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Phycotoxins by harmful algal blooms (HABS) and human poisoning: an overview

Abstract

Phycotoxins are potent natural toxins synthesized by certain marine algae and cyanobacteria species during "Harmful Algal Blooms", (HABs), often seen as water discoloration known as "Red Tides", "Green Tides". They are grouped by chemical structure, mechanisms of action, target tissues, biological and health effects. A constant threat to public health, and economy, environmental contaminants in aquatic ecosystems, seafood, drinking water, requiring multidisciplinary action at the local and international level to manage their potentially harmful effects. The 2015 bloom of toxigenic Pseudo-nitzschia along the west coast of North America resulted in domoic acid contamination of crab and clams, numerous harvesting closures and Consumer Warning issued by local public health authorities. Thereafter, in September 2016 the Oregon coast was closed to razor clam and mussel harvesting. Whereas, the massive cyanobacteria blooms reported in Florida in June 2016 lead to banning drinking water in some locations. Public health vigilance, monitoring, and research need to be maintained and enhanced. Despite scientific advancements, phycotoxin research relating to human exposure and health consequences are sparse, while, blooms of toxigenic species have become more prevalent worldwide. At present, phycotoxins poisonings diagnosis and management is largely based on the ability of health care provider to interpret presenting clinical symptoms, collect exposure history, identify and establish the exposure event. Several phycotoxins are neurotoxic, potentially lethal, and/or associated with chronic adverse health effects. Human intoxications are often misdiagnosed, under-diagnosed, and under-reported to public health authorities, hampering proper management and epidemiology data. Regulatory standards, alertness by public health organizations and primary health care providers, in regions with a history of HABs, helps to minimize and manage human health risks. Nonetheless, there are populations at higher risk of exposure due to cultural practices: recreational shellfish pickers, anglers children, aboriginals in coastal regions. Human exposure and poisoning can occur worldwide after consuming contaminated seafood while traveling or products imported from world location with limited analytical facilities and regulatory implementation.

Keywords: phycotoxins, harmful algal blooms, cyanobacteria, cyanotoxins, marine algal toxins, poisonings, human health

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Introduction

Phycotoxins by Harmful Algal Blooms (HABs) are a public health concern worldwide, outbreaks continuously occur, geographic distribution changes and expand, and new toxins are detected, increasing the risk of human exposure and toxic events. Climate change and environmental pollution are factors implicated in the appearance, geographic distribution and frequency of HABs, and phycotoxins.[1–4] Geographical expansion of HABs such as Pseudo-nitzschia species, known to synthesize domoic acid, are continuing to occur.[5,6] HABs adversely impact the economy, food, and water availability, locally and/or through trade; sports, recreation and tourism.[7–9] Several recent events portray the extent of HABs environmental contamination of aquatic ecosystems and food produce, its impact on the economy and population risk in some North American regions.[10–12]

HABs and phycotoxins are natural environmental contaminants of fresh, brackish and seawater, and encompass:

i. Cyanobacteria blooms (CyanoHABs) toxins "cyanotoxins", preferentially contaminants of soft water reservoirs and drinking water, with direct risk to human health.[13,14]

ii. Marine biotoxins/marine algal toxins by dinoflagellates and diatoms can accumulate at high concentrations in various tissues of aquatic organisms such as bivalve mollusks and fish, entering the food chain, threatening consumer's health.[15,16]

Public health warnings are issued for specific blooms and toxins based on data collected on identified toxin, contamination levels on water or specific seafood products, depuration times, and regulatory levels for each product and toxin group. A practical example is the domoic acid contamination of crab and clams that occurred in California November 2015, which lead to a Consumer Warning by California Department of Public Health (CDPH), showing levels of domoic acid in crabs that exceed US federal safety limits of 20 parts per million (ppm) in the meat and 30ppm in the viscera, with the highest level recorded of 190ppm in a yellow rock crab in the Monterey region.[17–19] The event prompted closing the year-round rock crab fishery and delaying the recreational and commercial Dungeness crab seasons. Established regulatory parameters, monitoring and infrastructure capabilities allowed the local preventive actions taken to minimize the risk of acute human exposure.

Diagnosis and treatment of intoxication are based on the history of exposure, identification of the contamination event, isolation of toxic compound and producing organism at the source, presenting symptoms associated with each group of toxins.[14,15,20–25] Emergency clinical management may help to prevent serious complications, including death. Long-term impairments may follow the acute event e.g amnesia and epilepsy seen during the domoic acid human poisoning event in Canada in 1987.[26] Although less is known about toxic effects induced by chronic, repeated exposure, some phycotoxins are carcinogenic or are linked to chronic degenerative neurologic disorders such as Amyotrophic Lateral Sclerosis (ALS).[27]

Human's health effects associated with most common phycotoxins from HABs: cyanobacteria and marine algae are summarized. Although not discussed here, information from domestic animals and wildlife intoxication have been key in the identification and follow-up of health effects, acute and chronic exposure in mammals, acting as sentinels for human health risk e.g. sea lions and domoic acid.[28–30] Experimental data helps to understand mechanisms of action, distribution, target tissues, biological effects and to establish guidelines, policy, and regulations.[16,31–36]

Phycotoxins health effects

In mammals, adverse health effects associated to phycotoxins and HABs can occur through oral, respiratory or dermal exposure to the toxins, their metabolites and/or theirs producing organisms, in aquatic or terrestrial environments.[14-16,20–24] For humans, the highest risks are: 1) Ingestion of seafood contaminated with toxins produced by diatoms and dinoflagellates; respiratory exposure through aerosols.[16,24,25,34,37] 2) Exposure to soft water contaminated with cyanotoxins, through drinking water, freshwater fish, dermal exposure e.g. bathing in contaminated lakes, or through contaminated equipment's or fluids.[20,22,38–40] Tables 1 and Table 2A, Table 2B summarizes the toxic effects of cyanotoxins and marine algal toxins described in humans, mechanism of action, presenting symptoms, clinical syndromes and prognosis. Most of the information available deals with acute exposure and effects. Several toxins are neurotoxic, can be lethal, but with proper clinical management, some may fully recover.[24,25,41,42] Table 2C includes marine algal toxins, identified as contaminants of aquatic environments, with harmful biological effects, but without identified adverse health effects in humans.[16,43,44]

Table 1 Cyanotoxins biological and human health effects[13,14,20,22,27,39,40,46,47,58]

Cyanotoxins	Mechanism action	Symptoms	Prognosis
Hepatotoxins			
Microcystin MCs	Inhibition of protein phosphatases type 1 and 2A Repeated low-level exposure: carcinogenesis, genotoxicity	Within 4–24h to few days: Diarrhea, vomiting, liver hemorrhage, shock, abdominal pain, jaundice, weakness. dyspnea respiratory distress, multiple organ failure	Can be lethal. Exposure: drinking water, contaminated dialysis fluid, soft water recreational environments
Nodularin	Inhibition of protein phosphatases type 1 and 2A	Diarrhea, vomiting, goose bumps, weakness, liver hemorrhage	
Cylindrospermopsin (CYN)	Glutathione and protein synthesis as well as cytochrome P450. Repeated low-level exposure: carcinogenesis, genotoxicity	Symptoms up to several days after exposure or later. Gastroenteritis abdominal pain, vomiting, bloody diarrhea, acute liver inflammation. Liver and kidney failure, hay fever, asthma	Chronic exposure linked to cancer e.g. colon
Neurotoxins			
Anatoxin-a / Homoanatoxin-a	Nicotinic receptors: Irreversible link to the nicotinic receiver S of acetylcholine in neuromuscular junction	Muscle twitching, cramping staggering, paralysis, convulsions, gasping, respiratory failure, death by suffocation	Can be lethal
Anatoxin-a(S)	Irreversible inhibitor acetylcholinesterase	Salivation, muscle twitching cramping, paralysis	
Saxitoxins	Neurotoxic, target the peripheral nervous system. Selective high affinity block sodium conductance in voltage-gated sodium channels, receptor site 1 at nerve fibers	Paralytic Shellfish Poison: Nausea, vomiting. peri-oral burning ataxia, drowsiness, paraesthesia, fever, tachycardia, muscular paralysis, respiratory failure, death	Death can occur within 2-12 hours after exposure. Good prognosis after 24hr, requiring good medical support system.
beta-Methylamino-L-alanine (BMAA)	Experimentally acts predominantly on motor neuron - excitotoxic through glutamate receptors	Not fully elucidated. Implicated on chronic neurodegenerative diseases	Chronic exposure linked to chronic neurodegenerative conditions: Amyotrophic Lateral Sclerosis
Irritants and Dermatotoxins			
Aplysiatoxins	Potent tumor promoters Potentiation of protein kinase C (PKC)	Skin irritation, asthma like symptoms	
Lyngbyatoxin	Potent tumor promoters Potentiation of protein kinase C (PKC)	Smooth muscle contraction. Skin irritation	

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Table 2A Marine algal toxins by diatoms and dinoflagellates: biological and human health effects[15,16,23,24,31,32,41,58,59,63,65,66,70]

Toxin group	Vector	Mechanism of action/effect	Exposure/ symptom	Syndrome	Prognosis
Azaspiracids (AZAs)	Shellfish Bivalves Mollusks	In vitro effect on actin cytoskeleton cell shape and adherence. Cytoskeleton damage is not reversible after toxin withdrawal	Food: Nausea, vomiting diarrhea, abdominal pain. Similar to DSP	Azaspiracids Poisoning (AZP)	No life threatening
Brevetoxins (BTX / PbTX)	Shellfish Bivalves Mollusks	Neurotoxic: Open sodium channels Immunological effects e.g.: release of inflammatory mediators	Food: nausea, vomiting, diarrhea, paresthesia, cramps, bronchoconstriction, paralysis, seizures and coma Aerosol inhalation: Rhinorrhea Asthma-like symptoms	Neurotoxic Shellfish Poisoning (NSP)	Symptoms start min to hours after consumption of contaminated food. Recovery in few days
Ciguatoxins (CTXs): Pacific (P-CTX), Caribbean (C-CTX), and Indian Ocean (I-CTX)	Tropical and sub-tropical fish e.g.: eels, snappers, groupers, mackerels, jacks or barracudas	Neurotoxic: Opens sodium channels by binding site 5. Influx of Na, provoke action potentials, cell swell, and blebs on cell's surface	Food: Vomiting, diarrhea, nausea, tingling, itching hypotension bradycardia arthralgia, myalgia hyporeflexia, dysphagia, ataxia paralysis	Ciguatera Fish Poisoning (CFP) Severity and type of symptoms varies with the type of CTX	Symptoms may start ~ 30 min. after ingestion of contaminated fish or delayed 24-48 hrs. Cardiorespiratory failure-risk of death. Recovery weeks to years. Neurological symptoms can become chronic
Saxitoxins (STXs) and related toxins	Shellfish Bivalve Mollusks Crustaceans	Neurotoxic: Target the peripheral nervous system Selective block sodium conductance in voltage-gated sodium channels receptor site 1 at nerve fibers	Food: Nausea vomiting peri-oral burning, ataxia, drowsiness, paraesthesia, fever Tachycardia, muscular paralysis, respiratory failure, death.	Paralytic Shellfish Poisoning (PSP)	Death can occur within 2-12 hours after exposure. Good prognosis after 24hr.

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Table 2B Marine algal toxins by diatoms and dinoflagellates: biological actions and human health effects15,16,24,25,26,31,32,36,37,58,60,61

Toxin group	Vector	Mechanism of action/Effect	Exposure/Symptoms	Syndrome	Prognosis
Okadaic acid (OA) and dynophysistoxins (DTXs)	Shellfish	Tumor promoter	Food: Abdominal pain, nausea, vomiting diarrhea, rarely fatal	Diarrheic Shellfish Poisoning	Symptoms start 30 min-
	Bivalve Mollusks	Inhibit essential serine/ threonine protein phosphatases 1(PP1) and 2A (PP2A); genotoxic, cytotoxic		(DSP)	few hours after ingestion – ends within three days. Potential long term effect as tumor promoter
Domoic acid group	Shellfish	Neurotoxic:	Vomiting, diarrhea	Amnesic Shellfish Poisoning (ASP)	Life threatening
	Mollusks	Cardiotoxic, a Excitatory	arrhythmia		Long term
	Crustaceans	neurotoxin, analogue of glutamate – acts through glutamate receptors.	cardiovascular		sequel after acute intoxication: anterograde amnesia period Potential developmental neurotoxicity
	Fish e.g.	Reproductive organs	collapse. Confusion,		Chronic repeated exposures linked to epilepsy
	Sardines		memory loss, seizure, , death		
	Anchovies				
Palytoxins	Shellfish	Neurotoxic:	Food: Nausea, vomiting	Toxic syndromes in association with PITXs:	High mortality rate ingested and/or inhaled, cases described after exposure to coral fumes and fish tanks
(PlTXs) and PITX like ompounds	Bivalve Mollusks, Crab, Fish e.g.	Target the sodium potassium-	myalgia, fever rhabdomyolysis,	Palytoxicosis/	
	Sardines	ATPase pump in cell membrane;	vasoconstriction	Clupeotoxism,	
	Anchovies	maintain the ionic gradients in cells. Membrane depolarization in excitable and non- excitable cells, contraction of muscle cell	heart and renal failure, delayed haemolysis	PITX like toxin is myotoxic: myalgia	
			Inhalation:	rhabdomyolysis, myoglobinuria after ingestion of cooked freshwater and brackish water fish, identified as "Haff Disease"	
			Rhinorrhea, cough bronchoconstriction		

Table 2C Marine algal toxins by diatoms and dinoflagellates without known human health effect15, 16, 43, 44, 52

Toxin group	Vector	Mechanism of Action/ Effect	
Pectenotoxins (PTXs)	Shellfish	Mechanism unknown	
	Bivalve Mollusks	Experimental data: Hepatotoxic	
		Congestion and bleeding of the liver. Tumor promoter and cytotoxic	
Cyclic imines Spirolides(SPXs), gymnodimines (GYMs), pinnatoxins (PnTXs) pteriatoxins (PtTXs)	Shellfish Bivalves Mollusks	Experimental data: Neurotoxic. Fast acting Experimental in rodents parenteral toxicity more potent than oral	No cases of human intoxication
Yessotoxins (YTXs)		Target cardiac muscle, mitochondria and myofibril Decrease cyclic AMP activate cellular phosphodiesterases (PDEs), cytoskeletal and adhesion molecules, caspase	No cases of human intoxication

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Health effects by cyanotoxins

Cyanotoxin is the term used for the secondary metabolites from cyanobacteria, toxic to living organisms including human.[14,20,22,38–40,45] They are divided into chemical groups, i.e., cyclic peptides (microcystin and nodularin), alkaloids (anatoxin-a, anatoxin-a(s), saxitoxins, cylindrospermopsin, aplysiatoxin, lyngbiatoxin-a), and lipopolysaccharides (LPSs). Grouped by biological effects, and target tissues affected: hepatotoxins, neurotoxins, cytotoxins, dermatoxins, and irritant toxins (Table 1).[20,22,38–40,45–47] Neurotoxic cyanotoxins are: Anatoxin-a /Homoanatoxin-a; beta-Methylamino-L-alanine (BMAA).[27] BMAA chronic, repeated exposure is linked to neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS),[27] and its toxicity is best described in association to exposure to the seeds of the Cycas circinalis plant in the diet of indigenous people of the Guam Island, and more recently from some diatoms.[48–50]

Bloom-forming toxic cyanobacteria are global hazards of increasing concern in waters affected by anthropogenic nutrient loads and climate change, occurring frequently in lakes and soft water reservoirs all over the world, causing damage to the biodiversity and equilibrium of aquatic ecosystems due to toxins released.[45] Nonetheless, some phycotoxins have properties with potential beneficial applications: antibiotics, algaecides, cytotoxic, immunosuppressive agents, and enzyme inhibitors.[51–54] Cyanotoxins acting as protease inhibitors and on cell cycle are some the compounds under investigation for anticancer activity e.g. Curacin A.[51,53]

Seafood poisoning syndromes by marine algal toxins

Marine algal toxins largely produced, but not exclusively, by dinoflagellates and diatoms are potent toxins, contaminate seawater environments, and accumulate at high concentrations in various tissues of aquatic animals such as bivalve mollusks, crustaceans, and fish, thus entering the food chain.[14,15] Bivalve mollusks: mussels, oysters, clams, cockles, and scallops are filter-feeding organisms, and can accumulate chemical and microbiological. Consumption of contaminated fish and shellfish is one of the main causes of seafood poisoning. Marine algal toxins are an important source of seafood contamination worldwide with serious adverse impacts to human health, wildlife, the economy, and the ecosystem. International guidelines and regulatory standards aim to maximize seafood products safety as a major internationally traded commodity.[15,16,32,34,36] Limited resources and analytical capabilities in developing countries, to detect toxins such as ciguatoxin, may hide serious environmental health problems and seafood safety.[55]

Table 2A, Table 2B summarize the principal clinical syndromes caused by marine algal toxins produced by dinoflagellates and diatoms, through ingestion of contaminated seafood,[15,16,23–25,34,36,41,56] exposure to aerosols, or contact.[37,57] The main and best-studied marine algal toxins seafood poisoning syndromes are diarrheic shellfish poisoning (DSP); paralytic shellfish poisoning (PSP); amnesic shellfish poisoning (ASP); neurologic shellfish poisoning (NSP); azaspiracid shellfish poisoning (AZP); ciguatera fish poisoning (CFP). Toxic syndromes associated with PITXs are Palytoxicosis, Clupeotoxism, and PITX-like myotoxic compound, characterized by myalgia, rhabdomyolysis, myoglobinuria (black urine) after ingestion of cooked freshwater and brackish water fish, identified as "Haff Disease.[56]" It differentiates from PITX toxicity by its preferential myotoxic rather than neurotoxic effects. Increasing public health concern exist for PITX poisonings through inhalation, cutaneous, ocular exposure during aquariums handling of soft corals contaminated with PITX.[57]

Neurotoxic and myotoxic phycotoxins

Neurotoxic phycotoxins produced by marine algae and/or cyanobacteria are potent toxins acting through various mechanisms at the cellular level, often involving ion channels modulation. SXTs selectively blocks voltage-gated sodium channels receptor, site 1 sodium pump, affecting motor neurons;[15,16,31,58] CTX opens sodium channels by binding site 5 leading to sodium cell influx and depolarization of nerve cell;[16,17,32,59] Domoic acid induces excitatory toxicity (excitotoxicity) by an integrative action on ionotropic glutamate receptors (iGluRs) on both sides of the synapse for which it has high affinity, preferentially the kainic acid (KA) subtype, coupled with an effect that prevents the channel from rapid desensitization.[36,60] PITXs a complex molecule that binds to extra- cellular sodium and potassium channels inhibiting the active transport of sodium and potassium across the membranes leaving the channel permanently open and causing cellular death by the excess of intercellular cations.[31,32,58] Neurotoxic cyanotoxins are: Anatoxin-a/Homoanatoxin-a, acting through an irreversible link to the nicotinic receptor receiver S of acetylcholine in neuromuscular junction; beta-Methylamino-L-alanine (BMAA) experimentally acts predominantly on motor neuron-inducing excitotoxicity mediated through glutamate receptors (GluRs).[49,56]

Medical management of phycotoxins poisonings

At present, diagnosis of phycotoxins poisoning is largely based on symptomatology and exposure history, identification of toxin in food or water, estimation of contaminated food/water consumption to calculate the amount of toxin ingested, while epidemiology is based on reports of acute events, toxic outbreaks of contaminated seafood, water or aquatic environments. Mild cases may not require medical attention or not be diagnosed. Respiratory and skin reactions may be confused with allergies.

Toxic symptoms appear within minutes to days following consumption of seafood product (fish or shellfish), freshwater fish, cooked or uncooked, local or imported, during traveling or after traveling to endemic regions. Public health warnings, population eating habits, recreational practices, are important for diagnosis. Populations at higher risk of exposure due to cultural practices include recreational shellfish pickers, anglers, aboriginals in coastal regions.[23,61,62] Age, pre-morbid history such as renal insufficiency, amount and type of food consumed are factors influencing the severity of intoxication.[36,60] The source of exposure and identification of toxin through analysis of food samples are important for public health management of outbreaks.

Despite that each toxin group has a different mechanism of action, characteristic clinical features and prognosis (Table 2A & Table 2B), acute intoxications by neurotoxic phycotoxins commonly affect: gastrointestinal (GI), cardiovascular, respiratory and nervous systems. The following combination of symptoms alert for a possible intoxication with these compounds: 1) self-limiting, non-specific gastrointestinal symptoms of various degree of severity: vomiting, nausea, diarrhea, abdominal pain; 2) nonspecific cardio-respiratory symptoms such as hypotension, tachycardia, arrhythmia, dyspnea;

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3) appearance of neurological symptoms of various degree of severity, ranging from perioral burning, paresthesia, to convulsions and coma. Gastrointestinal symptoms are usually the first to appear and neurological symptoms may be later with a time lapse between exposures and clinical symptoms from minutes to days. Symptoms increase in frequency and severity over the subsequent hours after consumption of a contaminated seafood meal. Reporting of the events to public health authorities is paramount to track outbreak events and develop an epidemiologic database. Mild cases shall also be reported.

No specific biomarker is available to confirm diagnosis or exposure, nonetheless some laboratory test aids e.g. urine test to measure myoglobin in cases of "Haff Disease" by PITX-like myotoxic compound,[56] or tests measuring STXs in urine,[63] which still needs validation and standardization.

For the poisoned patient emergency medical management should be organized and thoughtful, as suggested by Thompson et al.[64] Although the authors do not include phycotoxins in the list of poisoning substances, is a practical guideline. Phycotoxins poisoning is largely supportive and symptom-driven as no specific antidote are available for these toxins. Palliative measurements vary depending on the toxin group and its mechanism of action, e.g.: antiepileptic and drugs modulating glutamate receptors for potential domoic acid intoxication,[25] respiratory support for STXs intoxication.[65,66]

Little is known about long-term repeated exposure to neurotoxic phycotoxins or their mixtures. At present, the issue of domoic acid developmental toxicity and epilepsy deserves special consideration because of its relevance to public health as a potentially preventable cause of epilepsy and neurobehavioral impairments.[15,36,60,67,68] Rapidly accumulating data from experimental studies and episodes of wildlife intoxication and long-term repeated exposure support a cause-effect link.[36,67] Furthermore, it has been demonstrated in experimental models that domoic acid crosses the placenta and can be present in milk.[36] Consumer awareness of at-risk women during pregnancy and lactating require special attention, particularly during contamination outbreaks as those recently reported.[17,19] Dietary assessment is required to estimate exposure.[69]

Prevention and factors increasing the risk of human phycotoxins exposure

The key management tools are prevention, through policies and regulations, and monitoring systems of each toxin group and HABs, and warning by public health organizations to minimize the risk of human poisoning episodes.[7,16,17,34,70] Factors increasing the risk of human exposure include: 1) Marine algal toxins are odorless, tasteless, and do not deactivate by cooking; 2) Seafood product may appear unaltered by the accumulated toxins; 3) There are not known antidotes to algal toxins; 4) Dense human population in coastal regions, globalization, and food trade further enhance the risk of human exposure, a current issue of public health concern and an international management challenge; 5) Recreational harvesting of shellfish, and limited monitoring systems in many regions of the world increase the risk of exposure to contaminated seafood; 6) HABs tend to follow seasonal, oceanic and climate variation and appear in burst, often regional inhabitants and aquacultures sites suspect or predict a HABs event, or have monitoring systems. Avoidance of non-commercially harvested shellfish not tested for phycotoxins is the best way to prevent poisoning events. Nonetheless eating practices are influenced by cultural practices increasing risk of exposure e.g. shellfish recreational pickers. Travelers to regions with limited food regulatory control may present symptoms of intoxication after returning home. Awareness of environmental conditions and documentation of events are paramount for preventive management and development of forecasting systems. Detail clinical records, including food consumption history, symptoms, and reporting to public health authorities are essential for diagnosis and risk management.

Conclusion

Phycotoxins and associated human health effects are a public health concern worldwide. A summary of most common poisoning syndromes is presented here. Enhanced awareness by health care providers and consumers will improve clinical management, a collection of clinical history, reporting and epidemiology databases. However, a comprehensive insight into phycotoxins human health risk requires multidisciplinary, international collaboration, detail information on exposure: data on consumption and levels of contamination of seafood products or aquatic environments. Each toxin group involves specific parameters: synthesizing organisms, vectors, toxicology including toxic kinetics, biological effects, associated symptoms, and prognosis. Less is known about chronic effects. Biomarkers are needed to improve diagnosis, detection, and measurement of human exposure, allowing more accurate disease surveillance and epidemiology. At risk populations e.g.: arctic and American west coast native population, pregnant women, lactating infants need special attention and surveillance of potential chronic effects such as cancer and neurodegenerative disorders. Development of antidotes to phycotoxins with potentially lethal effects is an investigational challenge.

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Conflict of interest

The author declares no conflict of interest.

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