Heliyon 10 (2024) e27146

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

The health risks of marine biotoxins associated with high seafood consumption: Looking beyond the single dose, single outcome paradigm with a view towards addressing the needs of coastal Indigenous populations in British Columbia

Michael Joseph Lee [a,*], Sarah B. Henderson [a], Holly Clermont [b], Nikita Saha Turna [a], Lorraine McIntyre [a]

[a] Environmental Health Services, British Columbia Centre for Disease Control, 655 W 12th Ave, Vancouver, BC, V5Z 4R4, Canada
[b] Environmental Public Health Services, First Nations Health Authority, Snaw-naw-as Territory, Nanoose Bay, Canada

ARTICLE INFO

Keywords:
Seafood safety
Repeated exposure
Seafood contaminants
Marine biotoxins
Chronic health impacts
Low-dose exposure
Indigenous health

ABSTRACT

People who consume high quantities of seafood are at a heightened risk for marine biotoxin exposure. Coastal Indigenous peoples may experience higher levels of risk than the general population due to their reliance on traditional marine foods. Most evidence on the health risks associated with biotoxins focus on a single exposure at one point in time. There is limited research on other types of exposures that may occur among those who regularly consume large quantities of seafood. The objective of this review is to assess what is known about the unique biotoxin exposure risks associated with the consumption patterns of many coastal Indigenous populations. These risks include [1]: repeated exposure to low doses of a single or multiple biotoxins [2]; repeated exposures to high doses of a single or multiple biotoxins; and [3] exposure to multiple biotoxins at a single point in time. We performed a literature search and collected 23 recent review articles on the human health effects of different biotoxins. Using a narrative framework synthesis approach, we collated what is known about the health effects of the exposure risks associated with the putative consumption patterns of coastal Indigenous populations. We found that the health effects of repeated low- or high-dose exposures and the chronic health effects of marine biotoxins are rarely studied or documented. There are gaps in our understanding of how risks differ by seafood species and preparation, cooking, and consumption practices. Together, these gaps contribute to a relatively poor understanding of how biotoxins impact the health of those who regularly consume large quantities of seafood. In the context of this uncertainty, we explore how known and potential risks associated with biotoxins can be mitigated, with special attention to coastal Indigenous populations routinely consuming seafood. Overall, we conclude that there is a need to move beyond the single-dose single-outcome model of exposure to better serve Indigenous communities and others who consume high quantities of seafood.

* Corresponding author.
E-mail addresses: michael.lee@bccdc.ca (M.J. Lee), sarah.henderson@bccdc.ca (S.B. Henderson), holly.clermont@fnha.ca (H. Clermont), nikita.sahaturna@bccdc.ca (N.S. Turna), lorraine.mcintyre@bccdc.ca (L. McIntyre).

https://doi.org/10.1016/j.heliyon.2024.e27146
Received 6 June 2022; Received in revised form 16 February 2024; Accepted 25 February 2024
Available online 2 March 2024

1. Introduction

1.1. Seafood and coastal indigenous populations

Seafood is an important part of the diets of many coastal Indigenous populations [1]. For example, in British Columbia, Canada (BC) archaeological evidence indicates that coastal Indigenous peoples received 90% of their protein from marine sources, highlighting the traditional value of these foods [2]. In addition to retaining substantial cultural significance today, seafoods also provide Indigenous communities with livelihoods, contribute to overall well-being, support food security and sovereignty, and serve as an important source of dietary nutrients [1,3]. This importance is underscored by reports that Indigenous groups who consume more traditional foods, including seafoods, and less processed foods, have improved nutrient intakes and lower levels of obesity and other metabolic disorders such as type 2 diabetes [4,5].

1.2. Seafood consumption and marine biotoxins

Despite the importance of seafoods to coastal Indigenous populations, their harvest and consumption can be associated with significant health risks, including exposure to marine biotoxins [6]. Marine biotoxins are produced by different organisms including algae [7]. When environmental conditions are favorable (e.g., elevated nutrient concentrations), these algae proliferate in events called "harmful algal blooms" (HABs) [8]. During HABs that produce biotoxins, the toxins can be ingested and accumulated by different species of shellfish, fish, and other marine animals [7]. The primary route of human exposure to marine biotoxins is through the consumption of contaminated seafood [9].

There are several categories of marine biotoxins including, but not limited to Refs. [10,11]:

- Diarrhetic shellfish toxins (DSTs), primarily dinophysistoxins and okadaic acid
- Paralytic shellfish toxins (PSTs), primarily saxitoxin
- Amnesic shellfish toxins (ASTs), domoic acid
- Neurotoxic shellfish toxins (NSTs), primarily brevetoxins
- Azapiracid shellfish toxins (AZT), azapiracid
- Ciguatoxin (CTX)
- Tetrodotoxin (TTX)

Coastal Indigenous populations may be at a heightened risk of exposure to marine biotoxins because they generally practice higher rates of seafood harvesting and consumption than non-Indigenous populations [12]. For instance, Cisneros-Montemayor et al. [13]

Table 1
Action limits for the specified biotoxins in Canada and other countries. Values are maximum permissible levels for seafood tissue, unless otherwise specified.

Action level in mg/kg (equivalent to ppm and μg/g)							
Biotoxin poisoning	**Toxin group**	**Seafood tissue**	**Canada** [96]	**United States** [97]	**United Kingdom** [98]	**New Zealand** [99]	**European Union** [100]
Amnesic Shellfish Poisoning (ASP)	Domoic acid (DA)	Bivalve shellfish (edible tissue)	20	≥20	20	20	20
		All Fish[a]		≥20			
		Dungeness crab (viscera)		>30			
Diarrhetic Shellfish Poisoning (DSP)	Sum of dinophysistoxins, esters (DTX) and okadaic acid	Bivalve shellfish (edible tissue)	0.2	≥0.16	0.16	0.16	0.16
		Bivalve shellfish (digestive tissue)	1.0				
		Clams, mussels, oysters, and whole and roe-on scallops, fresh, frozen, or canned[b]		≥0.16			
Paralytic Shellfish Poisoning (PSP)	Saxitoxin and equivalent analogs (STX and STX-eq)	Bivalve shellfish (edible tissue)	0.8	≥0.8	0.8	0.8	0.8
		All Fish		≥0.8			

[a] In the FDA Fish and Fisheries guidance, the term "fish" and "fishery products" are defined in the Fish and Fishery Products Regulation (21 CFR 123.3(d) and 123.3(e)) as follows: Fish – Fresh or saltwater finfish, crustaceans, other forms of aquatic animal life (including, but not limited to, alligator, frog, aquatic turtle, jellyfish, sea cucumber, and sea urchin and the roe of such animals) other than birds or mammals, and all mollusks, where such animal life is intended for human consumption •Fishery products – any human food product in which fish is a characterizing ingredient.

[b] In the FDA Fish and Fisheries guidance, The term "shellfish" is defined in the NSSP as all species of: a. Oysters, clams, or mussels, whether: i. Shucked or in the shell; ii. Raw, including post-harvest processed; iii. Frozen or unfrozen; iv. Whole or in part; and b. Scallops in any form, except when the final product form is the adductor muscle only.

estimated that consumption rates of seafood per capita among more than 1900 coastal Indigenous populations in 87 different countries was, on average, 15 times higher than non-Indigenous populations.

There is growing evidence related to the health risks of exposures to a single marine biotoxin at a single point in time. Such short-term biotoxin exposures can result in many different symptoms ranging from diarrhea, vomiting, and nausea, to paralysis, memory loss, and death. Accordingly, most evidence and public health protections have been developed to understand and prevent the hazards associated with the ingestion of enough biotoxin at a single point in time to produce overt symptoms [11,14–16]. For instance, the regulatory limit for AST allowed in seafood in many different countries including Canada, the United States, the European Union, New Zealand, and Australia is based on the levels of toxin that produced acute symptoms in people during a 1987 AST outbreak in Prince Edward Island, Canada [17]. Regulatory limits for other marine biotoxins are also set at levels below the lowest amount of toxin documented to have produced symptoms in people during previous outbreaks and/or in animal studies [11,14,15,18]. In Canada, the federal Canadian Shellfish Sanitation Program (CSSP) closes harvest sites when biotoxins are found in monitored seafood above the associated regulatory limits [6,19]. Similar programs and regulatory levels (Table 1) exist in many other countries around the world and have generally been effective in preventing acute health effects of biotoxin exposures [14].

There is less known about exposures among populations that routinely consume seafood at rates higher than the general population, such as coastal Indigenous peoples [13,15]. Exposure to marine biotoxins among such populations may extend beyond an exposure to a single biotoxin at one point in time. Other scenarios may include exposure to one or multiple biotoxins repeatedly over both long- and short-term time scales and at a variety of dosages. Understanding the potential health impacts of these different kinds of exposures is important to establish strategies that adequately protect the health of Indigenous populations. For example, biotoxin regulatory guidance levels, derived by groups such as the Food and Agriculture Organization of the United Nations (FAO) and the European Food Safety Authority (EFSA), have been designed primarily to prevent acute toxic effects from single exposures (i.e., a large meal) and may not consider chronic effects or repeated exposure from daily consumption (i.e., multiple meals) because of a lack of available data [11,20,21].

1.3. Seafood, biotoxins, and Indigenous populations in British Columbia, Canada

In BC, Canada, there is a pressing public health need for increased and improved understanding, data, and surveillance of the marine biotoxin risks experienced within coastal Indigenous communities. First, in addition to knowledge gaps associated with the health effects of routinely consuming high quantities of seafood, members of these communities experience food insecurity at nearly five times the rate of the general population [22]. This underscores the importance of ensuring safe access to nutritious seafoods. Second, many harvesting areas remain under prolonged closures due to a lack of testing, despite the federal sanitation program (i.e., the CSSP) [6,23]. Others areas are under permanent sanitary sewage closures, even though water quality data is not available to establish trends that demonstrate continued water contamination. Community harvesters in these areas may ignore closures, as evidenced by a review of self-harvesting among Indigenous communities in BC that found 46% of paralytic shellfish poisoning (PSP) illnesses were linked to seafood harvested from closed areas [6].

To begin addressing this public health issue, BC Indigenous communities, the First Nations Health Authority, and the BC Centre for Disease Control established the "We All Take Care of the Harvest" (WATCH) pilot program [24]. The aim of this program is to address seafood safety, security, and sovereignty among BC coastal Indigenous populations in the context of climate change.

1.4. Objective of this literature review

As a part of the WATCH program, the objective of this manuscript was to provide a baseline assessment of what is known about the health impacts of the multi-faceted biotoxin exposure risks that may be experienced by coastal Indigenous populations in BC. In addition to potential exposure to a high dose of a single biotoxin during a single meal, other possible exposure scenarios among members of these communities include: (1) repeated exposures to low doses of a single or multiple biotoxins, (2) repeated exposures to high doses of a single or multiple biotoxins, and (3) exposure to high or low doses of multiple biotoxins at a single point in time. In this review, 'exposure' refers to contact with biotoxins through the consumption of seafood, and 'high' and 'low' dose refers to dosages above and below regulatory limits, respectively. We synthesize this literature to identify key knowledge gaps and highlight strategies to prevent and mitigate biotoxin risks in the context of BC coastal Indigenous communities.

2. Materials and methods

2.1. Literature review context

This review is focused on describing the health effects of the most important causes of marine biotoxin illnesses in BC, which are PST, DST, and AST. In BC, there have been 301 illnesses and five deaths due to PST since 1940 [6], 62 illnesses due to DST in 2011 [25]; and one suspect illness due to AST in 2016 [26]. These toxins are continually present in BC coastal waters [27,28].

2.2. Search strategy and narrative review

The aim of this review was to provide a baseline assessment of what is known about the health effects of marine biotoxins to inform the development of the evolving Indigenous-led seafood safety program in BC. Therefore, we performed a rapid literature search and

descriptive narrative synthesis. We focus on finding and synthesizing previous literature reviews because studies on the health effects of PST, DST, and AST have been previously collated and reviewed in more than twenty articles since 2010. We concentrate on these previous literature reviews, rather than systematically reviewing the primary literature, to avoid repeating the work of these previous authors.

This review of reviews is distinct from previous work because it synthesizes information specifically in the context of the public health need for an improved understanding of the unique marine biotoxin health risks experienced by coastal Indigenous populations in BC. While our search strategy is not meant to systemically appraise the entire body of research, it provides a comprehensive overview of the literature because each of the previous literature reviews included a wide ranging, and sometimes systematic review of the primary literature.

2.2.1. Inclusion and exclusion criteria

We included only reviews of the human health impacts of marine biotoxins that have been published since 2010. Earlier reviews were only considered if they provided information not covered elsewhere or if there were no literature reviews published since 2010. We excluded reviews not focused on human health, and reviews of biotoxin mechanisms of toxicity or clearance. For all phases of the search, studies were appraised for inclusion via their title and/or abstract.

2.2.2. Search methods

We conducted three literature searches to rapidly capture as many review articles as possible (Fig. 1; Table 2). In search 1, we searched Google Scholar (Google, California, USA) using the keywords "*specific biotoxin* review" (e.g., "saxitoxin review") separately for PST (saxitoxin), DST (okadaic acid and dinophysistoxins), and AST (domoic acid). We sorted the results by the 'relevance' criteria (i.e., Google seeks to determine the best match to entered search terms while considering the number of citations) and examined the first 150 publications per biotoxin [29]. In search 2, we entered the search terms "health review *specific biotoxin*" (e.g., "health review saxitoxin") into Google Scholar for each biotoxin. The results per biotoxin were initially sorted by relevance and the first 10 publications were examined followed by sorting the results by date and again examining the first 10 publications.

In search 3, we expanded our search to a separate database, PubMed. We searched PubMed using the terms "*specific biotoxin*" AND "health" (e.g., "okadaic acid" AND "health") to capture review articles that weren't associated with the term 'review'. If there were fewer than 100 results for a particular biotoxin, all search hits were assessed for inclusion. When there were more than 100 results for a particular biotoxin, we only assessed those published since the most recent review of that biotoxin found in searches 1 and 2. This was done to reduce the number of studies to screen for inclusion. For example, if a review on the human health effects of saxitoxin found in search 1 was published in 2018, in search 3 we assessed saxitoxin search results published 2018 and later for inclusion. Thus, we assumed that primary saxitoxin literature published prior to 2018 was included because it was covered in the 2018 review. Finally, we used citation searches within reviews to find additional publications.

All searches were carried out May–June 2021.

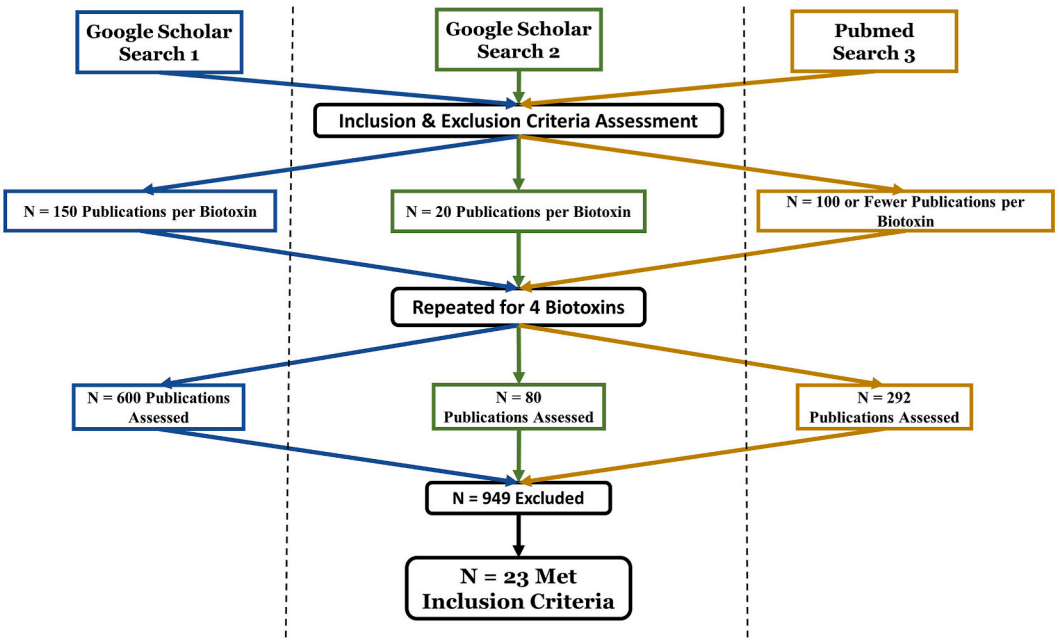

Fig. 1. Search flow chart.

Table 2
The literature search consisted of three distinct searches.

Search	Search String[a]	Database	Methods
1	"okadaic acid review"; "dinophysistoxin review"; "domoic acid review"; "saxitoxin review"	Google Scholar	• Repeated for each biotoxin • Sorted by relevance, examined the first 150 publications • N = 600 publications examined
2	"health review okadaic acid"; "health review dinophysistoxin"; "health review domoic acid"; "health review saxitoxin"	Google Scholar	• Repeated for each biotoxin • Sorted by 'relevance', examined the first 10 publications and then sorted by date and examined the first 10 publications. • N = 80 publications examined
3	"okadaic acid" AND "health"; "dinophysistoxin" AND "health"; "domoic acid" AND "health"; "saxitoxin" AND "health"	Pubmed	• Repeated for each biotoxin • If there were less than 100 search results for a particular biotoxin all results were examined • If there were more than 100 publications only those published since the most recent review of that biotoxin found in searches 1 and 2 were examined • N = 972 publications examined

[a] Keywords for each biotoxin are separated by a semicolon. Each set of keywords was searched individually for each biotoxin.

2.2.3. Narrative synthesis

Publications were read in full, and information was synthesized using a narrative framework synthesis approach [30]. Initially, this approach consisted of developing a set of *a priori* themes (Fig. 2) prior to reviewing the literature. These themes were identified by study authors and were designed to extract information on (1) the human health effects of different marine biotoxin exposure scenarios, (2) exposure risk mitigation and prevention, and (3) individual sensitivity to experiencing severe outcomes from exposure. Information related to themes was extracted from each review and was summarized in a single spreadsheet with themes as columns and biotoxins as rows. Evidence from multiple reviews was summarized for individual biotoxins in each row while citing the review. For instance, for the theme 'individual sensitivity' and saxitoxin, we extracted and summarized information about sensitivity from several reviews in a single spreadsheet cell. The spreadsheet was then used to compare themes across biotoxins and to synthesize the information into a cohesive narrative. These narratives were considered in the context of the wider literature in the 'results and discussion' section.

Conclusions and statements made in the narrative synthesis about trends and knowledge gaps in the primary literature are drawn from the previous literature reviews included in this work. For example, when a previous review concludes that there 'is limited human data about the health effects of a biotoxin' we re-report this directly in the results and discussion and cite the associated review(s). Primary literature is cited throughout the results and discussion to provide specific examples and to provide further context.

2.2.4. Focus on human health research

While there are data on the health impacts of biotoxins derived from experimental animal and in vitro studies, this information is difficult to translate to humans. Translation is difficult because dosages and toxicity are species dependent, different studies use different routes of exposure (ingestion vs. injection), and symptoms in animals can be different from those in humans [31–33]. For example, while rats can ingest 35–70 mg/kg of AST before displaying observable symptoms, humans begin to show signs of illness with as little as 0.9–2.0 mg/kg [17,34]. Because of these difficulties, this review focuses primarily on what is known based on human data.

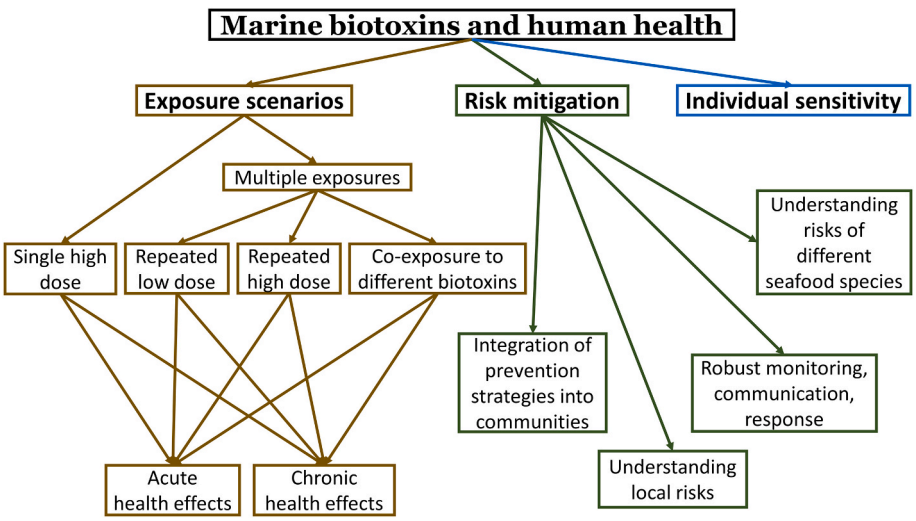

Fig. 2. A priori themes used to organize information from the literature.

Animal and in vitro studies on the health impacts of biotoxins are included only to support or contrast what is has been shown in humans.

3. Results and discussion

3.1. Summary of search results

Overall, we assessed 972 publications for inclusion in this review (Fig. 1). Of those, 23 met the inclusion criteria (Table 3) as literature reviews of the human health effects of PST, DST, or AST and were included in the narrative synthesis. In search 1 and 2, respectively, we assessed 600 and 80 publications for inclusion. In search 3, all search results were assessed for inclusion for dinophysistoxins (n = 75). There were more than 100 search results for domoic acid (n = 229), saxitoxin (n = 296), and okadaic acid (n = 485). Because the health effects of all these biotoxins were reviewed in detail by Vilariño et al. [11], which was found in search 1, we assessed only the search results published between 2018 and June 2021 for domoic acid (n = 54), saxitoxin (n = 82), and okadaic acid (n = 81). In search 3, we assessed a total of 292 publications for inclusion.

3.2. Health effects of biotoxins

3.2.1. Single high-dose exposure

Most of what is known about the human health effects of marine biotoxins is based on studies examining the acute health effects experienced by people exposed to a single biotoxin at a single point in time (i.e., studies of individual biotoxin poisonings). For example, Young et al. [16] found that 89.5% of the literature that measured the health effects of marine biotoxins on humans was based on a single exposure event to one biotoxin. While Young et al. (2020) made this conclusion for marine biotoxins in general, several other reviews corroborated their findings by making similar observations individually for PST, AST, and DST [11,17,35,36].

Acute symptoms from exposure to different biotoxins range from mild (e.g., nausea) to severe (e.g., respiratory difficulty, death) [11]. The severity of symptoms experienced during illness is generally associated with the amount of toxin ingested relative to that person's body size and metabolism and thus the concentration of toxin in a person's body [11,36,37]. When a person consumes only a

Table 3
Recent reviews on the human health effects of marine biotoxins. Biotoxins included paralytic shellfish toxin (PST), amnesic shellfish toxin (AST), and diarrhetic shellfish toxin (DST).

First author	Published in:	Year	Title	PST	AST	DST
Bates	Harmful Algae	2018	Pseudo-nitzschia, Nitzschia, and domoic acid: New research since 2011		✓	
Berdalet	Journal of the Marine Biological Association of the UK	2016	Marine harmful algal blooms, human health and wellbeing: challenges and opportunities in the 21st century	✓	✓	✓
Farabegoli	Marine Drugs	2018	Phycotoxins in Marine Shellfish: Origin, Occurrence and Effects on Humans	✓	✓	✓
Fu	Toxicon	2019	Okadaic acid (OA): Toxicity, detection and detoxification			✓
Grant	Neurotoxicology and Teratology	2010	Domoic acid: Neurobehavioral consequences of exposure to a prevalent marine biotoxin		✓	
Grattan	Harmful Algae	2016	Harmful algal blooms and public health	✓	✓	✓
James	Epidemiology and Infection	2010	Shellfish toxicity: human health implications of marine algal	✓	✓	✓
Karlson	Harmful Algae	2021	Harmful algal blooms and their effects in coastal seas of Northern Europe	✓	✓	✓
Lefebvre	Toxicon	2010	Domoic acid and human exposure risks: A review		✓	
Martinez	Springer Handbooks	2015	Marine Biotoxins	✓	✓	✓
Mello	Neurotoxicity Research	2018	Mechanisms and Effects Posed by Neurotoxic Products of Cyanobacteria/Microbial Eukaryotes/Dinoflagellates in Algae Blooms: a Review	✓		
Morabito	Natural Product Research	2018	How the marine biotoxins affect human health	✓	✓	✓
Murk	Chemical Hazards in Foods of Animal Origin	2019	Marine biotoxins: types of poisoning, underlying mechanisms of action and risk management programmes	✓	✓	✓
Nicolas	Global Food Security	2017	Marine biotoxins and associated outbreaks following seafood consumption: Prevention and surveillance in the 21st century	✓	✓	✓
O'Neill	Environmental Toxicology and Pharmacology	2016	Low dose extended exposure to saxitoxin and its potential neurodevelopmental effects: A review	✓		
Paredes	Toxicon	2011	Update of risk assessments of main marine biotoxins in the European Union	✓	✓	✓
Petroff	Pharmacology and Therapeutics	2021	Public health risks associated with chronic, low-level domoic acid exposure: A review of the evidence		✓	
Picot	Human and Ecological Risk Assessment	2011	A Preliminary Risk Assessment of Human Exposure to Phycotoxins in Shellfish: A Review	✓	✓	✓
Pulido	International Clinical Pathology Journal	2016	Phycotoxins by harmful algal blooms (HABS) and human poisoning: an overview	✓	✓	✓
Valdiglesias	Marine Drugs	2013	Okadaic Acid: More than a Diarrheic Toxin			✓
Vilariño	Toxins	2018	Human Poisoning from Marine Toxins: Unknowns for Optimal Consumer Protection	✓	✓	✓
Visciano	Frontiers in Microbiology	2016	Marine Biotoxins: Occurrence, Toxicity, Regulatory Limits and Reference Methods	✓	✓	✓
Young	Harmful Algae	2020	Marine harmful algal blooms and human health: A systematic scoping review	✓	✓	✓

Table 4
Human health effects of marine biotoxins. A summary of what is know about the human health effects of different kinds of exposures to paralytic shellfish toxin, amnesic shellfish toxin, and diarrhetic shellfish toxins.

Toxin	Single high-dose exposure		Repeated high-dose exposures	Co-exposure with other biotoxins	Repeated low-dose exposure	Potential groups with heightened sensitivity to complications[a]
	Acute health effects:	Chronic health effects:				
Paralytic Shellfish Toxin	Tingling sensation or numbness around the lips, tingling sensation in the fingertips and toes, drowsiness, headache, dizziness, difficulty swallowing **In severe cases:** Incoherent speech, tingling sensation in the arms and legs, stiffness and non-coordination of limbs, weakness, rapid pulse. Death may occur from respiratory failure without respiratory support	Unknown	Unknown	Unknown	Unknown	Infants, children
Amnesic Shellfish Toxin	Nausea, vomiting, diarrhea, abdominal cramps, muscle weakness, headache, disorientation, memory loss (inability to remember recent events following exposure), confusion, disorientation, seizures, other neurological dysfunction including coma	Possible chronic short-term memory (anterograde) dysfunction (i.e., issues forming certain kinds of new memories)	Unknown	Unknown	Limited human data suggest possible negative impacts on several measures of cognitive performance including memory	The elderly, neonates, the developing fetus, males, and people with pre-existing medical conditions such as chronic renal disease
Diarrhetic Shellfish Toxin	Diarrhea, nausea, vomiting, chills, headaches, and abdominal pain	Unknown	Unknown	Unknown	Unknown	The developing fetus

[a] There is limited review of characteristics associated with heightened susceptibility in humans in reviewed studies.

small amount of the toxin, they may not show signs of illness, while those who are exposed to a large amount may experience more severe symptoms. However, these dose-response relationships are highly dependent on the specific biotoxin consumed [38], the sensitivity of the consumer, and other factors. Acute symptoms of PSP caused by PST, amnesic shellfish poisoning (ASP) caused by AST, and diarrhetic shellfish poisoning (DSP) caused by DST are described in Table 4 [8,9,11,14,39].

While several chronic health outcomes have been described, these are poorly understood compared with the acute effects that occur immediately after exposure [16,39]. Following the only known outbreak of acute ASP, which occurred in Prince Edward Island, Canada in 1987, patients lost their recent memories around the time of exposure and some were left with persistent memory problems such as delayed recall of visuospatial objects [40,41]. Autopsies of those who died within days and months of poisoning revealed brain damage, including in regions associated with learning and memory [11,40]. It is unclear whether there are chronic health impacts associated with a single dose of PST [11,39] or DST [11,42]. This limited understanding of chronic health effects stems, in part, from a limited number of published longitudinal studies that have followed patients after recovering from acute poisoning events [14]. There is some evidence from animal and in vitro studies that suggest chronic effects may exist. For example, several in vitro and in vivo studies indicated that DST may be toxic to multiple organs and systems including the nervous system and the liver [42]. However, it is unknown whether these effects occur in people and the lack of human longitudinal studies may reflect a publication bias towards studies where an effect was observed, thus limiting the publication of studies that found no chronic health consequences.

3.2.2. Repeated low-dose exposures

Potentially significant health impacts of repeated low-dose exposures (i.e., exposure to low doses of biotoxins in multiple meals) are important to understand because regular consumers of seafood will be exposed when biotoxins are present in food at doses lower than regulatory limits. Enforcement of these regulations cannot prevent low-dose exposures because they only protect against consumption of doses higher than the regulatory limit. For example, AST biomarkers were detected in the urine of recreational razor clam harvesters in the USA Pacific Northwest 7–9 days after they consumed shellfish considered safe to eat by local regulations because the amount of biotoxin present was lower than regulatory limits [20]. These exposures below the regulatory limit are particularly important in this region given that AST has been persistently present in razor clams at both low and high levels over the last two decades [43,44].

There is a growing body of research indicating that repeated low-dose exposure to AST may have important health consequences. Several studies following a cohort of Indigenous people in the USA Pacific Northwest collectively found that decreases in measures of memory function occur at AST exposure levels below the regulatory limits (measured via clam consumption and AST levels in clams) [45,46]. However, the studies associated with this cohort represent some of the only research available that has investigated the impacts of repeated low-dose exposure to AST in humans. Given that these studies have found evidence of potential health impacts, it is important for future work to replicate these studies in other populations and/or to measure AST exposure more directly, such as through AST biomarkers in urine [20,46]. For more information about the studies on repeated low-dose exposure to AST associated

Box 1
Memory, amnesic shellfish toxin (AST), and razor clam consumption in Tribal nations of the U.S. Pacific Northwest

Some of the most detailed evidence about the health impacts of repeated low-dose exposure to AST comes from a community-based participatory research project following a cohort selected from among three Tribes in Washington State, USA: Quileute Indian Nation, Makah Tribe, and Quinault Indian Nation [12]. ***In a series of publications following this cohort over more than 8 years, researchers have found that the regular consumption of a higher number of razor clams, which were identified as a vector of AST, was consistently associated with slightly lower measures of memory function.***

Early work: A 2016 study followed 513 adults in the cohort and reported on measures of cognition and razor clam consumption over a four-year period [43]. *Indicators of memory included measures of verbal memory, attention and concentration, psychomotor speed and flexibility, and cognitive flexibility. The study found that consumers of 15 or more clams* per *month had lower verbal memory scores, while other measures remained unaffected. However, the lower memory scores among high razor clam consumers were still within normal limits and thus may not have been clinically important.*

Further research: *In 2018, the authors reported on 60 people from the cohort* [45]. *In the study, participants self-reported memory issues ("Everyday Memory Questionnaire-revised") along with clam consumption, including the number consumed and source beach in the past week and the past year ("Shellfish Assessment Survey"). AST levels in razor clams were assessed from beach collections and ranged between 8 to* 14 ppm *AST during the study period. High razor clam consumers, in both the past week and the past year, were more likely to report problems within specific measures in the everyday memory questionnaire. Later, in 2021, another study of 500 adults from the cohort found similar associations between measures of verbal recall and consumption of more than 15 razor clams* per *month* [47].

Supporting the effects described above, another study based on 142 cohort members described a dose-response relationship between a decreasing memory score (i.e., 'total learning recall') and increasing levels of AST exposure [46]. *This study indicated that the earlier research, which used the number of clams consumed as a proxy measure of AST exposure, may have measured an attenuated effect size because the range of doses was not examined (i.e., while people labeled as 'high consumers' may have eaten 15 clams in a month, others may have eaten 30 or more, however, these consumers were grouped together).*

Together, these studies are indicative of a link between repeated low-dose exposure to AST and cognitive impacts. However, future work should seek to replicate these studies in other populations and/or to measure AST exposure more directly [20,46].

with this cohort see Box 1.

There is limited human data available on the health impacts of repeated low-dose exposure to DST [11,42]. Several studies have found associations between proxy measures of DST with several types of cancer [11,48]. For example, Lopez-Rodas et al. [49] used shellfish consumption data as a proxy for DST exposure but did not measure DST levels in shellfish or people (i.e., people with higher self-reported shellfish consumption in a cross-sectional survey also had higher rates of cancer). As such, further work is required to establish a more direct link between any type of exposure to DST and chronic health outcomes.

There is also limited human data available on the impacts of repeated low-dose exposure to PST [11,35]. Case reports indicate that residents of coastal areas may be less likely to experience PST intoxication than non-residents, indicating that people who have been previously exposed develop tolerance [50]. Among 131 recorded instances in New Brunswick from 1944 to 1970 in which individuals consumed PST-contaminated shellfish, only 1 of 31 coastal residents experienced symptoms, while 48 of 100 non-residents became ill [50]. Although this finding differs from what has been reported for repeated low-dose exposure to AST, limited human data available for both AST and PST makes it difficult to draw conclusions about these different findings.

A comprehensive review of experimental studies by Petroff et al. [36] suggested that repeated exposure to low levels of AST may cause subtle neurotoxic effects in the structure, function, and physiology of the brains of different animals. One study found that cognitive effects of repeated low dose AST exposure in mice reversed once exposure ceased [51]. For DST, some animal and in vitro studies appear to support the preliminary data from humans by showing that DST can have tumor promoting and carcinogenic effects [11,42,52]. Finally, among the few experimental studies that have explored multiple exposures to PST, researchers found minimal impacts among several different animals [11,35,53]. Some rodent studies support the assertion that previous exposure to non-lethal doses of PST may increase tolerance [54]. This indicates that observations of putative tolerance in coastal Canadian populations may be a physiological response to repeated exposure [50]. Overall, limited evidence from both human and animal studies are suggestive, but inconclusive, of the potential health effects of repeated exposure to some biotoxins below their current regulatory limits.

3.2.3. Repeated high-dose exposure

Repeated high-dose exposure refers to repeated exposures to one or multiple biotoxins above limits that cause acute symptoms (i.e., exposure to high doses of biotoxins in multiple meals). Such exposures may be important in Indigenous communities where biotoxin monitoring may be less robust [55]. For example, HABs producing PST occurred (n = 119) every year between 2000 and 2017 along the pacific Canadian coast [28], indicating that multiple exposures are possible, particularly in areas with inadequate monitoring. However, there was limited discussion of the human health impacts of this exposure profile in previous reviews. The risks associated with multiple high-dose exposures may not have been widely discussed because regulations and safety limits are designed to prevent even a single exposure to a dose above the regulatory limits [11]. Regardless, information on chronic toxicity in these reviews sometimes referred to both repeated high- and low-dose exposures. In these cases, evidence was not clearly separated into categories of repeated high-dose and low-dose exposure, likely because the data that were available were based on animal studies in which dosages, metabolism, clearance rates, and routes of exposure differ from those in humans and between different animal models. Despite this, the majority of what is known about the health effects of biotoxins is based on a single high-dose exposure [16] and there is a lack of human data on repeated exposures in general, regardless of dosage [11,56–60].

3.2.4. Co-exposure to different biotoxins

People may be exposed to multiple biotoxins simultaneously through the consumption of seafoods containing multiple biotoxins or through the consumption of different species contaminated with different biotoxins. Peacock et al. [61] found that 99% of mussels sampled in San Francisco Bay, USA in 2012, 2014, and 2015 contained at least one of AST, DST, PST, or microcystins, and that 37% of mussels contained all four toxins simultaneously. However, it is unclear what the impacts of being co-exposed to different biotoxins may be [14,61]. There appears to be limited data for humans, and the available evidence from animal and in vitro studies have found that different toxin mixtures can have additive, synergistic, or antagonistic effects [14,62–65].

3.2.5. Summary: health risks associated with marine biotoxins

There are important uncertainties regarding the biotoxin health risks associated with high seafood consumption diets. The acute health impacts of a single exposure to a high dose of certain marine biotoxins can be severe and are comparatively well described. While there is some indication that a single exposure to some biotoxins can be associated with chronic health effects, there may be a lack of extended follow-up among exposed individuals. Repeated exposure to certain biotoxins at doses below their regulatory limits may also have health consequences, but the available evidence is limited. As such, it is unknown what levels of AST, PST, and DST may be safely consumed on a regular basis. Finally, evidence on the health impacts of multiple high-dose exposures and/or exposures to multiple biotoxins is also limited. While future research is needed to better elucidate these uncertainties, there are risk prevention strategies that may help to protect the health of coastal Indigenous populations and other people who consume seafood regularly.

3.3. Risk prevention strategies

There are no curative treatments following biotoxin exposure and medical intervention is supportive and/or focused on symptom management [8]. For example, for severe PSP, artificial ventilation may be required to prevent death while oral rehydration may be required for DSP [8,66]. Consequently, exposure prevention is important for mitigating health impacts [67]. In the following sections we describe potential prevention strategies that may reduce risks for Indigenous populations that regularly consume seafood.

3.3.1. Integration of prevention strategies into communities

It is important to develop prevention strategies with Indigenous communities, incorporating site-specific knowledge gathered over millennia [68]. Many of these communities have historically understood that there were risks associated with seafood. By monitoring those risks through their own harvesting and consumption, they were able to identify when and where shellfish were safe or unsafe to consume [69]. As an example, some Native American communities in California halted shellfish harvests when bioluminescence was observed in the water [70,71]. However, given global environmental degradation and a changing climate, it is critical to integrate this historically gathered information with strategies that account for changing trends and future events that may be unpredictable based on historical knowledge (e.g., increasing surface water temperature, changing currents, invasive species) [72].

In BC, the WATCH pilot program is an example of how seafood safety programs can be integrated into Indigenous communities in the context of climate change [24]. At important shellfish harvest sites, Indigenous staff monitor phytoplankton abundance and composition of species that generate AST, PST, and DST to provide early warnings when there is heightened risk for marine biotoxins. This real-time data and surveillance are also necessary to track and respond to unpredictable events resulting from climate change and other environmental stressors. Further, this project demonstrates the importance of directly involving Indigenous communities in the development of seafood safety programs, so that the information provided is useful for those it is intended to protect [14]. Such direct involvement helps to ensure that monitoring accounts for Indigenous harvest sites, the seafood species consumed, as well as cooking and consumption practices. For example, in Washington state, USA, members of Indigenous communities who participate in the SoundToxins program, monitor phytoplankton and provide early warnings to regulators of biotoxin threats in local areas [73]. SoundToxin monitoring strategically occurs when the State Department of Health is not scheduled to take samples and specifically in key harvest sites or in areas that require more sampling. Warnings from this program trigger regulators to take actions to mitigate risks locally by prioritizing testing samples from the at-risk sites, increasing testing from those areas, or pre-emptively closing harvest sites.

Failure to integrate prevention strategies into Indigenous communities may result in programs that do not account for the actual health risks experienced within these communities. Centralized biotoxin monitoring programs, which may be designed to protect the general population, are unlikely to account for the unique risks associated with the higher consumption rates and specific geographies of coastal Indigenous populations (section 3.1). Studies in Washington State, USA show how understanding local community risks can be used to improve and extend health guidance originally derived for the public. Members of Indigenous communities participating in these studies reported regularly consuming razor clams, which were identified as a vector of AST [20,46]. Existing regulatory limits of AST in Washington are based on the State Department of Health's threshold of 20 μg AST/g clam tissue. This limit was originally derived from the levels of AST which made people sick in the 1987 Prince Edward Island outbreak by calculating the lowest dose that produced symptoms in a victim, assuming a standard shellfish meal size (200g), and dividing by a safety factor of ~12 [18].

While this outbreak-derived limit has effectively prevented acute cases of severe ASP [36], it does not reflect the potential impacts of regularly consuming doses of AST below this limit (i.e., 19 μg AST/g per clam consumed), which may be the case for members of these communities who frequently consumed razor clams across multiple meals [17,20]. It also does not account for scenarios in which people eat meals larger than the assumed meal size. Therefore, it is important that regulatory limits, surveillance programs, and research into the health effects of biotoxins within Indigenous communities be established based on their actual exposure risks. Indeed, the information derived from these cohort studies, led to the Washington State Department of Health to release a recommendation to avoid eating more than 15 razor clams per month throughout the year – the threshold above which memory problems were noted in the studies (Box 1) [43]. More recently, medical leads at the BC Centre for Disease Control in nearby British Columbia, reduced the threshold for investigating suspected ASP cases to 10 mg/kg of shellfish or seafood (despite the regulatory limit of 20 mg/kg) based on the same studies in Washington State [74]. They use this new value as the threshold to confirm ASP cases with neurological symptoms when meal leftover or harvest area seafood samples are available and above the threshold. A "probable" case definition is assigned to cases with gastrointestinal symptoms when leftovers have values of 10 mg/kg or higher. While it may be prudent to adopt these recommendations in other jurisdictions where razor clams are a known vector of AST, future work is needed to more fully understand the risks associated with repeated low-dose exposure to AST.

Risks are also influenced by local cultural practices associated with seafood harvest and consumption. Indigenous communities may eat different species than the general population and their preparation, cooking, and eating practices may also differ [75]. As a result, a full understanding of local practices is essential to mitigate local biotoxin risks. For instance, in some Indigenous communities in BC, it is a tradition to consume herring eggs raw [76], which may be contaminated with the bacteria *Vibrio cholerae*. While *V. cholerae* in herring eggs is destroyed by cooking to at least 63 °C for 15 s [76], consumption of these eggs raw contributed to an outbreak of *V. cholerae* in 2018 in BC [76]. The biotoxin risks associated with specific seafoods may be similarly impacted by different consumption, preparation, and preservation practices (see section 3.3.3). Therefore, it is important to account for these differences to effectively understand and mitigate local risks.

3.3.2. Need for robust monitoring, communication, and response

One of the most important methods of preventing exposure is to ensure that there is a robust system of seafood biotoxin monitoring that clearly communicates timely risk information to harvesters and consumers. Without these data, individuals cannot make informed decisions about when and where it is safe to harvest seafood. Therefore, one of the first steps in preventing illnesses is to ensure that there is enough data available to communities. This need is apparent in BC, where biotoxin monitoring data are not made regularly available and harvesters may consume seafood from closed sites because they have been closed for prolonged periods with no follow-up testing [6]. Shellfish biotoxin maps can help communities develop safer harvesting and consumption habits, but only if they provide timely data on the actual risks in areas where people harvest [77].

Because different seafood species uptake and clear different biotoxins at different rates, monitoring programs should, ideally,

sample all the species expected to be consumed. Monitoring programs with this capability provide harvesters with information on which species are safe at any given time. For example, the Southeast Alaska Tribal Ocean Research biotoxin monitoring program tests any shellfish species that harvesters send to them for PST and AST and regularly monitors water and shellfish from specific harvest areas [78]. Programs with this capability bolster food security by giving communities the ability to switch between different seafoods and harvest areas as needed [14]. However, given higher costs associated with sampling more seafood species and monitoring more areas, it is important to focus on species consumed within communities and to monitor areas where seafood is harvested.

Programs can also monitor environmental variables associated with HABs to forecast blooms and biotoxins [79]. In the USA, the Pacific Northwest HAB bulletin monitors certain harmful phytoplankton offshore, forecasts transport via ocean currents and wind, and provides early warnings for coastal shellfish managers [80]. In BC, while there are no regular governmental HAB monitoring programs, there is an ongoing citizen science monitoring project that collects data on algae concentrations and a variety of environmental variables in the Strait of Georgia [81]. Other volunteer monitoring groups have been disbanded because of a lack of resources [82], but there are websites that report HAB events of interest to the community, such as the LEO network [83]. Although data have been used to investigate seasonal and environmental drivers of harmful algae, no models have been implemented for real-time forecasting in BC [79,81,82]. Further research is required to develop and implement models that forecast the occurrence of HABs and their impacts. Ideally, such models could inform when and where different seafood species will be affected, how long they will remain affected, and when and where harvest sites should be tested and retested [84].

3.3.3. Public health messaging

In the absence of adequate monitoring and knowledge of the effects of low-dose and repeated exposures, the risk of negative health outcomes may be reduced by tailoring messaging specifically to people who are particularly susceptible to experiencing adverse impacts from biotoxin exposure. For more information about who might be more sensitive to experiencing severe outcomes from biotoxin exposure see Box 2 and Table 4.

Community and public health messaging can be tailored to sensitive groups warning them of their heightened sensitivity and the potential consequences. Messaging should focus on helping people understand their own risks so that they can make informed decisions regarding limiting personal exposure.

In Indigenous communities relying on marine foods for protein as well as cultural and spiritual well-being, public health communication materials would ideally make recommendations regarding the risks associated with specific seafoods. However, the

Box 2
Sensitivity to the severe health impacts of marine biotoxins.

There is a limited amount of human-derived information on sensitivity to AST because documented cases are rare. During the 1987 AST incident in Canada, male sex and older age were associated with hospitalization and memory loss [85]. *Similar effects have been noted in rodent studies with older and male animals reacting more severely to the toxin* [36]. *Additionally, four of the 16 patients treated in the intensive care unit during the 1987 outbreak were under the age of 65, but all had co-morbidities including diabetes, chronic renal disease, and hypertension. Perl* et al. *(1990) suggested that these co-morbidities and increased age might each be associated with decreased kidney function. Indeed, the kidney has been identified as the primary route by which AST is eliminated from the bodies of studied animals. Together, this suggests that kidney problems may impair clearance of the toxin in humans and/or the toxin may exacerbate existing kidney dysfunction* [11,36].

AST may also affect other organs and systems, including the heart [36,85]*, and the immune system* [36]*, although there is limited human data to support this. Further study is required to understand whether pre-existing conditions associated with these systems might predispose individuals to worse outcomes* [36]. *Experimental evidence also indicates that AST may be able to cross the placenta and accumulate in the amniotic fluid of pregnant individuals* [11]. *Animal studies also indicate that AST transfer through breast milk is present at low levels; however, there is no human data available to confirm this* [11,36]. *While there are no human data on the impacts of AST on fetuses, neonates, or children, studies in animals indicate that damage to developing nervous systems is similar to that observed in adults at high doses, but that low-dose exposure causes a variety of unique neuropathological changes* [36]. *Experimental studies on the effects of early life exposure on memory and cognition have had mixed findings* [36].

DST causes a self-limiting illness. Links to possible severe outcomes, including cancer, are not well established [11]. *It is not clear whether specific risk factors are associated with worse outcomes. One study* [86] *found that DST can cross the placenta in pregnant mice, indicating that pregnant individuals and the developing fetus may be two potentially sensitive groups, but more research is required to fully understand the associated risks.*

Data from previous PSP outbreaks indicate that children are more susceptible to dying from exposure than adults [35]. *In an outbreak among 187 people who consumed contaminated clams in Guatemala, children less than six years old had a 50% mortality rate compared with 7% among those older than 18* [87]. *In addition to a higher acute risk of death, exposure may impact neurodevelopment, potentially making infants and children more sensitive* [35].

*Overall, there is some evidence that certain risk factors are associated with heightened sensitivity to experiencing the severe health effects of different biotoxins (*Table 4*). However, risk factors in the literature assessed in this review were mentioned only briefly. Future work may review case and outbreak reports of each biotoxin to determine whether there are consistent risk factors across reports.*

varying biotoxin risks associated with different foods, biotoxin analogs in different species, and preparation, cooking, and consumption practices are not fully understood [15]. For example, both razor clams and Dungeness crabs may be contaminated with AST, but an individual may eat many clams, exposing themselves to a high-toxin dose in one sitting, while they may only eat one crab per meal, potentially exposing themselves to a lower dose depending on the concentration of the toxin in the different species [17]. This becomes more complex when considering that biotoxins may only be present in certain tissues of different species, which may or may not be eaten [88]. For instance, PST is concentrated in the hepatopancreas of some crabs [89], an organ often avoided during consumption [90]. However, if boiled whole, PST may contaminate the rest of the crab [91]. For more information on the uncertainties associated with the risks posed by specific seafoods and consumption practices see Box 3.

Public health messaging associated with seafood risks must also balance the food security, cultural, and dietary importance of these foods [94]. For example, while seafood diets in Inuit populations provide high levels of the nutrients vitamin D and E, iodine and selenium, they may also be contaminated with persistent organic pollutants [95]. In such a scenario, especially in areas where there is limited access to healthy alternatives, messaging must carefully weigh both the risks and benefits associated with this diet and must make any uncertainties around the health impacts of contaminants clear.

3.4. Limitations

Our study was designed to rapidly assess a specific knowledge gap to help inform the development of a program to address an ongoing public health issue in BC, Canada. Despite this, our study was associated with important methodological limitations. First, this work was limited by our focus on reviews of the health effects of marine biotoxins, rather than reviewing the primary literature. As a result, any biases inherent to the search methodologies of those reviews and interpretation by those authors, would also be present here. However, our main findings were corroborated across different reviews. For example, the conclusion that there is limited research on the health effects of repeated low-dose exposure was made in multiple review articles for each biotoxin, all of which had their own methods and reviewed their own set of literature. The consistency across reviews supports the robustness of these findings. Second, because each literature review was conducted with a different methodology, reviewed a different subset of literature, focused on different biotoxins, and was synthesized through a different lens, we avoided enumerating and reporting the number of review articles that made a specific conclusion. This was important because the absence of a conclusion in a particular literature review may have been indicative of the overall goals of the synthesis rather than reflecting whether a conclusion was true for the primary literature reviewed. Instead, our qualitative narrative synthesis enabled us to describe the breadth of information across these literature reviews.

4. Conclusions

Human health impacts of repeated low-dose exposures, multiple high-dose exposures, and chronic health effects of marine biotoxins were rarely documented in the reviewed literature. The breadth of characteristics that may make people especially sensitive to experiencing severe health outcomes from biotoxins also does not appear to be well described. There are gaps in our understanding of which seafood species present risks in which areas, the impacts of different preparation, cooking, and consumption practices, and how these vary between different biotoxins and biotoxin analogs. Together, these knowledge gaps contribute to a limited overall understanding of how marine biotoxins impact the health of people who consume seafood at high rates. These gaps are pronounced for coastal Indigenous peoples and others who not only consume seafoods at higher rates than the general population, but also eat a greater diversity of species and employ different preparation and cooking practices. However, the potential risks to these communities can be prevented using a variety of strategies. Monitoring, testing, early warning systems, and public health messaging, tailored to the actual exposure risks are needed. Providing Indigenous communities with the opportunity to make informed harvest decisions based on timely local data, together with a better understanding of the clearance rates of biotoxins by these species, can help strengthen food security and food sovereignty. Finally, more research is needed to understand the risks associated with high seafood consumption diets to establish new regulatory and/or warning levels that adequately reflect those risks, particularly for repeated low- or high-dose exposures. Overall, there is a need to move beyond the single-dose single-outcome model of exposure to better serve Indigenous communities and other populations that routinely consume seafood.

Funding

This work was supported by the First Nations Health Authority as a part of their pilot project, We All Take Care of the Harvest, funded by the Health Canada HealthADAPT program and the Public Health Agency of Canada's Infectious Disease and Climate Change Fund.

Data availability statement

All data and conclusions made in this literature review can be found in the references cited in this article.

Ethics declaration

Review and/or approval by an ethics committee was not needed for this study because it was a review of the existing literature and did not include any new data collection or analysis.

Box 3
The complexities associated with the risks posed by specific seafoods and consumption practices.

Understanding which seafoods pose a risk for different biotoxins is complicated by several factors. First, marine species uptake, metabolize, clear, and store individual biotoxins in different ways. For example, anchovies clear AST from their tissues to undetectable levels within one week, while razor clams may hold the toxin for up to one year [17]. *Different species may also be contaminated with several 'analogs' of the same biotoxin, each of which may have varying levels of toxicity to humans, but are poorly studied* [15]. *There are at least 58 known analogs of PST, the comparative toxicities of which have not been fully assessed* [11]. *Further, the presence of biotoxins in shellfish depends on many environmental factors that promote or inhibit the growth of toxigenic phytoplankton, influence the production of biotoxins by phytoplankton, and affect the extent and rate of biotoxin transport* [67].

Food handling, storage, processing, and preparation/cooking practices also impact the risk. While clams may hold AST for up to one year in the ocean, they can hold it for several years after being canned or frozen [11]. *Further, while biotoxins are often regarded as being resistant to cooking* [91], *research indicates that this may vary between seafood species, biotoxins, and cooking practices. A study comparing AST concentrations in cockles and Manila clams following steaming found that while the concentration decreased in cockles, it increased in the clams because of a decrease in biomass with little change to the amount of toxin* [92]. *For DST, one study reported that cooking steaming and canning practices could result in increased toxin concentrations, through moisture loss without biomass loss and redistribution of toxins from digestive tissues to whole shellfish flesh* [93]. *Specifically, steaming mussels resulted in a 30–70% increase in DST, and canning resulted in a 70–84% increase in toxin concentration in whole shellfish flesh. Other research found that mild steaming (100°C for 5 min), industrial steaming (105°C for minimum* 2 min*), and sterilization temperatures (121°C) each had a different effect on DST analogs with some remaining stable and others decreasing* [101]. *This indicates that the risk varies between cooking practices, and between different analogs of the same toxin.*

CRediT authorship contribution statement

Michael Joseph Lee: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sarah B. Henderson:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Holly Clermont:** Writing – review & editing, Validation, Project administration, Funding acquisition, Conceptualization. **Nikita Saha Turna:** Writing – review & editing, Validation, Data curation. **Lorraine McIntyre:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge and thank the National Collaborating Centre for Indigenous Health for their review and insightful feedback on this work.

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