesteria* in

Sprague–Dawley rats. A hydrophilic toxin (PFTx) isolated from *P. piscicida* cultures when applied locally to the ventral hippocampus on repeated acquisition of rats in the radial-arm maze impaired choice accuracy and early learning which was persistent across 6 weeks of testing after a single administration of the toxin.

Adverse health effects, including cognitive disturbance, were found in humans following accidental exposure to *P. piscicida* in laboratory facilities. Cognitive deficits have also been described in people believed to be exposed to *Pfiesteria* through sea spray in coastal Maryland during a *Pfiesteria* bloom. These adverse health effects have been termed Possible Estuary-Associated Syndrome by the Centers for Disease Control and Prevention, symptoms of which include cognitive and visual contrast sensitivity deficits, pulmonary impairment, gastrointestinal disruptions, and immunologic dysfunction.

Pectenotoxins

Pectenotoxins (PTXs) are a group of polyether macrolides produced by the dinoflagellates of the genus *Dinophysis* (*D. fortii*, *D. acuminata*, *D. acuta*, *D. caudate*, *D. rotunda*, *D. norvegica*). PTXs have also been detected in *Protoperidinium divergens*, *P. depressum*, and *P. crassipes*. PTXs are suspected to be DSP toxins because they are detected with the same extraction methods and bioassays used for OA and were first isolated from the scallop, *Patinopecten yessoensis*. There is no evidence of adverse acute or chronic health effects of pectenotoxins in humans. IP injection of PTXs in mice leads to liver necrosis. The mouse LC_{50} values (IP) for PTXs range between 250 and 770 $\mu\text{g kg}^{-1}$ for PTX1, 2, 3, 4, 6, and 11 and greater than 5000 $\mu\text{g kg}^{-1}$ for PTX7, 8, 9, and 2-SA. Toxicity in other PTX analogues has not been demonstrated.

Yessotoxins

Yessotoxins (YTXs) are disulfated polycyclic polyethers that resemble brevetoxins, produced by the dinoflagellate *Lingulodinium polyedrum*. Like PTX, YTX was first isolated from the digestive glands of the scallop *P. yessoensis* and are suspected to be DSP toxins because they are detected with the same extraction methods and bioassays used for OA. There have been no reports of ill effects in humans attributable to YTX. IP injection of YTXs in mice leads to cardiac muscle damage. Mouse LC_{50} values (IP) range between 80 and 750 $\mu\text{g kg}^{-1}$ for YTX and its analogues.

Clinical Management

Very little clinical research has been conducted to determine effective treatments. Medical care is primarily supportive.

Medical treatment of CFP has been to a large extent symptomatic; a variety of agents, including vitamins, antihistamines, anticholinesterases, steroids, and tricyclic antidepressants, have been tried with limited results. If given within 3 days of exposure, intravenously, mannitol (1 mg kg^{-1} given rapidly over 1 h) has been demonstrated in a single-blinded control trial to resolve acute symptoms and prevent chronic symptoms, although repeated administrations may be necessary if symptoms return; a more recent clinical trial did not find an effect;

Table 1 US FDA action levels in seafood for natural toxins associated with shellfish and fish poisoning

Poisoning	US FDA action level
PSP	0.8 ppm (80 µg per 100 g) saxitoxin equivalents
NSP	0.8 ppm (20 mouse units per 100 g) brevetoxin-2 equivalents
DSP	0.16 ppm total OA equivalents (i.e., combined free OA, dinophysistoxins, acyl-esters of OA, and dinophysistoxins)
ASP	20 ppm domoic acid, except in the viscera of Dungeness crab, where the action level is 30 ppm
CFP	0.01 ppb P-CTX-1 equivalents for Pacific ciguatera and 0.1 ppb C-CTX-1 equivalent for Caribbean ciguatera
AZP	0.16 ppm azaspiracid equivalents

Source: US FDA. (April 2011). Fish and Fishery Products Hazards and Controls Guidance, fourth ed. Department of Health and Human Services, Public Health Service Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Safety.

however, this trial included subjects treated long after the initial 3-day window. Gut emptying and decontamination with charcoal have been recommended, although often the severe ongoing vomiting and diarrhea prevent this. Atropine is indicated for bradycardia and dopamine or calcium gluconate for shock. It is recommended that opiates and barbiturates be avoided since they may cause hypotension, and opiates may interact with maitotoxins. Amitriptyline (25–75 mg b.i.d.) and similar medications do seem to have some success in relieving the symptoms of chronic ciguatera such as fatigue and paresthesias. It is possible that nifedipine may be appropriate as a calcium channel blocker to counteract the effects of maitotoxins. Anecdotal food avoidance as mentioned above is also recommended. In addition, there is no immunity to these illnesses, and recurrences of actual ciguatera in the same individual appear to be worse than the initial illnesses. A rapid, accurate diagnosis and treatment of CFP within the first 72 h after exposure may be critical in preventing some of the neurologic symptoms that might otherwise become chronic and debilitating. The treatment of DSP caused by OA is symptomatic and supportive. In general, hospitalization is not necessary; fluid and electrolytes can usually be replaced orally.

Supportive measures are the basis of treatment for PSP that is caused by saxitoxins, especially ventilatory support in severe cases. In animals, artificial respiration is the most effective treatment. Up to 75% of severely affected persons die within 12 h without supportive treatment. When the ingestion of contaminated food is recent, gut decontamination by the gastric lavage and administration of activated charcoal or dilute bicarbonate solution is recommended. Care must be taken concerning aspiration with the neurologically compromised patient. In general, the only treatment available for exposure to cyanobacterial algal toxins is supportive medical treatment after complete removal from exposure. If the exposure was oral, administration of activated carbon to decrease gut absorption may be efficacious if given within hours of exposure. Based on past outbreaks, monitoring of volume, electrolytes, liver, and

kidney function should all be considered in the case of acute gastroenteritis associated with some of the cyanobacterial algal toxins.

Exposure Standards and Guidelines

Global seafood safety standards have not been established. In the United States, US Food and Drug Administration (FDA) enacted the Hazard Analysis and Critical Control Points (HACCP) program of 1997. The FDA has established action levels in suspected seafood for the toxins causing some of the shellfish poisonings (see Table 1). When an action level is reached, the HACCP plan must be followed to prevent unsafe products from reaching the consumer.

See also: Ciguatera; Okadaic Acid; Saxitoxin.

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- <http://www-cyanosite.bio.purdue.edu> – A Webserver for Cyanobacterial Research. Purdue University, Department of Biological Sciences.
- <http://www.issaha.org> – The International Society for the Study of Harmful Algae (ISSHA).