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Review

A review on aquatic toxins - Do we really know it all regarding the environmental risk posed by phytoplankton neurotoxins?

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ABSTRACT

Aquatic toxins are potent natural toxins produced by certain cyanobacteria and marine algae species during harmful cyanobacterial and algal blooms (CyanoHABs and HABs, respectively). These harmful bloom events and the toxins produced during these events are a human and environmental health concern worldwide, with occurrence, frequency and severity of CyanoHABs and HABs being predicted to keep increasing due to ongoing climate change scenarios. These contexts, as well as human health consequences of some toxins produced during bloom events have been thoroughly reviewed before. Conversely, the wider picture that includes the non-human biota in the assessment of noxious effects of toxins is much less covered in the literature and barely covered by review works. Despite direct human exposure to aquatic toxins and related deleterious effects being responsible for the majority of the public attention to the blooms' problematic, it constitutes a very limited fraction of the real environmental risk posed by these toxins. The disruption of ecological and trophic interactions caused by these toxins in the aquatic biota building on deleterious effects they may induce in different species is paramount as a modulator of the overall magnitude of the environmental risk potentially involved, thus necessarily constraining the quality and efficiency of the management strategies that should be placed. In this way, this review aims at updating and consolidating current knowledge regarding the adverse effects of aquatic toxins, attempting to going beyond their main toxicity pathways in human and related models' health, i.e., also focusing on ecologically relevant model organisms. For conciseness and considering the severity in terms of documented human health risks as a reference, we restricted the detailed revision work to neurotoxic cyanotoxins and marine toxins. This comprehensive revision of the systemic effects of aquatic neurotoxins provides a broad overview of the exposure and the hazard that these compounds pose to human and environmental health. Regulatory approaches they are given worldwide, as well as (eco)toxicity data available were hence thoroughly reviewed. Critical research gaps were identified particularly regarding (i) the toxic effects other than those typical of the recognized disease/disorder each toxin causes following acute exposure in humans and also in other biota; and (ii) alternative detection tools capable of being early-warning signals for aquatic toxins occurrence and therefore provide better human and environmental safety insurance. Future directions on aquatic toxins research are discussed in face of the existent knowledge, with particular emphasis on the much-needed development and implementation of effective alternative (eco)toxicological biomarkers for these toxins. The wide-spanning approach followed herein will hopefully stimulate future research more broadly addressing the environmental hazardous potential of aquatic toxins.

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1. Introduction

Aquatic toxins are potent natural toxins produced by certain cyanobacteria and marine algae species during harmful algal blooms - CyanoHABs when cyanobacteria dominate or HABs when dinoflagellates and diatoms are the dominant species (Anderson, 1994; Solter and Beasley, 2013; Pulido, 2016; Stauffer et al. 2019). These harmful bloom events are a public and environmental health concern worldwide in inland and coastal waters given their exponential growth dynamics and consequent biomass yield, as well as their toxic properties (Altamirano and Sierra-Beltrán, 2008; Paerl and Otten, 2013; Stauffer et al. 2019), which is further considered emergent as occurrence, frequency and severity are increasing due to ongoing climate change scenarios and anthropogenic impact (Bláha et al., 2009; Wells et al., 2015; Stauffer et al. 2019). In particular, increased CO_2, reduced pH and changes in nutrient availability in freshwater and marine ecosystems can exacerbate blooms (Pulido, 2016; Stauffer et al. 2019; Mutoti et al., 2022). CyanoHABs and HAB events across aquatic ecosystems are characterized by a high degree of heterogeneity (temporal and spatial) in species composition and nonpoint source factors that contribute to the blooms (Altamirano and Sierra-Beltrán, 2008; Stauffer et al. 2019; Chorus et al., 2021). This, coupled with fundamental questions regarding the biology and ecology of the organisms involved in these events and the toxins they produce, poses major challenges to the understanding, forecasting and ultimately mitigating of CyanoHABs and HABs (Stauffer et al. 2019; Chorus et al., 2021).

The toxins produced by harmful bloom events are natural environmental contaminants of fresh, brackish and seawater and mainly encompass: (i) cyanotoxins produced by cyanobacteria preferentially in freshwater reservoirs, rivers, lakes and other sources of drinking water, representing direct hazardous potential to human health (Visciano et al., 2016; Stauffer et al. 2019; Christensen and Khan, 2020); and (ii) phycotoxins mainly produced by marine dinoflagellates and diatoms, that can accumulate at high concentrations in various tissues of marine organisms such as bivalve molluscs and fish, consequently threatening human health (Visciano et al., 2016; Pulido, 2016). Among the most relevant and well-studied cyanotoxins are microcystins, nodularins, cylindrospermopsins, lyngbyatoxin-a, anatoxins, saxitoxins and β-N-Methylamino-L-alanine (BMAA) (Solter and Beasley, 2013; Christensen and Khan, 2020). The most relevant phycotoxins produced by diatoms and/or dinoflagellates include saxitoxins, domoic acid, brevetoxins, ciguatoxins, okadaic acid, yessotoxins, azaspiracids and cyclic imines (Solter and Beasley, 2013). Besides the obvious human health concerns linked to cyanotoxins and marine phycotoxins, these toxins are also capable of inflicting damage to the biodiversity and equilibrium of ecosystems, having an impact on both aquatic and terrestrial biota (Pulido, 2016; Chorus et al., 2021).

Indicatively, a search in ISI WoS for review papers made in April 2023 using the terms “cyanotoxins”, “aquatic biotoxins”, “phycotoxins”, “marine biotoxins” and “harmful algal blooms” retrieved a total of 432 hits for the Core Collection database (see Table S1). The majority of these reviews focus on health impacts and exposure routes of humans and human-related models to these toxins (48%), on aquatic toxins detection methods (24%), water treatment strategies and removal of toxins and algae blooms (10%), on aquatic toxins chemical characteristics/structures and environmental persistence/fate (7%), and to a lower extent on biotechnological applications of aquatic toxins (4%). In regards to cyanobacterial toxins, the most reviewed are microcystins, cylindrospermopsins and nodularins. Concerning marine toxins, okadaic acid, cyclic imines and azaspiracids are the most reviewed, followed by the neurotoxic saxitoxins, anatoxins, domoic acid and ciguatoxins. Despite the high number of existent reviews concerning the toxic effects of these toxins on human and related models’ health, more attention is needed regarding their ecotoxicological effects on non-human models only a reduced number of existent reviews (5%) refer to this critical topic. Other largely unexplored topics are the use of alternative detection methods, especially those based on genomic tools, specifically the establishment of effective biomarkers of exposure and effect for these toxins (2% of existent reviews).

Bearing the above in mind, the present review aims at examining the noxious effects of aquatic toxins, but going beyond the better-known toxicity pathways in humans and human health related models, i.e., exploring the information available on ecologically relevant model organisms and associated relevant exposure pathways. This approach provides a broad overview of the exposure and the hazard that these compounds pose for human and environmental health. The focus was tuned to neurotoxic cyanotoxins and phycotoxins (Fig. 1), many of them potentially lethal and/or associated with adverse health effects in humans. The reviewed neurotoxins were chosen taking in consideration their worldwide occurrence, the limited reports existent of cattle and wildlife exposure events and their relevance for human health, which serve as important indicators for their potential relevance for environmental health. Neurotoxins produced by cyanobacteria and/or marine phytoplankton are potent toxins acting through various mechanisms at the cellular level (Aráoz et al., 2010; Metcalf et al., 2021), as elaborated in the following sections. The revision of their geographical distribution, the regulatory measures and monitoring attention they are given worldwide, and importantly, (eco)toxicity data available follows. Critical research gaps and future directions on aquatic toxins research are also discussed, focusing in particular on the need to improve detection tools and methodologies, on the development and implementation of effective biomarkers of exposure and effect for these toxins and on opportunities to improve legislation and monitoring programs. Lastly, useful model organisms are suggested to stimulate future research addressing the environmental hazardous potential of aquatic toxins. Although wide-spanning, this structuring approach follows the preparatory search described above by tackling the lack of reviews on these topics.

2. Freshwater cyanotoxins

Cyanotoxins are secondary metabolites from cyanobacteria that are toxic to living organisms (Carmichael, 1997; Paerl and Otten, 2013). Cyanotoxins are cell-associated and they are typically released into the surrounding water during cell senescence, death, and lysis (Rodgers et al., 2018; Walls et al., 2018; Christensen and Khan, 2020). However, there are exceptions, for example, the neurotoxic anatoxin-a that may leak out of the cells during the growth phase, particularly in low light environments (Christensen and Khan, 2020). The production of cyanotoxins by cyanobacteria is associated with the presence of specific gene clusters, and their expression is induced by environmental conditions such as warmer water temperatures, salinity, adequate light and high nutrient availability, especially nitrate and orthophosphate concentrations (Bláha et al., 2009; Rodgers et al., 2018; Christensen and Khan, 2020; Macário et al., 2021). Cyanotoxins have many functions, namely: chemical defence against competing organisms such as algae (Paerl and Otten, 2013; Murray et al., 2011); cellular nitrogen storage (Murray et al., 2011); DNA metabolism (Murray et al., 2011); chemical signalling (Murray et al., 2011) and contribution to cellular physiology by improving homeostasis, photosynthesis and growth rates (Christensen and Khan, 2020).

Once cyanotoxins are released into the surrounding water, their persistence will depend of environmental factors (e.g., temperature and ultraviolet radiation), on the structure of the toxin itself and also on the persistence traits of the cyanobacteria species that produce them (Christensen and Khan, 2020). Complex mixtures of several cyanotoxins may occur, as a result of blooms of more than one cyanobacterial species at the same time in the same freshwater body (Dietrich et al., 2008; Manganelli et al., 2012; Hercog et al., 2017). This as well as the combined exposure to cyanotoxins and other environmental contaminants, may lead to exacerbated/unexpected toxic effects in the biota (Manganelli et al., 2012; Hercog et al., 2017; Tan et al., 2018; Martin et al.,

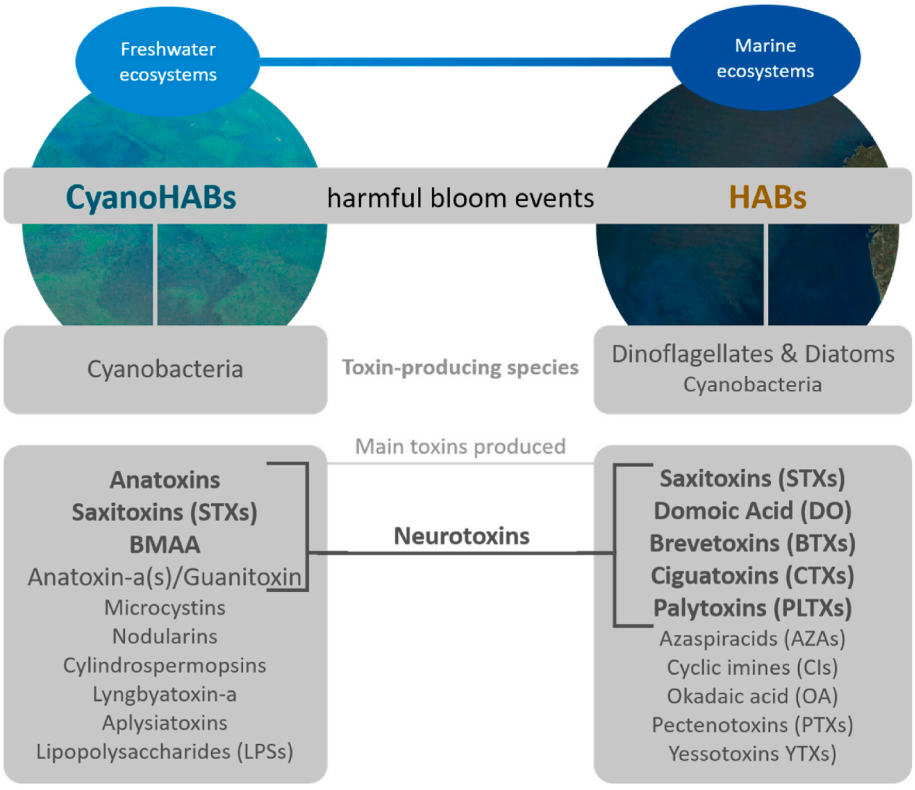

Fig. 1. Overview of bloom forming organisms and their toxins. The focal aspects of the present review are highlighted in bold. The photo illustrating HABs was sourced from the NASA visible earth catalogue.

2019; Wu et al., 2019; Metcalf and Codd, 2020). For example, exposure to mixtures of cyanotoxins often results in more severe effects on the feeding of daphnids than the sum of those expected for exposure to single cyanotoxins (Freitas et al., 2014).

Humans may be exposed to cyanotoxins through several routes. Dermal and inhalation exposure may occur with recreational (sports), professional (i.e., fishing), domestic (i.e., showering) or medical use of contaminated water (Carmichael et al., 2001; Žegura et al., 2011; Bittner et al., 2021). The most important exposure route is however the oral route, which occurs most frequently through the ingestion of contaminated drinking water or accidental swallowing of water during recreational activities (Funari and Testai, 2008; Žegura et al., 2011; Macário et al., 2021). Health effects of acute intoxication with cyanotoxins in humans is well known, but their potential for long-term adverse effects of chronic exposure to environmentally relevant concentrations bellow the established safe guideline values is an area where additional research is required (Žegura et al., 2011). Alongside humans, animals may also be acutely and chronically exposed to cyanotoxins (Landsberg et al., 2020). In fact, mass mortalities of domestic and wild animals, namely dogs, sheep, cows, fish, birds and bats, occur as a result of exposure to cyanobacteria and their toxins (Landsberg, 2002; Briand et al., 2003; Stewart et al., 2008; Landsberg et al., 2020; Metcalf et al., 2021).

Cyanotoxins are a diverse group of compounds, both from the chemical and the toxicological points of view (Bláha et al., 2009; Pulido, 2016), as summarized in Table 1 (chemical structures provided in Fig. 2). In terms of their primary toxicological target, cyanobacterial toxins are classified as hepatotoxins, neurotoxins, dermatoxins and irritant toxins; yet, other toxic effects aside from those resulting from attack to primary targets have been documented for some cyanotoxins (Table 1). Additionally, cyanotoxins can be classified into three main chemical groups: cyclic peptides, alkaloids, and lipopolysaccharides (Bláha et al., 2009; Pulido, 2016; Christensen and Khan, 2020).

Among the most studied and widespread cyanotoxins frequently occurring in fresh and brackish water blooms are microcystins and nodularins, respectively, as well as cylindrospermopsins (Žegura et al., 2011; Bittner et al., 2021) (Table 1). Microcystins are cyclic peptides and are the cyanotoxins most frequently found in the environment (Bláha et al., 2009; Visciano et al., 2016; Macário et al., 2021). Their main mechanism of toxicity is through the inhibition of protein phosphatases, leading to the hyperphosphorylation of cellular proteins and ultimately resulting in the disruption of important cellular processes such as cell division or DNA damage repair (Bittner et al., 2021). Nodularins, also cyclic peptides, have a chemical structure and main toxicity targets similar to those of microcystins (Žegura et al., 2011; Bittner et al., 2021). However, current data indicates that the genotoxic and carcinogenic potential of nodularins might be even stronger than that of microcystins (Žegura et al., 2011; Yilmaz et al., 2022). Cylindrospermopsins are alkaloids that irreversibly inhibit protein synthesis, leading to DNA damage and genomic instability (Bittner et al., 2021). Interestingly, some studies assessed the neurotoxic potential of this cyanotoxin, with Takser and collaborators (2016) reporting cylindrospermopsins-induced apoptosis and inflammation in *in vitro* cultured murine neuroblastoma and glial cells.

Despite its name, anatoxin-a(s)/guanitoxin has no structural similarity to anatoxin-a and it is an organophosphate that inhibits the activity of acetylcholinesterase (Rodgers et al., 2018; Fiore et al., 2020), thus these are potent neurotoxins that inhibit the hydrolysis of acetylcholine at synapses, which leads to an over stimulation of the muscles, convulsions, muscle fatigue, and ultimately respiratory arrest (Fiore et al., 2020). Aplysiatoxin and lyngbyatoxins are alkaloids mainly produced by the marine and estuarine cyanobacteria Lyngbya majuscula (Osborne et al., 2001; Solter and Beasley, 2013), that bind to phorbol esters receptors and activate protein kinase C, which results in excessive phosphorylation of proteins and potent tumour promoting activity (Bláha et al., 2009; Solter and Beasley, 2013). Exposure to lyngbyatoxins can result in acute dermatitis and ocular and respiratory tract irritation. Tumour promotion is also potentially an important consequence of

Table 1
Main groups of cyanotoxins based on their primary mode of action (hepatotoxins, neurotoxins and dermatotoxins and irritants) and known producing species. Data available on environmental persistence (half-life in natural waters), their acute toxicity (LD50) and toxicity pathways are also provided for a general view on the hazardous potential of cyanotoxins. This table was compiled from: Aronstam and Witkop (1981); Mahmood and Carmichael (1987); MacKintosh et al. (1990); Aimi et al. (1990); Carmichael (1992); Stewart et al. (2006); Stewart et al. (2008); Bláha et al. (2009); Lundholm et al. (2009); Takser et al. (2016); Buratti et al. (2017); Sanseverino et al. (2017); Rodgers et al. (2018); Christensen and Khan (2020); Nunes-Costa et al. (2020); Chen et al. (2021) and Chorus and Welker (2021). Chemical structures for representative molecules are available in Fig. 2.

Toxins	Class (No. variants)	Toxin-producing genera	Persistence (half-life)	LD_{50}[a]	Primary mechanism of action	Toxicity pathways
Hepatotoxins						
Microcystins	Cyclic heptapeptides (250)	*Microcystis, Planktothrix, Dolichospermum, Anabaenopsis, Anabaena, Annamia, Nostoc, Geitlerinema, Calothrix and Hapalosiphon*	≤120 days	25–1000	Inhibition of protein phosphatases 1 and 2A	Genotoxic, immunotoxic, carcinogenic, reproductive toxicity, mutagenic and possibly neurotoxic
Nodularins	Cyclic pentapeptides (9)	*Nodularia* and *Nostoc*	≤18 days	30–70	Similar to Microcystins	Genotoxic, carcinogenic and possibly immunotoxic
Cylindrospermopsins	Guanidine alkaloids (4)	*Raphidiopsis*, *Aphanizomenon*, *Anabaena*, *Chrysosporum, Microseira, Hormoscilla* and *Umezakia*	11–56 days	200–2100	Inhibition of protein synthesis and induction of ROS generation	Genotoxic and possibly carcinogenic, immunotoxic, reproductive toxicity and neurotoxic
Neurotoxins						
Anatoxins	Tropane-related alkaloids (5)	*Chrysosporum, Dolichospermum, Anabaena, Raphidiopsis*, *Oscillatoria, Planktothrix, Cuspidothrix, Cylindrospermum, Blennothrix, Geitlerinema, Kamptonema, Microcoleus, Phormidium* and *Tychonema*	≤5 days	250–375	Irreversibly binds to cholinergic receptors	Possibly cytotoxic and genotoxic
Anatoxin-a(s)/ Guanitoxin	Guanidine methyl phosphate ester (1)	*Dolichospermum*	NA	20–40	Inhibitor of acetylcholinesterase at the nerve synapse	NA
Saxitoxins	Carbamate alkaloids (57)	*Aphanizomenon*, *Raphidiopsis*, *Dolichospermum*, *Planktothrix*, *Microseira*, *Anagnostidinema*, *Scytonema*, *Phormidium* and *Cylindrospermum* (Also produced by some marine dinoflagellates)	9–69 days	10–30	Blockage of sodium conductance in axons	Possibly genotoxic, cytotoxic, teratogenic, immunotoxic and epigenetic toxicity
BMAA	Non-proteinogenic amino acid	*Anabaena*, *Calothrix*, *Microscystis*, *Nostoc*, *Scytonema*, *Synechococcus* and *Trichodesmium* (Also produced by some dinoflagellates and diatoms)	NA	118	Glutamate agonist at AMPA, kainite and NMDA receptors	Possibly genotoxic, cytotoxic and epigenetic toxicity
Dermatoxins and endotoxins (irritants)						
Lyngbyatoxin-a	Alkaloid (3)	*Lyngbya**, *Moorea** and *Okeania**	NA	250	Activation of protein kinase C and consequent excessive protein phosphorylation	Carcinogenic
Aplysiatoxin	Alkaloids (2)	*Leibleinia, Schizotrix*, *Phormidium* and *Lyngbya**	NA	100–120	Similar to Lyngbyatoxin-a	Carcinogenic
Lipopolysaccharides (LPSs)	Lipopolysaccharides	All cyanobacteria (All gram-negative bacteria)	NA	40000–250000	Induction of tissue inflammation that leads to a strong response from the immune system	Possibly immunotoxic

[a] LD50: median lethal dose of a substance, acute toxicity in mouse bioassay (intraperitoneal injection exposure, LD50 - μg/kg body). NA – not available. *– taxonomic uncertainty.

lyngbyatoxin-a exposure, not only for humans but also for wildlife populations (Osborne et al., 2001; Solter and Beasley, 2013). Lipopolysaccharides are dermatoxins and endotoxins (irritants) produced by all cyanobacteria (Pilotto et al., 2004; Stewart, Schlute r & Shaw, 2006; Bláha et al., 2009; Monteiro et al., 2016; Metcalf et al., 2021). A lot remains to be investigated regarding the broader toxicity mechanisms of these endotoxins, but they are thought to impair glutathione-based detoxification pathways, which may lead to enhanced toxicity of other co-occurring toxins (Monteiro et al., 2016).

3. Marine phytoplankton toxins

Marine phytoplankton toxins are potent toxins that are largely produced, but not exclusively, by dinoflagellates and diatoms (Fire and Van Dolah, 2012; Morabito et al., 2018). Among the several dinoflagellate and diatom species that produce marine toxins the species belonging to the genera *Alexandrium*, *Gymnodinium*, *Karenia*, *Dinophysis* and *Pseudo-nitzschia* are the main producers of marine toxins with severe implications for human health (Visciano et al., 2016; Farabegoli et al., 2018).

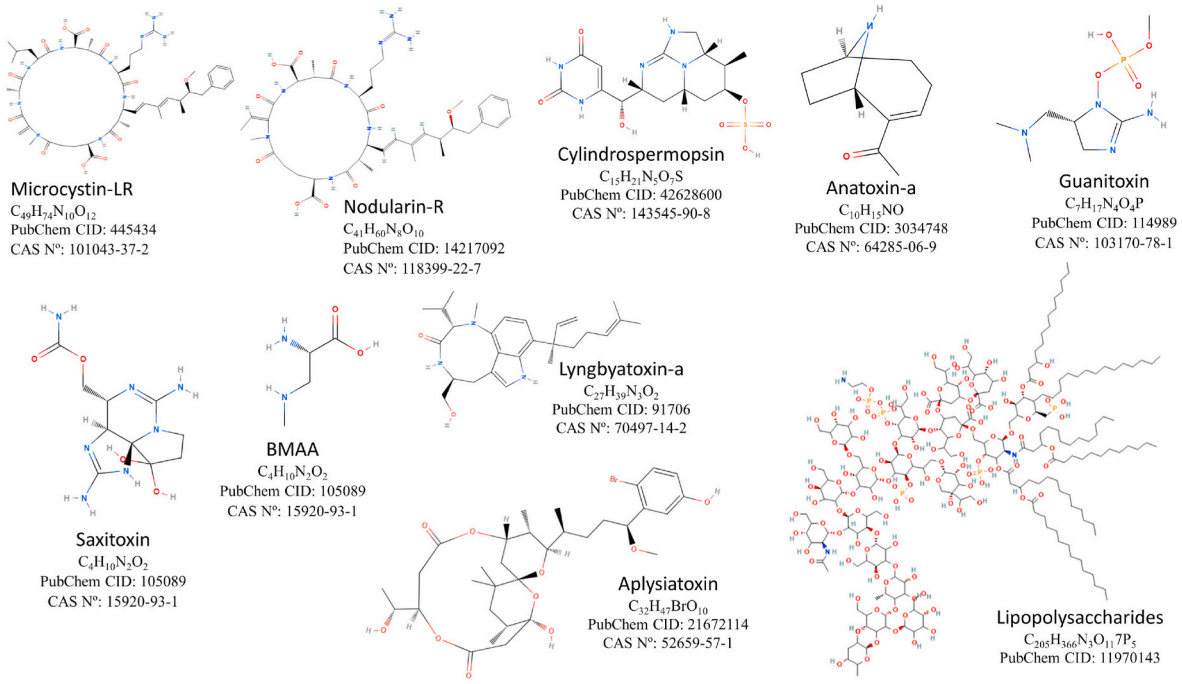

Fig. 2. Chemical structures (built in the MolView free software; https://molview.org) of representatives of major cyanotoxins within main groups based on their primary mode of action (hepatotoxins, neurotoxins and dermatotoxins and irritants), illustrating the information provided in Table 1. PubChem CID - Identifier from NCBI. CAS - Chemical Abstracts Service Identifier.

The main routes of exposure to marine toxins produced by dinoflagellates and diatoms are through ingestion of contaminated seafood, aerosols inhalation and direct contact, i.e., cutaneous and ocular exposure (Vale et al., 2008; Paredes et al., 2011; Fire and Van Dolah, 2012; Pulido, 2016). These compounds contaminate seawater environments and accumulate at high concentrations in various tissues of aquatic animals such as bivalve molluscs, crustaceans and fish (Ciminiello and Fattorusso, 2006; Vale et al., 2008; Gerssen et al., 2010; Pulido, 2016), making their way through the food chain. Marine toxins may persist in aquatic organisms' tissues for many months after the algal bloom has disappeared, leading to intoxication events as a result of eating contaminated food long after the occurrence of toxic algal blooms (Toyofuku, 2006; Hess, 2010; Gaboriau et al., 2014; Visciano et al., 2016; Nicolas et al., 2017). The persistence of these toxins particularly in shellfish is mainly due to the prevalence of slow natural detoxification metabolisms in affected species (Bricelj and Shumway, 1998; Hess, 2010; Botelho et al., 2020). Exposure to complex mixtures of several marine toxins is possible (e.g., Fire et al., 2011; Zamorano et al., 2013; García et al., 2016), often leading to additive or synergistic toxic effects both in humans and other species (Sosa et al., 2013, 2022; Berdalet et al., 2016; Ferron et al., 2016; Alarcan et al., 2018).

Marine toxins can be distinguished as hydrophilic and lipophilic according to their solubility (Altamirano and Sierra-Beltrán, 2008; Visciano et al., 2016). However, the most common way of grouping marine toxins is through the poisoning syndromes they cause. Outbreaks of intoxication in humans due to marine toxins can have a wide range of symptoms linked to the specific toxic compound (Farabegoli et al., 2018). The main and best-studied marine phycotoxin seafood poisoning syndromes are: paralytic shellfish poisoning (PSP), amnesic shellfish poisoning (ASP), diarrheic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), ciguatera fish poisoning (CFP) and pufferfish poisoning (PFP) (Poletti et al., 2003; Altamirano and Sierra-Beltrán, 2008; Nicolas et al., 2017). DSP and CFP have been the most prevailing poisoning syndromes related to marine toxins (Nicolas et al., 2017; Farabegoli et al., 2018).

More practically, marine toxins can be classified into ten main groups (Table 2; chemical structures provided in Fig. 3), according to their chemical structure – namely the azaspiracids (AZAs), brevetoxins (BTXs), cyclic imines (CIs), domoic acid (DA), okadaic acid (OA), pectenotoxins (PTXs), saxitoxins (STXs), yessotoxins (YTXs), palytoxins (PLTXs) and ciguatoxins (CTXs) groups (Visciano et al., 2016; Nicolas et al., 2017).

4. Freshwater and marine neurotoxins

Following the focus of this review, the subsequent subsections address in detail the neurotoxins produced in freshwater and marine environments by phytoplankton that have been touted as more relevant for human and environmental health. Under this latter criterion, we will not review anatoxin-a(s)/guanitoxins considering that there are little confirmed human exposures to these toxins (Fiore et al., 2020), the neurotoxic bacteria-produced tetrodotoxin since it is not produced by phytoplankton species (Lago et al., 2015) or cyclic imines since the hazard they pose to human health is thought to be negligible (Otero et al., 2011; Moreiras et al., 2020). The geographical distribution, the regulatory and monitoring attention neurotoxins are given worldwide, as well as (eco)toxicity data available so far, were reviewed, providing a broad overview of the exposure and effects in humans and other biota.

4.1. Anatoxins

There are three categories of anatoxins, i.e.: anatoxin-a, homoanatoxin-a, dihydroanatoxin-a and dihydrohomoanatoxin-a (Fiore et al., 2020). We will cover in detail anatoxin-a, as this is the most studied and the most common anatoxin analogue in freshwaters. Anatoxin-a (Table 1; Fig. 2) is an alkaloid that mimics the neurotransmitter acetylcholine and binds irreversibly to the nicotinic receptor receiver S of acetylcholine in neuromuscular junctions, therefore interfering with nerve cells throughout the body and also disrupting the messages that these nerve cells send to the brain (Pulido, 2016; Rodgers et al., 2018; Christensen and Khan, 2020). Anatoxin-a is not degraded by acetylcholinesterase, thus muscles become overstimulated, including

Table 2
Overview of the major marine toxins. Data available on their class, human poisoning syndrome, known producing genera/species, acute toxicity (LD_{50}) and mechanisms of toxicity, providing a general view on the hazardous potential of marine toxins. This table was compiled from (Narahashi et al., 1964; Bialojan and Takai, 1988; Habermann, 1989; Leira et al., 2002; Alfonso et al., 2003; Espiña and Rubiolo, 2008; Paz et al., 2008; Lundholm et al., 2009; Araoz et al., 2011; Otero et al., 2011; Suzuki and Quilliam, 2011; Valdiglesias et al., 2013; Cusick and Sayler, 2013; Stivala et al., 2015; Jal and Khora, 2015; Alfonso et al., 2016; Pulido, 2016; Patocka et al., 2018; Murk et al., 2019; Wietkamp et al., 2020 and Boundy et al., 2020; Pasinszki et al., 2020; Boente-Juncal et al., 2021 and Hort et al., 2021). Chemical structures for representative molecules are available in Fig. 3.

Toxins	Structure (No. variants)	Poisoning syndrome	Toxin-producing genera/species	LD_{50}[a]	Primary mechanism of action	Toxicity pathways
Saxitoxins (STXs)	Carbamate alkaloids (57)	Paralytic Shellfish Poisoning (PSP)	Dinoflagellates: *Gymnodinium catenatum, Alexandrium* spp., *Pyrodinium bahamense, Centrodinium punctatum*. (Also produced by cyanobacteria)	10–30	Blockage of sodium conductance in axons	Neurotoxic and possibly genotoxic, cytotoxic, teratogenic, immunotoxic and epigenetic toxicity
Brevetoxins (BTXs)	Cyclic polyethers (More than 10)	Neurotoxic Shellfish Poisoning (NSP)	Dinoflagellates: *Kare*nia spp.	170	Binding and activation of voltage-gated sodium channels	Neurotoxic, immunotoxic, genotoxic, cytotoxic and possibly carcinogenic and epigenetic toxicity
Domoic acid (DA)	Cyclic tricarboxylic amino acid	Amnesic Shellfish Poisoning (ASP)	Diatoms: *Pseudo-nitzschia* spp., *Nitzschia bizertensis* and *Nitzschia navis-varingica*. (Also produced by the red macroalgae *Chondria armata*)	3600	Agonist of the kainite receptors, induction of excitotoxicity.	Neurotoxic and possibly genotoxic, cytotoxic, teratogenic, immunotoxic and gene expression modulating effects
Ciguatoxins (CTXs)	Cyclic polyethers (47)	Ciguatera Fish Poisoning (CFP)	Dinoflagellates: *Gambierdiscus* spp. and *Fukuyoa* spp.	0.45–1	Activation of the sodium channels	Neurotoxic and possibly cytotoxic, teratogenic, immunotoxic and gene expression modulating effects
Azaspiracids (AZAs)	Cyclic polyethers (32)	Azaspiracids Poisoning (AZP)	Dinoflagellates: Azadinium spp. and Amphidoma languida	200	Interfering with volume-regulated anion channels	Cytotoxic and possibly neurotoxic and carcinogenic
Palytoxins (PLTXs)	Polyethers (20)	Palytoxin Poisoning (PP)	Dinoflagellates: *Ostreopsis* spp. (Also produced by the zoanthid *Palythoa* spp.)	0.45	Binding to extra-cellular sodium and potassium channels	Neurotoxic, carcinogenic, cytotoxic and possibly teratogenic and immunotoxic
Yessotoxins (YTXs)	Polyethers (100)	No acute toxicity towards humans recorded	Dinoflagellates: Protoceratium reticulatum, Lingulodinium polyedrum, Gonyaulax spinifera and G. taylorii	380–460	Activation of phosphodiesterase	Cardiac toxicity and cytotoxic
Okadaic acid (OA)	Polyethers (12)	Diarrheic Shellfish Poisoning (DSP)	Dinoflagellates: *Dinophysis acuta; D. acuminata; D. caudata; D. fortii; D. infundibulum; D. miles; D. norvegica; D. ovum; D. sacculus; Prorocentrum arenarium; P. belizeanium; P. concavum* and *P. lima*	192	Inhibition of serine/threonine protein phosphatases	Carcinogenic, cytotoxic and possibly epigenetic toxicity, genotoxic, teratogenic, immunotoxic and neurotoxic
Pectenotoxins (PTXs)	Polyethers (More than 10)	Diarrheic Shellfish Poisoning (DSP)	Dinoflagellates: *Dynophysis* spp.	244	Binding to actin and preventing its polymerization	Hepatotoxic and cytotoxic
Cyclic imines (CIs)	Cyclic imines (More than 30)	No acute toxicity towards humans	Dinoflagellates: A. ostenfeldii, Vulcanodinium rugosum, Karenia selliformis and Prorocentrum spp.	6.9–96	Inhibition of cholinergic receptors	Neurotoxic and possibly gene expression modulating effects
Tetrodotoxin	Non-proteinogenic toxin (10)	Pufferfish Poisoning (PFP)	Bacteria	2–10	Similar to STXs	Neurotoxic

[a] LD50: median lethal dose of a substance, acute toxicity in mouse bioassay (intraperitoneal injection exposure, LD50 - μg/kg body). NA – not available.

respiratory muscles, leading to fatigue and ultimately death by respiratory failure (Christensen and Khan, 2020).

4.1.1. Anatoxin-a production, distribution and regulation

The *ana* gene cluster responsible for anatoxin production, is upregulated under stress conditions such as nitrogen-starvation, the presence of competing organisms, such as algae, and sub-optimal light and/or temperature ranges (Murray et al., 2011; Boopathi and Ki, 2014). Anatoxin-a is only known to be produced by freshwater cyanobacteria (Colas et al., 2021), with an estimated 41 freshwater species capable of producing it (Christensen and Khan, 2020). Anatoxin-a is believed to be stable in acidified (pH < 3) conditions, with an estimated half-life of 1–2 h under normal light and pH conditions (pH 8 to 9) (Christensen and Khan, 2020; Chorus and Welker, 2021). However, low light conditions and low temperatures (under 20 °C) can lead to higher anatoxin-a persistence and increased half-life to about 5 days in the absence of light even at pH 9 (Kaminski et al., 2013; Christensen and Khan, 2020).

Anatoxin-a has a worldwide distribution that includes temperate, tropical and cold climatic regions (Pulido, 2016; Chorus and Welker, 2021). In the USA, variable anatoxin-a concentrations up to 35 μg/L were measured in water samples collected from eight Nebraska reservoirs between 2009 and 2010 (Al-Sammak et al., 2014; Chorus and Welker, 2021). Also in the USA, the highest anatoxins levels (1170 μg/L) were found in Washington State, in long-term recurring blooms (Trainer and Hardy, 2015; Chorus and Welker, 2021). A similar situation occurred in German and Irish freshwater lakes and reservoirs having anatoxin-a and homoanatoxin-a concentrations ranging from 13.1 to 34 μg/L (Bumke-Vogt, Mailahn and Chorus, 1999; Furey et al., 2003; Chorus and Welker, 2021). These quantified levels of anatoxin-a are within the ranges found to elicit relevant ecotoxicological effects in the aquatic biota as explored in section 4.1.2.

Currently, only Canada and New Zealand established and enforce provisional maximum concentration values for anatoxin-a in drinking water of 3.7 μg/L and 6 μg/L, respectively (Sanseverino et al., 2017). In the USA, each State establishes their respective guideline for anatoxin-a with the drinking water guidelines ranging from 1 to 20 μg/L and the recreational guideline ranging from 1 μg/L up to 300 μg/L (Farrer et al., 2015; Mehinto et al., 2021). More broadly, the World Health Organization (WHO) has also established provisional guideline values for anatoxin-a in drinking waters (30 μg/L) and in recreational waters (60 μg/L) (World Health Organization, 2020a).

4.1.2. The known and the suspects regarding anatoxins (eco)toxicity

Acute human health effects of anatoxin-a poisoning include

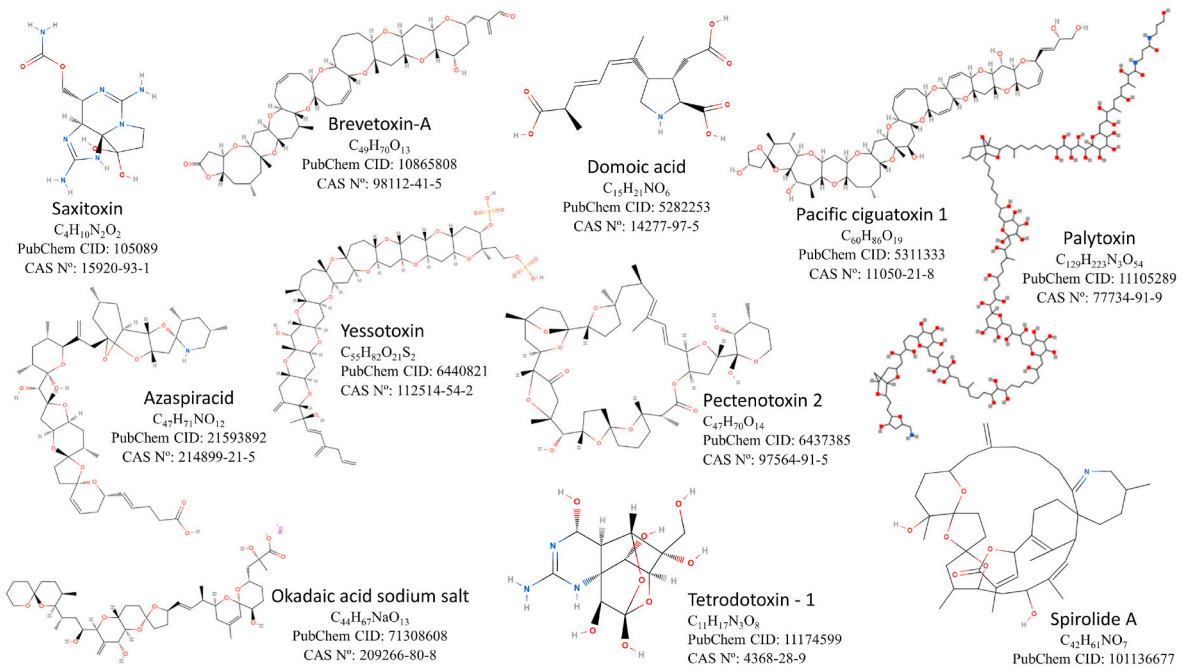

Fig. 3. Chemical structures (built in the MolView free software; https://molview.org) of major marine toxins, illustrating the information provided in Table 2. PubChem CID - Identifier from NCBI. CAS - Chemical Abstracts Service Identifier.

convulsions, muscular twitching, imbalance, paralysis and in severe cases respiratory failure (Christensen and Khan, 2020). Although it has been proposed that anatoxin-a is unlikely to be of significant concern with regard to long-term exposure (Žegura et al., 2011), such a claim should not be uptake so lightly. For example, insecticides acting similarly such as neonicotinoids were largely demonstrated to have chronic effects in aquatic invertebrates (e.g., Van den Brink et al. 2016; Ewere et al., 2021) and vertebrates (e.g., Hong et al. 2018).

Anatoxin-a (4 μg/mL) showed cytotoxic effects in non-neuronal cells and can induce ROS formation, ultimately leading to secondary DNA damage and activation of caspase-3 in cultured rat thymocytes (Lakshmana Rao et al., 2002). Accordingly, anatoxin-a (1 μg/mL) is able to activate caspases 3/7 in carp cells, indicating a potential apoptotic inducing effect (Sierosławska and Rymuszka, 2013). Additionally, zebrafish exposed to anatoxin-a (0.8 μg/g bw) via intraperitoneal injection developed early proteome changes in brain and muscle tissue, with proteins involved in carbohydrate metabolism, energy production, cell structure maintenance, cellular transport, protein folding, stress response, detoxification and protease inhibition showing altered levels (Carneiro et al., 2015). In addition to constraining protein activity, anatoxin-a is also capable of modulate gene expression, with Schwarzenberger and Martin-Creuzburg (2021) reporting increased expression of genes for nicotine-acetylcholine receptors following *Daphnia magna* exposure to cyanobacteria producing anatoxin-a (161.8 ng/mg carbon). Anatoxin-a also induced significant increase on the activity of several biochemical biomarkers, like acetylcholinesterase, glutathione s-transferase and ethoxyresorufin-O-deethylase activity, in the rainbow trout exposed via intraperitoneal injection at concentrations ranging from 0.2 to 0.31 μg/g (Osswald et al., 2013). The increased activity of acetylcholinesterase was dose-dependent and possibly represents an attempt to cope with overstimulation of muscle activity by the toxin, which competes with acetylcholine for nicotinic receptors binding (Osswald et al., 2013). The results obtained by Osswald et al. (2013) suggest that a continued exposure of fish to anatoxin-a may lead to motor and metabolic difficulties, ultimately making them more vulnerable to predators. Consistently, anatoxin-a exposure (0.1–100 μg/L) also induced neurobehavioral and physiological alterations on *Caenorhabditis elegans*, such as substantial locomotive behavioural alterations, altered pharyngeal pumping frequency and reduced sensory function (Ju et al., 2014); the locomotor activity of cockroaches was affected by cyanobacterial extracts containing anatoxin-a (Dos Santos et al., 2019); exposure of *D. magna* to anatoxin-a (0.5–50 μg/mL) resulted in decreased swimming speed, abdominal claw movements and heart rate (Bownik and Pawlik-Skowrońska, 2019); juvenile carps (*Cyprinus carpio*) exposed to the cyanobacterial suspensions containing anatoxin-a showed rapid opercular movement and abnormal swimming, this behavioural alterations may have negative consequences on fish populations due to changes in reproductive and predator–prey interactions (Osswald et al., 2007); and zebrafish exposed to pure anatoxin-a (400 μg/L) showed altered hearth rates (Oberemm et al., 1999). Feeding inhibition of *D. magna* was also reported following exposure to cyanobacterial extracts containing anatoxin-a (Rivetti et al., 2015).

Daphnia pulex exposed to anatoxin-a (1 μg/mL) exhibited decreased population growth rate with higher temperature influencing the sensitivity of *D. pulex* to anatoxin-a (Claska and Gilbert, 1998), which may leave this species more susceptible to anatoxin-a toxic effects in light of ongoing climate change scenarios.

4.2. Saxitoxins

Saxitoxins (Tables 1 and 2 and Figs. 2 and 3) are potent naturally occurring neurotoxins (Metcalf and Codd, 2009; Christensen and Khan, 2020). Saxitoxin and its derivatives (STXs) selectively block voltage-gated Na^+ and Ca^{2+} channels and are K^+ channel gating modifiers in excitable cells, affecting neural impulse generation (Murray et al., 2011; Christensen and Khan, 2020). Subsequently, the stimulation of muscles is suppressed that can result in paralysis (Christensen and Khan, 2020).

Originally, STXs were isolated from shellfish where they accumulate from marine dinoflagellates (Wiese et al., 2010; Orr et al., 2013), promoting the PSP poisoning syndrome (Table 2). The main symptoms of STXs acute toxicity include burning, numbness, cramps, vomiting, diarrhoea, signs of paralysis, blocking of respiration, excessive perspiration, salivation and headache (Visciano et al., 2016; O'Neill et al., 2016; Rutkowska et al., 2019). Despite the wide association of STXs with marine environments, the same variants are produced by some species

of freshwater cyanobacteria (Žegura et al., 2011; Christensen and Khan, 2020). In fact, STXs production by cyanobacteria is believed to be an ancient trait, obtained by vertical inheritance of a gene cluster responsible for saxitoxin production around 2.1 million years ago (Murray et al., 2011; Christensen and Khan, 2020). It is suggested that the saxitoxin gene cluster (*stx*) has a vital role in the survival of the species that possess it, since there is a strong conservation of this gene cluster over time (O'Neill et al., 2016). The hypothesis that STXs are not synthesized by algae themselves in marine environments but rather by endosymbiotic bacteria (cyanobacteria) was already raised. However, the production of these toxins is anchored in the genetic code of algae (Pearson et al., 2010; Akbar et al., 2020), yet thought to be the result of a close interaction that existed or perhaps still exists between certain bacteria and toxin producing algae (Cusick and Sayler, 2013; Murk et al., 2019). Recent studies uncovered that dinoflagellates might have a different set of *stx* genes for saxitoxin biosynthesis, due to the fact that their evolution occurred independently from cyanobacteria, which led to the secondary loss of key gene cluster elements (Akbar et al., 2020; Cembella and Durán-Riveroll, 2021).

More than 50 derivates of the main toxin STX are known (Visciano et al., 2016; O'Neill et al., 2016; Murk et al., 2019; Leal and Cristiano, 2022), e.g., gonyautoxins, neosaxitoxin, decarbamoyl-saxitoxin, decarbamoyl-neosaxitoxin, decarbamoyl-gonyautoxins, hydroxybenzoates, sulfated-benzoates, acetate and deoxy-decarbamoyl derivatives (O'Neill et al., 2016; Farabegoli et al., 2018; Raposo et al., 2020). These toxins can be assigned to 3 main groups, of which the carbamoyl toxins are toxicologically the most significant, whilst the decarbamoyl and the N-sulfocarbamoyl derivates have much lower toxicity (European Food Safety Authority, 2009; Murk et al., 2019). Only a few are directly produced by cyanobacteria and/or dinoflagellates, with the others being formed after enzymatic and chemical reactions that typically occur in vector species tissues (Bricelj and Shumway, 1998; Vale, 2010; Wiese et al., 2010). The constant discovery of new STX analogues is making PSP monitoring a challenging task (Vale, 2010; Wiese et al., 2010; Farabegoli et al., 2018).

4.2.1. Saxitoxin production, distribution and regulation

The saxitoxin producing gene cluster (*stx*) is upregulated by high temperatures, high light intensity and extracellular NaCl but downregulated by high levels of nitrogen and dark conditions (Boopathi and Ki, 2014). Compared with anatoxin-a, the number of freshwater species capable of producing STXs is much lower, with only 15 species identified so far (Christensen and Khan, 2020). The main toxin STX is stable at low pH conditions (2–4) but its half-life is considerably higher when compared to anatoxin-a (Pereira et al., 2004; Harland et al., 2015). STXs half-life ranged from about 9 to 28 days in irrigation drain water and river water, up to 69 days in sterile water at 25 °C and neutral pH (Jones and Negri, 1997). However, STXs often transform from low toxicity N-sulfocarbamoyl derivates, highly unstable at low pH, to more stable high toxicity analogues, resulting in increased toxicity (Pereira et al., 2004; Harland et al., 2015).

STXs-producing cyanobacterial species have been found in many freshwater locations around the world, namely the Arctic, New Zealand, Canada and Europe, with concentrations of 0.09 μg/L to 193 μg/L (Boyer, 2008; Trainer and Hardy, 2015; Chorus and Welker, 2021) that meet ranges inducing sub-lethal ecotoxicological effects (see section 4.2.2). In Australia, Brazil and New Zeeland a guideline value of 3 μg/L is recommended for STXs in drinking waters (Sanseverino et al., 2017). In the USA, each state establishes their respective guideline for STXs with Ohio being the only state with a drinking water guideline of 0.2 μg/L and the recreational guideline ranging from 0.8 μg/L up to 75 μg/L (Farrer et al., 2015; Mehinto et al., 2021). The WHO has established guideline values for STXs of 3 μg/L in drinking waters and of 30 μg/L in recreational waters (World Health Organization, 2020b).

The main producers of PSP toxins in marine environments are dinoflagellates from the genera *Alexandrium*, *Gymnodinium* and *Pyrodinium*, which occur primarily along the Atlantic and Pacific coasts (O'Neill et al., 2016; Visciano et al., 2016; Botelho et al., 2019). *G. catenatum* has also been found in the Mediterranean Sea (Ordás et al., 2004). Despite the numerous fatal cases of PSP that are reported globally each year (see section 4.2.2 below for more details), the successful implementation of monitoring programs in many countries has helped to minimize health risks and reduce human illnesses and fatalities (Vale et al., 2008; Cusick and Sayler, 2013; O'Neill et al., 2016; Murk et al., 2019). In the European Union (EU), Regulation (EC) No 854/2004 establishes weakly monitoring and sampling plans targeting marine toxins and of toxin-producing phytoplankton species in bivalve production areas (European Commission, 2004); the total STXs content in seafood (measured in the whole body or any part edible separately) should not exceed 800 μg/kg of seafood. This latter limit corresponds to most limits established in countries outside the EU, including USA, Australia and Japan (Murk et al., 2019; Laughrey et al., 2022).

It is likely that production of STXs will be an increasing concern as producing species growth has been predicted to increase with the projected future changes to climate (Cusick and Sayler, 2013; O'Neill et al., 2016), and considering that STXs are found in fresh and marine waters worldwide. A lot remains to be investigated mainly regarding biological effects other than the neurotoxic effects related to the STXs primary mechanism of toxicity. Additionally, and as a parallel is made with insecticides with a similar primary mechanism of toxicity such as pyrethroids (sodium channel modulators), diverse effects resulting from chronic, low-level exposure to STXs should definitively be expected in the aquatic biota (e.g., Xiang et al. 2019; Groh et al. 2015; Rasmussen et al. 2013).

4.2.2. The known and the suspects regarding saxitoxins (eco)toxicity

A high number of human PSP intoxication cases through the consumption of contaminated seafood, cephalopods and fish are reported every year, especially in Japan and South America (Visciano et al., 2016; O'Neill et al., 2016; Murk et al., 2019). STXs accumulation generally occurs in the viscera of contaminated seafood, while in the common octopus and squid, STXs accumulate to a greatest extent (390 up to 2680 mg/kg) in the digestive gland (Lopes et al., 2014; Chorus and Welker, 2021). Fish used for human consumption have also been shown to accumulate STXs, primarily in livers (up to 0.6 mg/kg FW) but also in muscle tissue (up to 0.02 mg/kg FW) (Testai et al., 2016). Bivalves are also known for accumulating STXs, with a study reporting that some Patagonia fishermen were intoxicated by consumption of bivalve contaminated with up to 8575 mg of STX/100g of shellfish meat (Garcia et al., 2004). In Portugal, two human STXs intoxication cases were reported in 2018 after consumption of STXs-contaminated blue mussels (*Mytilus* spp.) (0.104 up to 0.12 mg of STX/kg) (de Carvalho et al., 2019). Despite being extensively studied in the marine environment context and the recognition that STXs are powerful freshwater toxins, a lot remains to be elucidated regarding oral exposure to this toxin through contact and/or ingestion of freshwater (Metcalf and Codd, 2009; Christensen and Khan, 2020), yet similar responses are expected.

STXs have been confirmed or implicated in the deaths of several marine species such as sea birds (ingestion of contaminated fish), whales and monk seals (Cusick and Sayler, 2013; O'Neill et al., 2016). Given STXs mode of action, a vast amount of studies report on neurotoxicity-related effects of this toxin in several species. Ferrão-Filho et al. (2010) reported that STXs (0.0003–3.48 μg/L) inhibit swimming and physiological parameters in *D. pulex* exposed to contaminated water. Similar results were obtained by Ferrão-Filho & da Silva (2020) with *D. similis* exposed to several concentrations of cells of a STXs-producing cyanobacteria strain (*Raphidiopsis raciborskii*), namely impairment of swimming, reduced thoracic limb movement that impaired the feeding of the exposed organisms and decreased heart rate. Lefebvre et al. (2005) exposed Pacific herring (*Clupea harengus pallasi*) larvae to purified STXs (50 μg/L to 1700 μg/L) and reported significant reduction in spontaneous and touch-activated swimming behaviour.

Dusek et al. (2021) reported head shaking, excessive drinking, regurgitating, wing twitching, tail "wagging" and mortalities in mallards (*Anas platyrhynchos*) exposed to purified STXs.

There are limited experimental data for sub-chronic exposure, reproductive, teratogenic or carcinogenic effects of STXs (Žegura et al., 2011). Oberemm et al. (1999) stated that pure STXs (500 μg/L) led to malformations (i.e., lateral and ventral body curvature and oedema) and increased mortality in zebrafish embryos. Similar results were obtained by Bif and collaborators (2013) in sea urchins (*Arbacia lixula* and *Lytechinus variegatus*) larvae exposed to cyanobacterial extracts containing environmentally relevant concentrations of STXs (2.06–2.96 μg/L), and at 25 μg/L, the eggs of sea urchins showed development delays (Bif et al., 2013). At the sub-cellular level, 7.37 to 23.24 μg STX/100 g fish tissue can cause oxidative stress, DNA damage and osmoregulatory alterations in the freshwater cichlid fish (Geophagus brasiliensis) (de Morais Calado et al., 2020). Similar effects were reported by Melegari et al. (2015) that reported STXs (0.5–64 nM) may trigger multiple cellular mechanisms, cause DNA fragmentation and G0/G1 cycle cell arrest leading to cell death through an apoptotic process in mammalian cell lines. STXs also promoted the expression of vascular development-related genes DLL4 and VEGFC, and altered the transcriptional regulation of apoptosis-related genes (BAX, BCL-2, P53 and CASPASE 3) in zebrafish (*Danio rerio*) embryos after exposure to levels as low was 14.96 μg/L (Chen et al., 2020). Da Silva and collaborators (2011) exposed the wolf fish (*Hoplias malabaricus*) to STXs-contaminated prey and reported an inhibition of the antioxidant system in the brain and an increased superoxide dismutase activity, plus, lipoperoxidation, protein carbonylation and an increase in DNA strand breaks. Mat and collaborators (2013) demonstrated that exposure of the Pacific oyster *Crassostrea gigas* to *Alexandrium* microalgae producing STXs, induces genotoxicity as well as transcriptional repression of genes involved in oxidative and mitochondrial metabolism, endogenous clock regulation, detoxification processes and the activation of immune response machinery (Mat et al., 2013). Roncalli et al. (2016) exposed the copepod *Calanus finmarchicus* to STXs-producing dinoflagellates and also demonstrated a down-regulation of transcripts involved in lipid biosynthesis, growth and reproduction following exposure, which suggests that copepods exposed to STXs have less energy available and lower egg production and quality. Although there are no parallel studies in environmentally-relevant models for confirmation, STXs induced cytotoxicity and altered DNA methylation patterns (increased methylation of cytosines) in neuro-2A mouse neuroblastoma cells exposed to extremely low concentrations of STXs (0.75 nM) (Perreault et al., 2011).

4.3. β-N-Methylamino-L-alanine

BMAA (Table 1; Fig. 2) is a non-proteinaceous amino acid typically associated with soil but that can also be produced by freshwater cyanobacteria and marine phytoplankton species (Pierozan et al., 2020; Christensen and Khan, 2020). This neurotoxin acts predominantly on motor neuron-inducing excitotoxicity mediated through glutamate receptors (Rodgers et al., 2018; Pulido, 2016).

4.3.1. BMAA production, distribution and regulation

In a screen of 30 laboratory strains and some environmental samples of cyanobacteria, 97% were found to produce BMAA as both a free amino acid and associated with cyanobacterial proteins (Cox et al., 2005). Due to the ubiquitous distribution of cyanobacteria, BMAA can be widely spread in water resources required for human and animal use (Violi et al., 2019; Christensen and Khan, 2020). Accordingly, analyses carried out in the UK, Netherlands, South Africa and Australia have indicated that a high percentage of environmental cyanobacterial bloom samples contained BMAA, with concentrations of free BMAA in the water ranging from 27 to 147 μg/L (Metcalf and Codd, 2009). BMAA is known for co-occurring with microcystins, nodularins, anatoxin-a, saxitoxins and LPSs (Metcalf and Codd, 2009; Rodgers et al., 2018; Violi et al., 2019); the appraisal of the risks posed by these apparently common mixtures of toxins has been largely disregarded (Rodgers et al., 2018; Violi et al., 2019). BMAA is stable in surface waters and degradation was found to be slower in natural water when compared with deionized water (Chen et al., 2018; Cao et al., 2019). To date, no safety guidelines have been suggested for BMAA (Sanseverino et al., 2017; Chorus and Welker, 2021). This can be linked to controversy concerning the BMAA link with neurodegenerative diseases (Chernoff et al., 2017), the poor feasibility of BMAA detection and quantification methods (Lance et al., 2018) and the low relevance of some BMAA toxic effects at unrealistic high concentrations (Chernoff et al., 2017). The inexistence of BMAA toxicity at environmentally relevant concentrations was challenged by Dunlop et al. (2021) and some ecotoxicological testing results as detailed in section 4.3.2. Recent evidence seems to confirm that BMAA indeed has a role in slow-developing neurodegenerative diseases (Nunes-Costa et al., 2020). Thus, and although further studies employing ecologically realistic exposure designs are needed to finally settle this controversial matter, it is reasonable to argue that safety guideline values for BMAA in fresh and marine waters should rapidly be established in order to protect human and environmental health.

Whilst initially thought to be restricted to cyanobacteria, BMAA production has more recently been detected in other phytoplankton groups, such as marine diatoms and the marine dinoflagellate *G. catenatum* (Rodgers et al., 2018; Pierozan et al., 2020). Accordingly, BMAA has been found in high concentrations in bivalves, fish and crustaceans (0.07 up to 352.2 mg/kg FW) (Lance et al., 2018; Chorus and Welker, 2021). In addition to ingestion of BMAA-contaminated water and agricultural plants, consumption of contaminated seafood are the likely routes of human BMAA exposure (Lance et al., 2018; Rodgers et al., 2018; Chorus and Welker, 2021).

4.3.2. The known and the suspects regarding BMAA (eco)toxicity

In vitro and *in vivo* toxicity studies with BMAA have shown neurodegenerative effects in animals, such as damage to motor neuron cultures (Rao et al., 2006; Karamyan and Speth, 2008); neuromorphological changes (de Munck et al., 2015), protein misfolding and enzyme inhibition that ultimately led to neuroinflammation (Nunes-Costa et al., 2020) and impaired neurotransmission (excitotoxicity) (de Munck et al., 2015; Carion et al., 2020). Similar neurological and behavioural symptoms are reported in environmental model organisms, with mangrove rivulus (*Kryptolebias marmoratus*) exposed to BMAA concentrations of 20 μg/L and 15 mg/L showing increased expression of neuromodulator genes calmodulin and monoamine oxidase A (Carion et al., 2020), reduced motor capabilities and impaired response to environmental stimulus, resulting in a reduced overall fitness and altered behavioural patterns of the exposed fish (Carion et al., 2018). In invertebrates such as *D. magna,* several sub-lethal effects such as reduction in the physical activity of exposed organisms were noticed only as a consequence of high concentrations of BMAA (354 μg/mL) (Błaszczyk et al., 2021); reduced mobility and reproduction in response to BMAA concentrations of approximately 40 μg/L (Lürling et al., 2011); and dopaminergic neurons degeneration leading to reduced reproduction capability and population growth at concentrations ranging from 200 to 1000 μg/L (Brooke-Jones et al., 2018). Also, in the brine shrimp (*Artemia salina*) loss of phototaxis following exposure to BMAA at concentrations higher than 500 μg/L was reported (Purdie et al., 2009).

In addition to the above effects related to neurotoxicity, BMAA (7.5 μg of dissolved BMAA/mussel) induces transient DNA damage, leading to a short-term cellular death of haemocytes from mussels (Lepoutre et al., 2018). However, whether this neurotoxin has directly induced DNA strand breaks and cell cytotoxicity, or rather indirectly via pathways such as oxidative stress or protein misfolding, remains to be investigated (Lepoutre et al., 2018). Interestingly, a study by Esterhuizen-Londt et al. (2011) reported that BMAA (at concentrations ranging from 0.5 to 100 μg/L) triggered oxidative stress indirectly in

macrophytes. Another study conducted by Esterhuizen-Londt et al. (2015), using *Daphnia magna*, also concluded that 100–1000 μg BMAA/L can induce oxidative stress by inhibiting oxidative stress defence mechanisms and biotransformation enzymes, therefore impairing the detoxifying capabilities of the exposed organisms. However, further studies are required to determine the exact mechanism by which BMAA inhibits these antioxidant enzymes.

BMAA was found to be clastogenic and inducing complex genomic alterations, including structural chromosomal rearrangements and gene amplification in human peripheral blood cells (Gerić et al., 2019); these findings provide new evidence that BMAA can induce genomic instability that might lead to cancer onset, especially as a result of chronic exposures (Gerić et al., 2019; Mutoti et al., 2022). Additionally, BMAA reduced global DNA methylation in neuronal rat cells, indicating that the persistent nature of the BMAA-induced effects may be related to epigenetic alterations that interfere with the neural stem cell programming (Pierozan et al., 2020). Importantly, the changes induced by BMAA in neural stem cells were mitotically inherited to daughter cells, which helps explain how early-life exposure to BMAA may lead to adverse long-term consequences and potentially predispose for neurodevelopmental and neurodegenerative disorders later in life (Pierozan et al., 2020; Carion et al., 2020).

In fact, avermectin, an insecticide sharing the main mechanism of toxicity with BMAA, was already proven to induce long-term effects in fish following chronic exposure, including changes in lipid profiles, growth, weight, immunity and antioxidant capacity impairment (Domingues et al. 2016; Mahmoud et al. 2021; Zhang et al., 2022), which confirms the need for further studies to better understand the full breadth of potential noxious effects of BMAA. It is however important to point out that some of the toxic effects herein reviewed result from exposure to high concentrations of BMAA that are not environmentally relevant, therefore future studies should focus on the use of lower concentrations closer to the ones found in the environment.

4.4. Domoic acid

Domoic acid (DA) (Table 2; Fig. 3) is a cyclic tricarboxylic amino acid with structural and functional similarities with kainic acid, an analogue to the neurotransmitter and excitatory amino acid L-glutamate (Visciano et al., 2016; Murk et al., 2019). DA induces excitatory toxicity (excitotoxicity) by an integrative action on ionotropic glutamate receptors on both sides of the synapse for which it has high affinity, coupled with an effect that prevents the channel from rapid desensitization (Berman and Murray, 1997). Over-stimulation of these glutamate receptors lead to the production of ROS and sometimes cell death, through NMDA receptors activation (Berman and Murray, 1997).

4.4.1. Domoic acid production, distribution and regulation

Domoic acid was first detected in red algae of the species *Chondria armata* (Meda et al., 1986). However, the marine diatoms of the genus *Pseudo-nitzschia* are responsible for the single ASP poisoning syndrome reported, and are the most prevalent DA producing organisms (Orsini et al., 2004; Visciano et al., 2016; Saeed et al., 2017). DA has been detected in numerous bivalves and some other species that uptake it either through filtration of phytoplankton or as a result of grazing on benthic algae (Wohlgeschaffen et al., 1992; Ji et al., 2022). Beside bivalves, other organisms such as crabs, octopuses and fish have occasionally accumulated domoic acid (Costa et al., 2004; Lefebvre et al., 2007; Schultz et al., 2013). Since DA mostly accumulates in the digestive tract of these species, hardly any or no toxin is usually found in tissues suitable for human consumption (Jeffery et al., 2004; Murk et al., 2019). Despite humans' main exposure routes to DA being the consumption of contaminated seafood, surface marine waters can also be contaminated. For instance, DA surface water concentrations measured in 18 sites in the Pacific Ocean were found to range from 0.0002 to 220 ng/L, depending on the presence of DA-producing phytoplankton blooms (Silver et al., 2010). These concentrations of DA in the water column represents a hazard for both human and aquatic biota health.

Compared to STXs, the number of cases of human illness associated with DA is virtually non-existent, with a unique ASP outbreak reported in Canada in 1987 involving 150 people that consumed contaminated mussels (DA concentrations ranging between 1 and 128 mg/100g of mussel tissue) (Bates et al., 1988; Jeffery et al., 2004; Pérez-Gómez and Tasker, 2021). However, mild cases that went unreported cannot be ruled out (Visciano et al., 2016; Pérez-Gómez and Tasker, 2021). The assumed low number of DA human intoxication events is claimed to be due to effective monitoring programs put in place in various countries (Nicolas et al., 2017; Farabegoli et al., 2018). The EU Regulation (EC) No 853/2004 states that when DA concentrations in bivalves exceed 20 mg/kg of seafood, shellfish production sites must be closed (European Commission, 2004). The same regulatory limit is established by many countries outside the EU, including the USA and Canada (Farabegoli et al., 2018; Murk et al., 2019; De Witte et al., 2022).

4.4.2. The known and the suspects regarding domoic acid (eco)toxicity

In humans, DA toxicity symptoms range from gastrointestinal effects to neurological disorder signs like confusion, lethargy, disorientation, paraesthesia and short-term memory loss; in extreme cases coma or death can occur (Visciano et al., 2016). Additionally, lesions in the human brain, particularly in the hippocampus, were reported in human ASP cases (Farabegoli et al., 2018; Jaramillo et al., 2020). Curiously, the CA1 and CA3 areas of the hippocampus, brain areas responsible for learning and memory processing, are thought to be particularly susceptible to DA toxicity (Morabito et al., 2018; Pérez-Gómez and Tasker, 2021). DA also induces intracellular free radical generation at the level of the mitochondria and its accumulation leads to the oxidation of vital macromolecules including lipids, proteins and DNA (Farabegoli et al., 2018; Jaramillo et al., 2020). Ultimately, this phenomenon can lead to apoptosis or necrosis of neurons and glia (Farabegoli et al., 2018). Another organ also associated with long-term DA toxicity is the heart, with DA reported to cause loss of myofibrillar arrangement and severe mitochondrial alterations in rat heart tissue (Vieira et al., 2016). Finally, DA was also shown to cause genomic instability by increasing the frequency of micronuclei and nuclear buds, as well as the induction of primary DNA strand breaks in non-target human peripheral blood cells (Gajski et al., 2020).

Exposure to DA (at concentrations higher than 10 mg/L) induced several physiological and behavioural responses in *C. elegans* such as: reduced forward movement of nematodes, significantly reduced pharyngeal pumping rates, reduced lifespan, oxidative stress (through the activation of the P38 MAPK signalling pathway) and intestinal toxicity (Tian and Zhang, 2019). Similar behavioural responses occurred in seabream (*Sparus aurata*) exposed to doses of DA ranging from 0.9 to 9 mg/kg via intra-coelomic injections, with exposed fish showing abnormal swimming behaviour (Nogueira et al., 2010). Tiedeken and collaborators (2005) obtained similar behavioural (convulsions and reduced touch response reflexes) and developmental (reduced hatching success) adverse effects in zebrafish embryos exposed to DA via microinjection to fertilized eggs (0.12–17 mg DA/kg egg weight). Marine mussels (*Mytilus edulis*) showed DNA fragmentation in digestive glands after exposure to DA via intra-muscular injection at concentrations ranging from 1 to 500 ng/g body weight (Dizer et al., 2001). DA has also a toxic effect in marine birds and mammals, most notably a chronic DA epileptic syndrome characterized in sea lions between 1998 and 2006 (Scholin et al., 2000; Bejarano et al., 2008). In sea lions, DA induces endocrine dysfunction, inflammation and changes in hippocampal connectivity (Pérez-Gómez and Tasker, 2021).

At the gene expression level, several studies have suggested that chronic low-level DA exposure at asymptomatic doses results in adverse effects, among them transcriptional changes mainly in the central nervous system (Jing et al., 2018). Hiolski and collaborators reported that genes and biological functions related to neurological function and

development in zebrafish were significantly altered after exposure to DA (concentrations lower than 0.86 mg DA/g fish) via intracoelomic injection (Hiolski et al., 2014). Exposure to this compound led to upregulation of genes responsible for maintaining mature neural networks, anti-inflammatory response and apoptotic responses (Hiolski et al., 2014), clearly broadening the range of pathways potentially affected by DA. Complementary results were obtained by Lefebvre et al. (2009) with DA-exposed zebrafish (0.47 μg DA/g total fish weight) exhibiting altered expression of 306 genes in the central nervous system, the majority of the downregulated genes being involved in brain signal transduction, ion transport, immune function, RNA processing and transcription factor functionality.

4.5. Brevetoxin

Brevetoxins (BTXs) (Table 2; Fig. 3) are polyether ladder compounds responsible for massive fish and marine mammal mortality mainly in the Gulf of Mexico, but also along the East coast of the USA, Japan and New Zealand (Flewelling et al., 2005; Cassell et al., 2015; Murk et al., 2019). These toxins bind to and activate the site 5 of voltage-gated sodium channels in cell membranes, leading to the depolarization of neuronal and muscle cell membranes (Catterall and Gainer, 1985; Cassell et al., 2015).

4.5.1. Brevetoxin production, distribution and regulation

BTXs are confirmedly produced by the dinoflagellates *Karenia brevis, K. brevisulcatum*, *K. mikimotoi*, *K. selliformis* and *K. papilionacea* (Visciano et al., 2016; Farabegoli et al., 2018; Murk et al., 2019). Other algae species, such as *Chattonella antiquam*, *C. marina*, *Fibrocapsa japonica* and *Heterosigma akashiwo*, have been reported to produce BTX-like compounds (Farabegoli et al., 2018). As shown for *K. brevis*, BTXs seem to play an essential role in non-photochemical quenching in the chloroplast (Cassell et al., 2015).

Despite being implicated in the death of a large number of fish and in the morbidity and mortality of marine mammals, there has been only a small number of reported cases of NSP in humans and none resulted in fatalities (Abraham et al., 2021). BTXs intoxication due to ingestion of contaminated clams (with BTXs concentrations up to 42.9 mg/kg) was reported in the USA and in New Zealand (Terzagian, 2006; Nicolas et al., 2017; Farabegoli et al., 2018). Symptoms such as nose and throat irritation were rather linked to concentrations of up to 4.32 ng/m^3 in aerosol samples collected during a *K. brevis* bloom in Florida (Pierce et al., 2005). Other study reported BTXs air concentrations between 0.01 and 80 ng/m^3 during red tide events in the Gulf of Mexico (Cheng et al., 2005). BTXs surface water concentrations ranged from 4 to 20 μg/L during a *K. brevis* bloom event in Jacksonville Beach, Florida (Pierce et al., 2003). As a result of the relatively low number of human NSP cases the implementation of strict monitoring programs and legislation regarding the limits of BTXs in shellfish is lagging behind. In the EU, no limit exists for these toxins, despite BTXs-producing species being already found in European waters (Arnich et al., 2021). Contrarily, in the USA, Australia, Japan and New Zealand a limit of 800 μg of BTXs/kg in shellfish is established (Farabegoli et al., 2018; Murk et al., 2019; Arnich et al., 2021). Close regulation and monitoring of this toxin is then urgently required, especially in the EU.

4.5.2. The known and the suspects regarding brevetoxin (eco)toxicity

In humans, BTXs are the causative agents of NSP poisoning syndrome and asthma-like symptoms mainly through inhalation exposure (Visciano et al., 2016; Farabegoli et al., 2018). NSP syndrome is characterized by both neurological and gastrointestinal effects which include nausea, vomiting, diarrhoea, paraesthesia, cramps, bronchoconstriction, paralysis, seizures, coma and ultimately death (Visciano et al., 2016). Most known human BTXs intoxications occurred through inhalation of aerosolized BTX toxins and through the consumption of contaminated clams, oysters and mussels (Farabegoli et al., 2018; Murk et al., 2019). To date, specific antidotes against brevetoxins do not exist (Arnich et al., 2021).

Like STXs and DA, BTXs also have cytotoxic and genotoxic effects. Brevetoxins activation of voltage-gated sodium channels can lead to several biological impacts including cell proliferation, altered gene transcription, cytokine production and even apoptosis (Murrell and Gibson, 2011). Specifically, BTXs causes significant DNA damage (double-strand breaks) and significant increase in expression of several genes whose products are involved in cell cycle checkpoint, cell cycle arrest, apoptosis, DNA repair and inflammation in Jurkat E6-1 cells (Murrell and Gibson, 2011). The upregulation of these genes associated with DNA repair may be related to BTXs capacity to form DNA adducts with cytidine (Murrell and Gibson, 2011). Walsh and collaborators (2003) exposed mice to BTXs via intraperitoneal injection and reported changes in gene expression of 29 genes in liver tissue and of 9 genes in the brain, with these affected genes being involved in various physiological, cell cycle, neurological and immunological processes. Sea turtles (*Trachemys scripta*) orally and intratracheally exposed to BTXs showed an increase in oxidative stress in general, a decrease in lysozyme activity, inflammation and upregulated expression of genes involved in cellular stress (heat shock protein 90), oxidative stress (glutathione S-transferase and thioredoxin), inflammation (transferrin, serotransferrin and ferritin heavy chain), cell cycle (cell cycle progression) and immune function (TCR delta chain) (Walsh et al., 2019). Zebrafish embryos exposed to BTXs (2–25 nM) showed increased levels of ROS specifically in three brain region that are telencephalon, mesencephalon and cerebellum; several altered levels of metabolites related to mitochondrial oxidative metabolism, hormonal system and neurotransmission; and lastly increased lethality of embryos (Annunziato et al., 2022).

These data support the idea that this neurotoxin triggers complex reactions involving both inflammation, immune function modulation and cell death. Worryingly, the immune systems of individuals exposed to BTXs during HAB events may be at risk, since human lymphocytes were shown to accumulate extensive genotoxic damage (primarily DNA damage) upon BTXs exposure (Sayer et al., 2005; Pierre et al., 2018). Brevetoxins were also shown to cause cell proliferation inhibition and chromosomal alterations, including gaps and breaks, in Chinese hamster CHO–K1–BH4 cells (Sayer et al., 2006). BTXs has epigenetic effects, increasing histone phosphorylation (a marker of DNA damage) and decreasing genome-wide DNA methylation in the Eastern oyster *Crassostrea virginica* exposed to BTXs-producing *K. brevis* (5 *K. brevis* cell/mL to 1000 *K. brevis* cell/mL) (Gonzalez-Romero et al., 2017). As reasoned above for STXs, parallels with insecticides sharing the main BTXs mode of action suggest that individual and supra-individual effects following sub-lethal exposure should be expected in the aquatic biota (e.g., Xiang et al. 2019; Groh et al. 2015; Rasmussen et al. 2013), hence the need for further research with ecologically-relevant models to better understand the risks that BTXs may represent in this context.

4.6. Ciguatoxin

Ciguatoxins (CTXs) (Table 2; Fig. 3) are lipid-soluble polyether compounds that activate the sodium ion channels, leading to cell membrane excitability, sodium and calcium influx into the cell and depolarization of nerve cells (Nicholson and Lewis, 2006). This mode of action is similar to what is described for brevetoxins and the adverse effects resulting from exposure to both toxins are also similar (Lombet et al., 1987; Murray, 2021).

4.6.1. Ciguatoxin distribution, monitoring and regulation

CTXs are produced by benthic dinoflagellates of the genus *Gambierdiscus toxicus*, whose distribution includes tropical and subtropical coral reef areas (Skinner et al., 2011; Visciano et al., 2016; Pierre et al., 2018). CTXs accumulate primarily in large predatory fish, such as Spanish mackerels, moray eels, barracuda and snappers (Visciano et al., 2016; Costa et al., 2021), and cause adverse effects at very low doses as

summarised in section 4.6.2. The geographical distribution of Ciguatera Fish Poisoning syndrome (CFP) was originally limited to tropical regions with extended coral reefs, such as the Caribbean and various island regions within the Pacific and Indian Oceans (Soliño and Costa, 2018). In recent years, a spread of CFP cases has been observed near European, North American and Asian coasts, due to the increase of tropical reef fish imports (Soliño and Costa, 2018; De Witte et al., 2022), and now the CFP syndrome is the most common foodborne illness worldwide, with a frequency of 20,000 to 50,000 cases annually (Friedman et al., 2017; Pierre et al., 2018; Murk et al., 2019). For example, a CTXs intoxication event due consumption of contaminated fish (CTXs concentration of 1 ng/150g) occurred in the Canary Islands (Spain), affecting six persons (Pérez-Arellano et al., 2005). A comprehensive study conducted by Hossen et al. (2015) regarding CTXs intoxication events that occurred in Guadeloupe (French West Indies) revealed that CTXs concentration in contaminated fish consumed by 21 individuals that presented CFP symptoms ranged from 0.0220 up to 0.4708 μg/kg of fish (Hossen et al., 2015).

Due to CTXs high toxicity potential, strict regulatory limits regarding CTXs concentration in fish were established in the USA and Japan of 0.01 μg/kg and 0.2 μg/kg, respectively (Caillaud et al., 2010; Murk et al., 2019). In the EU, to date, no guidance limits are stipulated and little monitoring of CTXs in surface water and in potential vector species is made (De Witte et al., 2022), with the exception of Canary Islands (Spain) and Madeira Islands (Portugal) (Canals et al., 2021; Costa et al., 2021). However, the EU regulation (Regulations (EU) 2017/625 and (EU) 2019/627) complies with a zero-tolerance policy towards CTXs (Nicolas et al., 2017) by demanding that fishery and seafood products containing CTXs are not allowed placement on the market (EFSA Panel on Contaminants in the Food Chain, 2010; De Witte et al., 2022).

4.6.2. The known and the suspects regarding ciguatoxin (eco)toxicity

The acute period of the CFP syndrome is characterized by gastrointestinal problems such as nausea, vomiting, abdominal pain and diarrhoea (Munday and Reeve, 2013; Visciano et al., 2016). Cardiovascular (bradycardia and hypertension) and neurological complications such as paraesthesia, dysesthesias, and hyperesthesia may occur within a few hours to two weeks after exposure (Munday and Reeve, 2013; Visciano et al., 2016).

A number of cellular effects secondary to voltage-gated sodium channels activation induced by CTXs were reported (Rubiolo et al., 2018; L'Herondelle et al., 2020). Among them, nodal swelling in frog myelinated nerve fibbers exposed to 10 nM CTXs, due to entry of osmotically driven water, subsequent to the increased intracellular concentration of sodium and potassium (Mattei et al., 2014). Other cellular effect of CTXs exposure is the modulation of gene expression as a result of Ca^{2+}-activated intracellular signalling pathways that lead to gene transcription (L'Herondelle et al., 2020). In mouse primary cortical neurons, CTXs exposure led to expression modulation of a number of genes, including upregulation of the immediate-early genes *Arc* and *Egr* and downregulation of the glutamate NMDA and AMPA receptors (Rubiolo et al., 2018). CTX-exposed mouse also displayed down-regulated expression of metabolic genes that code for essential enzymes such as glutathione reductase, glutathione S-transferase and methionine adenosyltransferase (Ryan et al., 2007). In the marine copepod *Tigriopus japonicus* exposed to CTX-producing *Gambierdiscus* sp. cells (100–2000 cells/mL), down-regulated expression of metabolic genes that code for essential detoxification enzymes also occurred, leading to the impairment of the process (Lee et al., 2014).

Similar to BTXs, CTXs are thought to interfere with the human immune system owing to their ability to recruit and activate macrophages (Pierre et al., 2018). Other way by which CTXs interfere with the immune system is through the upregulation of inducible nitric oxide synthase, tumour necrosis factor-α and interleukins IL-1β, IL-6 and IL-10 as seen in RAW 264.7 macrophages after exposure to low nanomolar CTXs concentrations (Matsui et al., 2010). The limited available data suggests that the systemic immune response following acute CTXs exposure is an anti-inflammatory Th2 response to neuroinflammation (Pierre et al., 2018). Interestingly, it is possible that a major histocompatibility complex variant genetically predisposes individuals to develop a persistent ciguatera syndrome (Ryan et al., 2015; Pierre et al., 2018). Whether a parallel to the aquatic biota can be traced in this regard concerning CTXs remains to be further investigated, but immune responses of fish exposed to deltamethrin (pyrethroid, i.e., a sodium channel modulator) were already recorded (e.g., Vineetha et al. 2022), and Yan et al. (2017) reported immune dysfunction in marine medaka (*Oryzias melastigma*) embryos following exposure to CTXs (0.53–1.07 ng CTXs/g of fish). Additionally, these relatively low concentrations of CTXs induced other detrimental developmental and physiological effects in the marine medaka embryos including hatching failure, caudal fin malformation, spinal deformities, internal damage to embryos, and altered behavioural patterns/muscle physiology (Yan et al., 2017). Medaka (*Oryzias latipis*) embryos exposed to CTXs via microinjection into the egg yolk also exhibited extensive adverse developmental effects ranging from cardiovascular, muscular and skeletal abnormalities to significantly reduced hatching success (Edmunds et al., 1999). These results indicate that CTXs may represent a still largely unrecognized threat to the reproductive success of marine fish, with direct impacts on environmental health. Similar results were obtained by Lee et al. (2014), who exposed the marine copepod *T. japonicus* to CTX-producing *Gambierdiscus* sp. cells (100–2000 cells/mL) and reported increased mortality, abnormal swimming and paralysis in exposed adult females.

4.7. Palytoxin

Palytoxins (PLTXs) (Table 2; Fig. 3) are potent non-protein marine compounds firstly isolated in corals belonging to the genus *Palythoa* (Gleibs et al., 1995; Louzao et al., 2011; Visciano et al., 2016; Farabegoli et al., 2018). PLTXs are complex molecules that bind to extra-cellular Na^{2+} and K^{+} channels inhibiting the active transport of these ions across the membranes through leaving the channels permanently open, which causes cellular death by the excess of intracellular cations (Wu, 2009; Alfonso et al., 2015; Patocka et al., 2018).

4.7.1. Palytoxin distribution, monitoring and regulation

PLTXs are produced by dinoflagellates of the genus *Ostreopsis*, which have a wide global distribution in temperate and tropical waters (Fukui et al., 1987; Gleibs et al., 1995; Tubaro et al., 2011; Visciano et al., 2016; Farabegoli et al., 2018). Cases of human PLTXs poisoning have been associated with oral, cutaneous, inhalational and ocular exposure routes, with oral exposure after the ingestion of contaminated fish or crustaceans being the most harmful for human health (Deeds and Schwartz, 2010; Tubaro et al., 2011; Thakur and Jha, 2017; Patocka et al., 2018; Farabegoli et al., 2018). Despite this, limited information is available about PLTXs human exposure (Tubaro et al., 2011; Visciano et al., 2016; Farabegoli et al., 2018). The vectors of PLTXs are mainly crabs, goldspot herring, parrotfish and serranid fish (Noguchi et al., 1988; Fukui et al., 1987; Alcala et al., 1988; Taniyama et al., 2002, 2003). Biré and collaborators (2013) reported high levels of PLTXs in fish tissues (range: 2–61.6 μg/kg) after HAB events in southern France, which constitutes a severe danger for human health since the safe PLTXs concentration is thought to be under 30 μg/kg of shellfish (Biré et al., 2013; Nicolas et al., 2017). Moreover, the popularity of home aquaria containing living soft corals accumulating PLTX has increased, causing concern for the associated impact on human health (Pelin et al., 2016).

No country has established PLTX regulatory limits concerning vector species (Farabegoli et al., 2018; Patocka et al., 2018; Murk et al., 2019). The inexistence of regulatory limits and monitoring programs for PLTXs worldwide is mainly due to limited knowledge regarding the entailed toxicity mechanisms, human exposure routes and reduced number of reported human exposure events. However, the European Food Safety Authority advises for a limit of 30 μg PLTXs/kg shellfish flesh (Silva

et al., 2015), that should rapidly be enforced by EU legislation. The implementation of effective guidelines and monitoring programs for PLTXs should also be put in place as soon as possible not only in the EU but around the world, in order to ensure human and environmental health.

4.7.2. The known and the suspects regarding palytoxin (eco)toxicity

Several symptoms were described after the consumption of shellfish with PLTXs accumulation, among them a metallic taste, gastrointestinal malaise, diarrhoea, nausea, vomiting, ataxias, dizziness myalgia, dyspnoea, convulsion, bradycardia, tachycardia, myocardial damage, respiratory failure and even death in the worst cases (Visciano et al., 2016; Farabegoli et al., 2018).

A link between PLTXs and carcinogenicity has been established since 1986 (Fujiki et al., 1986). Palytoxin was characterized as a non-TPA-type skin tumour promoter, i.e., not directly damaging DNA but altering signal transduction pathways (Wattenberg, 2011). Accordingly, PLTXs was reported activate the three major mitogen-activated protein kinases (MAPKs) (Valverde et al., 2008), which mediate the action of a wide variety of stimuli and play a key role in regulating cell fate and function in many systems (Wattenberg, 2011; Cunha et al., 2022). Palytoxins can disrupt the regulation of MAPKs signalling pathways by several different mechanisms through changes on cell ion flux that lead to the activation of protein kinase cascades that ultimately activate JNK, p38, and ERK5 (Valverde et al., 2008; Wattenberg, 2011); and in cells that express oncogenic Ras, PLTXs promote the down modulation of MKP-3, while the loss of this negative regulator of ERK1/2 results in the accumulation of the active phosphorylated form of ERK1/2 known to cause changes in cell proliferation and survival (Wattenberg, 2011). One specific physiological role of MAPKs is cytoskeleton rearrangement (Louzao et al., 2011). Therefore, damages at the cytoskeleton level induced by PLTXs are to be expected. Accordingly, PLTXs were reported to cause depolymerization of actin filaments in intestinal and neuroblastoma cells (Bellocci et al., 2011; Louzao et al., 2011; Farabegoli et al., 2018). In addition, this neurotoxin is also capable of inhibit human cell proliferation *in vitro* through apoptosis and autophagy (Valverde et al., 2008; Alfonso et al., 2015).

Following oral administration of palytoxin (600 μg/kg) in mice, several behavioural responses (scratching, jumping, respiratory distress and paralysis) were observed and also increased plasma levels of creatine phosphokinase, lactate dehydrogenase and glutamic-oxaloacetic transaminase were observed, confirming that PLTXs are neurotoxic, immunotoxic and cytotoxic to mammals (Sosa et al., 2009). Cavion et al. (2022) obtained similar results with *A. franciscana* exposed to concentrations ranging from 1 to 10 nM of PLTXs: the crustaceans exhibited reduced hatching, increased mortality, decreased motility, increased ROS formation and increased catalase, glutathione s-transferase and superoxide dismutase activity. White shrimps (*Litopenaeus vannamei*) exposed to *Ostreopsis* cf. *ovata* extracts containing PLTXs (358.8 ng/mL) showed immobility, altered activity of antioxidant enzymes, oxidative damage and increased mRNA expression of three immune system related genes (Cen et al., 2019). Toxic effects of PLTXs in *Xenopus laevis* embryos include several teratogenic and developmental effects at non-environmental relevant concentrations ranging (99–991.6 μg/L) (Franchini et al., 2008).

5. Gaps and future directions on aquatic toxins research

Despite the recent advances made in aquatic toxins research over the past few years, a lot remains to be elucidated covering different fields. Within the specific context of the present Review, three particular fields should be highlighted and addressed in detail through this section: (i) the toxic effects beyond those typical of the recognized disease/disorder each toxin causes following acute exposure in humans, especially concerning aquatic biota that are major obvious ecological targets of these toxins; (ii) a better understanding of the adverse effects for human and other biota health as a result of exposure to multiple toxins; and (iii) rationales (e.g. molecular) allowing the improvement of monitoring methods for better human and environmental safety insurance.

Studies on the genotoxicity, carcinogenicity and neurotoxicity that include an appraisal of the molecular drivers of monitored effects at the level of the genome, epigenome and transcriptome resulting from long-term low-level chronic exposure are limited even for humans (Visciano et al., 2016; Stauffer et al. 2019; Christensen and Khan, 2020; Griffith and Gobler, 2020; Metcalf et al., 2021). Long-term low-level chronic or pulse exposure studies are especially relevant for neurotoxins since the main toxicological targets of these toxins are believed to be particularly susceptible to the long-term actions of low concentrations of toxic compounds (Metcalf et al., 2021), and because both continued (as per toxins' persistence) and sequential (as per the growth dynamics of producing species) exposures are likely to occur. Moreover, the impact and fate of marine and freshwater toxins in local food webs, along with toxin dynamics (for example: timescales for uptake, tolerable daily intakes, retention and depuration) in humans and potentially affected aquatic and terrestrial species are largely unknown (Visciano et al., 2016; Stauffer et al. 2019; Griffith and Gobler, 2020; Colas et al., 2021). It is fair to recognize that some toxins such as microcystins, nodularins, cylindrospermopsins and BMAA have received some attention in this context (Bláha et al., 2010; Huisman et al., 2018; Christensen and Khan, 2020; Bittner et al., 2021), but research on the remaining toxins, especially on the remaining neurotoxic cyanotoxins is also required. The same happens to the marine toxins, with some information being available for saxitoxins, domoic acid, brevetoxins and ciguatoxins (Solter and Beasley, 2013; Saeed et al., 2017) and the other neurotoxic phycotoxins receiving little attention. It is important to build on the results already obtained and investigate deeper, since a better knowledge of the toxic effects of aquatic toxins, especially in key aquatic species, allied with improved understanding of the effects of toxins in human health are essential conditions for the future development of better monitoring methods and possibly mitigation strategies that will improve both human and environmental safety regarding these toxins.

Another research area that has received little attention is the effects of combined exposure to multiple neurotoxins. In fact, co-occurrence is a confirmed scenario (see sections 2 and 3) and the number of studies addressing this critical aspect is limited. Co-occurrence of aquatic toxins is becoming increasingly more common due to climate change and human activity that potentiates toxin-producing species co-occurrence in the same water body and increased toxicity (Munday and Reeve, 2013; O'Neill et al., 2016; Rodgers et al., 2018; Bittner et al., 2021). Exposure to a cocktail of toxins is therefore increasingly likely to happen and it is known that exposure to a combination of these compounds may lead to exacerbated or unexpected toxic effects, which constitutes a serious threat to human and wildlife health (Munday and Reeve, 2013; Rodgers et al., 2018; Bittner et al., 2021).

The effective mitigation of the negative effects caused by toxins relies on accurate and reliable warning methods for detection and quantification of these toxins in aquatic and food samples (see section 5.1); besides the technicalities, there is a prominent need to better understand the dynamics of waterborne concentrations of aquatic toxins as this is a critical exposure feature constraining potential effects in the aquatic biota. On the other hand, feasible predictive frameworks that can anticipate related ecological effects which can only be achieved by improving our understanding of the toxins (eco)toxicity at a mechanistic level (see section 5.2).

While the developments on efficient monitoring are critical for preventing human exposure and linked health problems, such link cannot be established so directly for the biota as exposure prevention is unrealistic. In this context, the development of methods to remove aquatic toxins from contaminated waters is paramount to tackle this particular aspect. Related research has been once again focusing on the removal of cyanobacterial toxins from drinking water and it marginally meets the specific focus of the present review, but the relevance of the topic

Box 1
Summary of strategies that have been investigated regarding potential in the removal of cyanotoxins from water, with their main advantages and disadvantages. Compiled from: Cousins et al., 1996; Hitzfeld et al., 2000; Rositano et al., 2001; Jurczak et al., 2005; Gijsbertsen-Abrahamse et al., 2006; Teixeira and Rosa (2006); Henderson et al., 2008; Edwards et al., 2008; Lemes et al., 2008; Antoniou et al., 2009; Dixon et al., 2011; Coral et al., 2011; Zamyadi et al., 2012; Hu et al., 2012; Pantelić et al., 2013; Merel et al., 2013; He et al., 2016; Mohamed (2016); Liu et al., 2017; Sharma and Bhattacharya (2017); Chen et al., 2018; Laszakovits and MacKay (2019); Barešová et al., 2020; Mashile et al., 2020; Mohamed et al., 2021 and Varsha et al., 2022.

Coagulation/flocculation using ferric chloride or aluminium sulphate	Some success in dealing with cyanobacterial cells	Not very efficient with soluble toxins; Leads to lysis of cyanobacterial cells and the release of toxins into water
Dissolved air flotation	Good results with cyanobacterial cells	Not very efficient with soluble toxins; Very different rates of success depending on the cyanotoxin being treated
Rapid filtration through sand, gravel and/or anthracite filters	Affordable and highly used in water treatment plants	Little or no impact on the removal of toxic cyanobacteria and toxins; cell lysis may occur by shear stress, inadequate backwashing or cell ageing
Chlorination	Affordable and highly used in water treatment plants; Microcystins, nodularins, cylindrospermopsins and BMAA are effectively inactivated	Anatoxin-a and STXs are not destroyed; Cell lysis may occur and some byproducts can be formed, which increases the quantity of dissolved toxins in the water
Ozonation and potassium permanganate	Effective in inactivating microcystins, anatoxin-a and BMAA	STXs are not destroyed by this process; Potentially leads to increased dissolved toxins in water due to cell lysis
Activated carbon adsorption	Effective in removing extracellular microcystins, nodularins, cylindrospermopsins, anatoxin-a and STXs	More systematic studies are needed to ascertain which type of activated carbon, dosage and contact time is more appropriate in dealing with the vast array of freshwater toxins
Biodegradation	Extensively validated in dealing with microcystins	Further research is needed to develop and validate this method for the remaining aquatic toxins
Photocatalysis using titanium dioxide and UV radiation	Quickly degrade several cyanotoxins	Not suitable for water with high levels of suspended solids, turbidity, colour or soluble organic matter; High energy consumption
Membrane-based nanofiltration	Great potential in removing microcystins, cylindrospermopsins, anatoxin-a and STXs	Expensive; High energy consumption

justifies a note on this herein. The topic is excellently reviewed elsewhere (Westrick et al., 2010; Pantelić et al., 2013; He et al., 2016; Kumar et al., 2019; Teixeira et al., 2020; Varsha et al., 2022), hence only a summary is provided in Box 1 on the main water treatment strategies that have been discussed to target freshwater cyanotoxins, namely hepatotoxins and neurotoxins, with different levels of success in dealing with dissolved toxins. A continuous effort is necessary to ensure that the current water treatment strategies are sufficient in dealing with soluble aquatic toxins, especially the ones less studied so far. Concerning the removal of marine toxins, the developments are again related to human health safety and are scarcer. Different strategies have been suggested to remove aquatic toxins in bivalves, with the obvious one being the detoxification by transfer to clean waters, however it implies high operating costs (Lagos et al., 2001). Treatments targeting the reduction of toxins toxicity by steaming or boiling (Lawrence et al., 1994; Wong et al., 2009) or in combination with pH changes were also searched (Lagos et al., 2001; Reboreda et al., 2010; RENAPRA, 2009). Among the limited alternatives for toxins removal in bivalves, one of the most frequent is the application of chitosan as a facilitator in bivalves (Xie et al., 2013; Yang et al., 2021).

5.1. *Challenges and prospects in the detection and quantification of toxins*

The detection of aquatic toxins is currently primarily performed using chemical analysis (primarily using Liquid chromatography–mass spectrometry and Liquid Chromatography with Fluorescence Detection) and to a lesser extent *in vivo* assays (mainly the mouse bioassay) (Merel et al., 2013; Nicolas et al., 2017; Morabito et al., 2018; Vogiazi et al., 2019; Liang et al., 2022). Additionally, other rapid testing methods have been developed, such as antibody-based lateral flow assays, potentiometric sensors and biosensors and ELISA kits which allow sensitive screening of DA, OA, BTXs, PTXs, YTXs, AZAs, STXs, cylindrospermopsins, microcystins and anatoxin-a (Nicolas et al., 2017; Cruz et al., 2018; Cunha et al., 2018; Vogiazi et al., 2019; Murk et al., 2019; Raposo et al., 2020; Liang et al., 2022). Despite some being effective, these methodologies have limitations, such as lacking specificity and sensitivity towards some toxins, being expensive, laborious and time consuming, difficult to implement at a large scale and the raising of ethical concerns for mouse bioassay (Merel et al., 2013; Nicolas et al., 2017; Morabito et al., 2018; Murk et al., 2019). It is important to point out that the use of the mouse bioassay has been abolished in the European Union, the United States and in New Zealand, but this assay is still used around the world (Merel et al., 2013; Nicolas et al., 2017; Murk et al., 2019).

In vitro cell-based assays seem to represent one of the more promising alternative monitoring tools (Nicolas et al., 2017; Huisman et al., 2018; Morabito et al., 2018). To date, one of the most common *in vitro* cell-based assays used for aquatic toxins screening is the competition receptor-binding assay (Murk et al., 2019; Pasinszki et al., 2020). This assay allows for the indirect detection and quantification of toxins since it uses fluorescence and chemically labelled molecules that compete and

bind to the same binding site as the target aquatic toxin. For example, an assay using tritium labelled kainic acid competes with DA for binding to glutamate receptors (Van Dolah et al., 1997; Murk et al., 2019). Therefore, the levels of DA can be estimated using scintillation counting to determine the quantity of bound tritium labelled kainic acid, that is inversely proportional to the quantity of DA present (Van Dolah et al., 1997; Murk et al., 2019). In addition to DA detection, competition receptor binding assays have been developed for detecting and quantifying saxitoxins, BTXs and CTXs (Van Dolah et al., 1997; McCall et al., 2014; Pasinszki et al., 2020).

Real-time qPCR assays can also be used efficiently to detect aquatic toxins (Durán-Vinet et al., 2021; Feist and Lance, 2021). This method involves the processing of environmental samples, extraction of DNA or RNA and qPCR using target-specific assays, in order to detect the presence of genes responsible for aquatic toxins synthesis (Durán-Vinet et al., 2021; Feist and Lance, 2021). Many studies have shown strong correlations between gene copy numbers and toxin concentrations, showing that this technique is robust and efficient in bloom events monitoring (Antonella and Luca, 2013; Wood et al., 2013; Hatfield et al., 2019; Zhang et al., 2020). However, there are still limitations to this methodology, namely consistency, usability, cost-effectiveness and inability to distinguish between living and dead organisms (Durán-Vinet et al., 2021).

On the other hand, biomarkers are currently recognized as an important tool in water quality monitoring programs (Gupta, 2019; de Morais Calado et al., 2020). In toxicology, biomarkers are often divided into biomarkers of exposure, effect and susceptibility (Gupta, 2019; Campos et al., 2020). There are also several types of biomarkers such as biochemical (enzyme activity measurement), chemical (detection and quantification of compounds), genotoxicity (DNA damage measurement and DNA mutations), neurotoxicity (behavioural changes and neurotransmitters quantification), morphological (histopathology), molecular (gene transcriptional changes and specific genomic and epigenetic markers), metabolomic (metabolites measurement) and physiological (ion regulation) (Gad, 2019; de Morais Calado et al., 2020).

Biomarkers of exposure can be used for the early-warning signalling of toxins' presence in aquatic environments (Silins and Högberg, 2011). Behavioural and physiological parameters can be used in this context, especially using non-vertebrate species that raise less ethical concerns (Cazenave et al., 2008; Ferreiro et al., 2015; Herrera et al., 2015; Yan et al., 2017; Bownik and Pawlik-Skowrońska, 2019; Gutiérrez-Praena et al., 2019; Reynolds et al., 2020; Queirós et al., 2021; Han et al., 2021). For example, behavioural and physiological parameters (swimming speed, heart rate, oxygen consumption, thoracic limb activity and post-abdominal claw movement) in *Daphnia* have demonstrated high sensitivity to anatoxin-a or STXs, even at low concentrations as usually found in the environment (Bownik and Pawlik-Skowrońska, 2019; Ferrão-Filho et al., 2010). Transcriptional changes can also be used as potential biomarkers of exposure, with Hiolski and collaborators (2014) reporting upregulation of several essential genes in zebrafish exposed to environmentally relevant concentrations of DA. Rivera et al. (2021) also identified ten genes in *in vitro* cultured Neuro-2a cells as good candidate biomarkers for STXs detection, due to variations in their expression being directly related to STXs exposure and response. Nicolas and collaborators (2015) exposed Neuro-2a cells to PLTXs and reported that seven genes (involved in cell survival, apoptosis and neuronal development pathways) are potential biomarkers for PLTXs exposure. Biochemical biomarkers may also be used as biomarkers of exposure, however with more limited success than other types of biomarkers (Paskerová et al., 2012). Due to the difficult interpretation of results, the lack of specificity of the majority of the biomarkers of this type and the difficulties in linking alterations in enzyme activity to the specific action of toxins, biochemical biomarkers are potentially more suited as biomarkers of effect for aquatic toxins since they are often used as confirmatory tools in mechanistic studies (Paskerová et al., 2012). Despite this, Freitas et al. (2016) demonstrated that cholinesterase activity in *Pseudosida ramosa* and *D. magna* can be used to indicate the presence of the neurotoxin anatoxin-a(s)/guanitoxin. Lastly, Yau et al. (2019) identified several metabolomic/neurotoxic biomarkers of exposure (neurotransmitters and metabolites related to neurotransmission) in marine medaka (*Oryzais melastigma*) exposed to BTXs at two sub-lethal dose levels (0.5 and 2.5 μg/L) for 12 h.

The development of biomarkers of exposure for aquatic toxins, based on the individual mechanism of action of each toxin, are promising alternatives to existent detection methods. However, the application of these biomarkers under field conditions is still difficult. Alternative screening solutions capable of detecting and quantifying toxins at and below regulatory levels with high throughput, low cost and high reproducibility are therefore urgently required. The interplay between these alternative tests and the established chemical and *in vivo* analytical techniques, as confirmatory tools, will allow the identification of thus far unknown toxins, add to our understanding of their occurrence and hopefully raise awareness for the need of a new generation of aquatic toxins monitoring programs (Fig. 4) (Nicolas et al., 2017; Bodero et al., 2018; Reid et al., 2019; Liang et al., 2022).

5.2. Challenges and prospects for better understanding the (eco) toxicological effects of toxins

5.2.1. Development of reliable biomarkers of effect

Alongside screening, toxicological biomarkers can also be used to predict and identify the sublethal effects of these aquatic toxins, including their understudied genotoxic, carcinogenic, cytotoxic, neurotoxic, immunotoxic and epigenetic effects.

Among the several *in vitro* assays used for accessing DNA damage, the micronucleus test and the comet assay have gained popularity due to their sensitivity for detecting cytogenetic and DNA strand damage/breaks and the relative short time needed to be executed (Çavaş and Könen, 2008; Glei and Schlörmann, 2014; Puerto et al., 2018). The application of these assays to aquatic vertebrates (e.g., Sasaki et al., 2002; Rocco et al., 2012; Hayashi, 2016; Gajski et al., 2019) and invertebrates (e.g., Erbe et al., 2011; Pellegri et al., 2014; Reis et al., 2018) is wide, thus their routine implementation in studies addressing the effects of toxins in the aquatic biota should not represent a difficult challenge. Regarding DNA mutagenicity analysis the gold standard remains the Ames test, that has suffered several modifications over the years to increase its sensitivity (Puerto et al., 2018; Zeiger, 2019). These assays have been routinely used for studying the genotoxic effects of cyanobacterial toxins (mainly of microcystins and cylindrospermopsins) and algal toxins (mainly OA, AZAs and DA) (Çavaş and Könen, 2008; Valdiglesias et al., 2013; Dörr, 2014; Puerto et al., 2018; Murk et al., 2019; Díez-Quijada et al., 2019; Gajski et al., 2020). However, the extrapolation of the results of the Ames test to reason on mutagenicity following exposure of organisms to environmental stressors has been challenged, even when human health assessment is in place and despite the strong implementation of the assay in such context (e.g., Landsiedel et al. 2022).

Cytotoxicity is often analysed using cell division assays, cytoskeleton disfunction assays, cellular viability assays, ROS production assays, mitochondrial activity assays and antioxidant enzymes activity assays (Perreault et al., 2011; Buratti et al., 2017). One of the more utilized *in vitro* assays for determining cytotoxicity is the MTT cell viability assay (Perreault et al., 2011; Bodero et al., 2018; Murk et al., 2019). This *in vitro* cell based assay is effective in detecting a variety of freshwater and marine toxins such as: saxitoxins, anatoxin-a, microcystins, cylindrospermopsins, BTXs, CTXs, tetrodotoxin, CIs, AZAs and YTXs (Takser et al., 2016; Bodero et al., 2018; Murk et al., 2019; Hinojosa et al., 2019). Due to their sensitivity, cellular mortality, mitochondrial activity and antioxidant enzymes activity assays have been increasingly used as cellular/biochemical biomarkers for both screening and study the toxicity of freshwater and marine toxins (Perreault et al., 2011). These assays can also be conducted on *in vitro*-cultured cell models relevant for

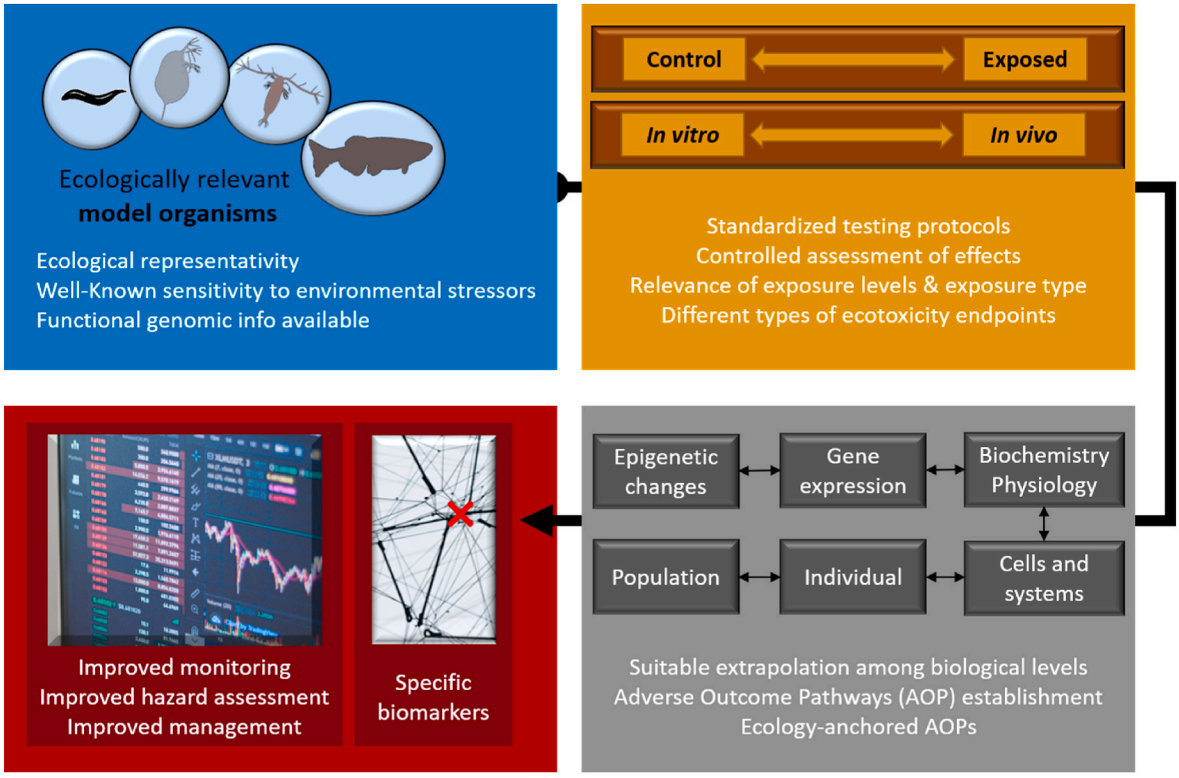

Fig. 4. Conceptual pipeline for an integrative establishment of new omics-based biomarkers of exposure and effect targeting aquatic toxins and focusing on ecosystem health, yet also allowing also improvement in human health safety management. Key aspects are represented, namely: (i) the promotion of ecologically relevant and ecotoxicologically well-known models in toxins research; (ii) the need to establish suitable test settings that can deliver feasible and relevant data on a diverse array of endpoints covering for different levels of biological organization, building upon the wide existing experience with the experimental models; (iii) availability of accurate quantification of exposure-effect relationships, appropriately analysed using robust statistical and bioinformatic tools when relevant, and suitability of integration linking molecular effects to ecosystem-level impairment; (iv) use of integrated effect flows to identify specific molecular biomarkers of exposure and effects that, once validated, should allow a both the establishment of improved environmental monitoring and a more accurate appraisal of the environmental hazardous potential of aquatic toxins, necessarily leading to the development improved management strategies targeting this global problem.

environmental health (such as on commercially available fish cell lines, e.g., Hernández-Moreno et al., 2022 and Zenke and Okinaka, 2022) and therefore serve as useful tools for the understanding the ecotoxicological effects of aquatic toxins.

To date, several studies have focused on the epigenetic, genotoxic, carcinogenic and cytotoxic effects of microcystins, nodularins, cylindrospermopsins, STXs, anatoxins and BMAA in model organisms and *in vitro* cell models and have obtained promising preliminary results that have the potential of being used as cellular and molecular biomarkers for these cyanotoxins toxicity (Lakshmana Rao et al., 2002; Bláha et al., 2010; Perreault et al., 2011; Sierosławska and Rymuszka, 2013; Huguet et al., 2014, 2019; Štern et al., 2019; Zhao et al., 2019; Pierozan et al., 2020; Bittner et al., 2021). Among these biomarkers the most common ones are the cell viability biomarkers, oxidative damage biomarkers, DNA damage biomarkers and alteration of expression patterns of candidate genes involved in cell toxicity response, cell cycle regulation and DNA damage repair (Lakshmana Rao et al., 2002; Bláha et al., 2010; Sierosławska and Rymuszka, 2013; Huguet et al., 2014, 2019; Takser et al., 2016; Buratti et al., 2017; Hercog et al., 2017; Laugeray et al., 2018; Štern et al., 2019; Valério et al., 2020; Bittner et al., 2021; Rivera et al., 2021). For STXs, DA, OA, AZAs, BTXs, CTXs and PLTXs, the vast majority of studies focuses on cell viability, oxidative damage and DNA damage effects; quantification of neurotransmitters and their metabolites; and also on the evaluation of expression patterns of candidate genes, that have the potential of being used as biomarkers for these toxins (Lefebvre et al., 2009; Nicolas et al., 2015; Yan et al., 2017; Souid et al., 2018; Cao et al., 2018; Giuliani et al., 2019; Bodero et al., 2019; Yau et al., 2019; Campos et al., 2020; Gajski et al., 2020; Pasinszki et al., 2020; Han et al., 2021; Corriere et al., 2021; Domínguez-Pérez et al., 2021).

Indeed, the recent advances in omics-based technologies (such as genomics, transcriptomics, proteomics, metabolomics and epigenomics) and the ongoing characterization of the genomes of several model organisms promoted the development of new molecular biomarkers that improve our knowledge on how environmental stressors cause toxicity in humans and also in ecologically relevant organisms (Suarez-Ulloa et al., 2015; Chintalapati and Barile, 2019; Perera et al., 2019; Ning et al., 2020; Ma et al., 2021). An elucidating example is the analysis of gene expression profiles using RNA-sequencing coupled with bioinformatic analysis, allowing the identification of differentially expressed genes upon exposure and also the identification of their functional role in the response to environmental stressors (Suarez-Ulloa et al., 2013; Costa-Silva et al., 2017; Zhou et al., 2018; Marie, 2020; Jeremias et al., 2021; Pinto et al., 2022). The expensive whole genome RNA-sequencing can be replaced by cheaper Real-Time-qPCR techniques when target genes responding to the exposure are identified, showing high efficacy in detecting alterations in gene expression profiles in response to freshwater and marine toxins (Martínez et al., 2015; Zhou et al., 2018; Bodero et al., 2019; Valério et al., 2020; Marie, 2020). These approaches have the potential of elucidating on mechanisms of toxicity triggered at the transcriptomic level, potentially allowing the identification of sensitive molecular biomarkers of toxin effects, but also exposure (Zhou et al., 2018; Marie, 2020; Jeremias et al., 2021).

A current cornerstone within omics-based technology in this context is the assessment on the epigenome. Epigenetic modifications can regulate gene expression profiles in a very specific manner, which gives

these mechanisms the ability to mediate phenotypic plasticity ranges in critical traits of (aquatic) organisms responding to environmental stressors, thus they have the potential to become very feasible biomarkers of exposure and effects (Jeremias et al., 2018a). These epigenetic modifications as caused by aquatic toxins can be used as biomarkers for these environmental toxins (Chintalapati and Barile, 2019; Ma et al., 2021). The few studies addressing epigenetic changes promoted by aquatic toxins focus on DNA methylation rates in the whole genome or in specific genomic areas relevant for toxicity response, as well as on specialized histone variants expression or in histone post-translational modifications (i.e., phosphorylation and acetylation) (Suarez-Ulloa et al., 2015; Gonzalez-Romero et al., 2017; Ma et al., 2021). Untargeted DNA methylation approaches is generally addressed using methylation-specific restriction enzymes (like the Methylation Sensitive Amplified Polymorphism protocol) or genome-wide bisulfite sequencing (Suarez-Ulloa et al., 2015; Gonzalez-Romero et al., 2017; Jeremias et al., 2020; Šrut, 2021), although there are alternatives that may render the analysis more sustainable (e.g., targeted bisulfite sequencing and reduced representation bisulfite sequencing; Jeremias et al., 2018a). Histone modifications upon toxicant exposure are mainly studied using chromatin immuno-precipitation sequencing, the colorimetric histone antibody test, western blots and by assessing the expression of histone modifier genes (Jeremias et al., 2018a; Šrut, 2021). The emergence of epigenetic biomarkers capable of serving as early warning signals for toxicity is particularly valuable for public health risk assessment and also aids in finding possible new treatments for cyanotoxin and phycotoxin toxicity (Chintalapati and Barile, 2019; Perera et al., 2019; Ma et al., 2021). Additionally, it is important to point out that some epigenetic marks are inheritable (for example, DNA methylation), and these often constitute the basis for long-term adaptations to adverse environmental conditions (Suarez-Ulloa et al., 2015; Trijau et al., 2018; Pierozan et al., 2020; Schwarzenberger and Martin-Creuzburg, 2021; Šrut, 2021). In this context, environmentally induced epialleles can act similarly to alleles at genetic loci and enrich the ground for natural selection to act, thus acting as powerful drivers of adaptation (Jeremias et al., 2018a). Therefore, a better understanding of the epigenetic dynamics involved in the response of ecologically relevant organisms to aquatic toxins may help us understand how these organisms evolve to cope with these toxins, and potentially use these organisms as sentinels for the presence of toxins in contaminated waters and for human health risk (Jeremias et al., 2018b; Šrut, 2021).

The development of reliable and efficient epigenetic biomarkers is of the upmost priority especially for neurotoxins. It has indeed been confirmed that exposure to neurotoxicants, including the cyanotoxin BMAA, may lead to epigenetic changes linking to neurodegeneration, alterations in neurological development and maturation (Sher, 2017; Pierozan et al., 2020). Brain development is regulated by epigenetic mechanisms such as DNA methylation, and epigenetic modifications caused by neurotoxic toxins particularly in neural stem cells have the potential of being used as early indicators of the toxicity of these dangerous compounds. Despite this general evidence, our understanding of the relevance of specific epigenetic changes in aquatic toxins toxicity and human disease is still limited. Over recent years the number of studies linking cyanobacterial toxins (in particular microcystins, cylindrospermopsins, STXs and BMAA) with DNA methylation rate changes and modulation of chromatin remodelling has been rising (Perreault et al., 2011; Huguet et al., 2014; Zhao et al., 2019, 2021; Pierozan et al., 2020). The full-length epigenetic impacts of marine toxins are still unknown, but there are some studies focused on the impact of marine toxins (in particular STXs, BTXs, OA and DA) in DNA methylation (Suarez-Ulloa et al., 2015; Gonzalez-Romero et al., 2017; Bodero et al., 2018), and a relationship was found between marine toxins exposure and DNA hypomethylation leading to altered gene expression (Gonzalez-Romero et al., 2017). Studies focusing on the effects of these toxins in the remaining epigenetic mechanisms, such as histone modifications and chromatin remodelling, are also mildly available; these show that chromatin-related genes are differentially expressed in response to OA and BTXs, having great potential of being reliable biomarkers of effect (Suarez-Ulloa et al., 2013, 2015; Gonzalez-Romero et al., 2017; Reynolds et al., 2020). However, there is still a need to further build on these studies and develop efficient epigenetic biomarkers for diverse aquatic toxins.

The number of studies focusing on developing molecular biomarkers for aquatic toxins will hopefully keep rising as greatly needed, owing to the growing ability to generate and analyse high-throughput data in a broader range of model organisms (Williams et al., 2014; Suarez-Ulloa et al., 2015; Marie, 2020). The reviewed *in vitro* and molecular assays and tools show great potential as alternatives for the more traditional assays, particularly the mouse bioassay. However, they require additional fundamental studies and highly trained technicians with access to special laboratory facilities to be performed (Suarez-Ulloa et al., 2015; Bodero et al., 2018; Murk et al., 2019). Depending on the assay, the results produced need to be carefully considered since significant differences exist between toxicity to isolated cells or to membranes and toxicity to an entire organism, in which excretion and detoxification mechanisms are present and may well prevent the substance from reaching the target organs or cells that showed sensitivity *in vitro* (Chorus et al., 2021).

5.2.2. Model organisms for addressing cyanotoxin and phycotoxin ecotoxicity

For the effective response of toxicological biomarkers, it is paramount to choose a good biological model that provides qualitative and quantitative responses to the target toxins (de Morais Calado et al., 2020). *In vitro* and other toxicity bioassays can be done on a variety of organisms, usually selected for their ecological relevance and sensitivity (Fig. 4) (Perreault et al., 2011). Ahead, we briefly reason on four examples of species that can be promoted as models for the study and development of biomarkers for aquatic toxins, focusing in neurotoxins. All these models have been thoroughly used in (eco)toxicology addressing the effects of a wide array of environmental stressors (including aquatic neurotoxins as reviewed in sections above) in a wide range of molecular, physiological, individual and supra-individual endpoints. Moreover, they have high quality genomic information available (Howe et al., 2013; Lee et al., 2019; Jørgensen et al., 2019; Queirós et al., 2019), which has been largely rendering them suitable for use in studies relying in omics platforms, in particular genomics, transcriptomics and epigenomics.

Daphnia is a freshwater crustacean with a central ecological role as a phytoplankton grazer and prey item for secondary consumers; because of this and of its high and characterised sensitivity to a wide array of environmental stressors, daphnids are widely used as a model in ecotoxicology (Herrera et al., 2015; Jeremias et al., 2018b; Trijau et al., 2018; Bownik and Pawlik-Skowrońska, 2019). These invertebrates feed on various bacteria, unicellular and filamentous cyanobacteria and protozoans, thus they represent primary recipients of cyanobacterial toxins in freshwater ecosystems (Suarez-Ulloa et al., 2015; Herrera et al., 2015; Bownik and Pawlik-Skowrońska, 2019). The fact that *Daphnia* is a parthenogenetic organism with short life cycle that is clonally propagated in laboratory, brings a significant advantage for molecular studies, since responses can be mechanistically studied independently of genetic variation (e.g., Jeremias et al., 2018b; Trijau et al., 2018).

A useful parallel to *Daphnia* but focusing marine toxins produced during HAB events are copepods. Phytoplankton, including toxin-producing HAB species, are grazed primarily by zooplankton making copepods direct recipients of marine toxins (Turner, 2014; Abdulhussain et al., 2020). Copepods are an important link between primary producers and higher trophic levels, which makes them one of the main entry points for marine toxins in food webs (Raisuddin et al., 2007; Turner, 2014). Algal toxins may have direct, negative effects on the survival of these mesozooplanktons, making them good model organism for the study of marine phycotoxins owing to their sensitivity to these

toxins and being easily cultured (Raisuddin et al., 2007; Turner, 2014; Roncalli et al., 2016; Abdulhussain et al., 2020; Han et al., 2021). Furthermore, the fact that copepods, behavioural, biochemical and molecular responses to exposure to diverse environmental stressors and chemicals is well known brings an important advantage for their use to develop toxicity biomarkers (Raisuddin et al., 2007; Tarrant et al., 2019; Han et al., 2021).

Fish are good biological models in aquatic ecosystems because they represent predators and hence the final link in the food web allowing considerations on trophic transfer dynamics of aquatic toxins. *Danio rerio* has been perhaps the most used fish species in aquatic toxins research (Berry et al., 2007; Lefebvre et al., 2009; Sher, 2017; de Morais Calado et al., 2020; Chen et al., 2020; Corriere et al., 2021). The fact that *D. rerio* embryos are readily permeable to small molecules added to their incubation medium and transparent chorion, makes this organism a good model for neurological/behavioural, morphological and molecular studies focusing on evaluating the effects of different environmental stressors, including aquatic toxins (Lefebvre et al., 2009; Beliaeva et al., 2010; Norton and Bally-Cuif, 2010; Dai et al., 2014; Williams et al., 2014; Fitzgerald et al., 2021; Torres et al., 2021). The use of the zebrafish as a model in the human health arena (Howe et al., 2013) extends the significance of studying the effects of aquatic toxins with this species. Furthermore, *D. rerio* is an excellent model organism for environmental monitoring of toxins owing to the suitability of various transgenic zebrafish lines to improve specific monitoring sensitivity (Dai et al., 2014; Williams et al., 2014; Torres et al., 2021).

Lastly, the nematode *Caenorhabditis elegans* has emerged as an important animal model in the fields of neurobiology, developmental biology and genetics (Leung et al., 2008; Queirós et al., 2019; Tian and Zhang, 2019). Several characteristics of this animal model have contributed to its success including: easy genetic manipulability, invariant and fully described developmental program, well characterized and sequenced genome and epigenome, well understood cell signalling pathways, structural and functional similarities to the human nervous system, ease of maintenance and a short life cycle (Leung et al., 2008; Ruszkiewicz et al., 2018; Queirós et al., 2019). Furthermore, *C. elegans* is a nematode of worldwide distribution in the wild, found in the soil and in lesser extent in freshwater environments where it is likely exposed and has sensitivity to aquatic toxins (Yunhui et al., 2009; Queirós et al., 2019; Tian and Zhang, 2019). Additionally, linking behavioural changes with specific neuronal damage is relatively simple in *C. elegans*, which brings an invaluable advantage for the development of neurotoxicity biomarkers (Queirós et al., 2021). These characteristics have led to an increasing use of *C. elegans* in toxicology, both for mechanistic studies and high-throughput screening approaches and show *C. elegans* can serve as a valuable bioindicator for evaluating cyanotoxin and phycotoxin toxicity (Leung et al., 2008; Yunhui et al., 2009; Ruszkiewicz et al., 2018; Tian and Zhang, 2019; Queirós et al., 2021).

The model organisms here reviewed are only examples of good model organisms for the development of molecular and epigenetic biomarkers since there is a wide range of potential model organisms covering different aquatic ecosystems, further underlining the potential of environmental biomarkers in the detection of aquatic toxins and in accessing the effects of these toxins (Jeremias et al., 2020).

6. Conclusions and future perspectives

(1) Harmful bloom events populate freshwater, brackish and marine environments and they are growing all over the world regarding frequency, severity and biogeographical level. Due to climate change and increased pollution levels, it is likely that the occurrence of cyanobacteria and algal blooms in aquatic environments will keep rising, likely leading to increased toxins production and potentially inducing the production of a wide range of currently unknown toxins, thus enhancing the already significant public health, ecological and economic concerns.

(2) Despite toxic blooms cannot be easily eliminated, their negative repercussions should be managed and mitigated through strategic policy enforcement, by developing new improved monitoring methodologies, mitigation plans, and lastly by investing in fundamental scientific research that can support a better understanding of the (ecological) effects of aquatic toxins.

(3) So far, research has not yet definitively determined why aquatic toxins are produced, with our understanding being limited in terms of what triggers their production and release, as well as which effects, particularly subtle sublethal effects and side toxicity pathways, they have at environmentally relevant concentrations on the ecosystems, on the wildlife and on human health. Despite recent advances, a lot remains to be investigated in this regard.

(4) An effort should be made in future studies focusing on effects of aquatic toxins regarding: (i) the use of *in vivo* environmentally relevant species and not only human-related models and/or *in vitro* cultured cells; (ii) the focus in hazard assessment at environmentally relevant conditions, using environmentally relevant concentrations and more relevant exposure pathways, i.e., avoiding intraperitoneal, intravenous and intratracheal exposure and focusing on oral exposure, the most relevant uptake route for toxins on humans and the other biota; and (iii) increase the use of algal extracts containing a mixture of toxins and other secondary metabolites in acute and chronic exposure studies. These improvements will make the obtained toxicological data more ecologically relevant and of better-quality data, leading to a more complete understanding of the (eco)toxicological effects of these compounds, to the potentially establishment of adverse outcome pathways for these toxins, that in time will help to better ascertain the actual risk they pose for environmental and human health towards well-adjusted safety guideline values and mitigation strategies.

(5) The development of sensitive molecular biomarkers based on omics presents a promising cutting-edge venue for the study of the effects of aquatic toxins effects and for their screening. However, there are still knowledge gaps and critical research challenges that should be overcome in order to efficiently use these biomarkers for such purposes. These relate essentially to specificity and linkage of biomarker responses to individual and supra-individual effects, as well as potential technical constraints.

(6) The continuously rising and lasting implications for individual organisms and entire ecosystems, as well as the possibility of increased fatal poisonings in freshwater and marine environments, amplifies the need for conducting additional research on aquatic toxins.

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.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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Abbreviations

ASP	amnesic shellfish poisoning
AZAs	azaspiracids
BMAA	β-N-Methylamino-L-alanine
BTXs	brevetoxins
CFP	ciguatera fish poisoning
CIs	cyclic imines
CTXs	ciguatoxins
CyanoHABs	cyanobacterial harmful algal blooms
DA	domoic acid
DSP	diarrheic shellfish poisoning
EU	European Union
HABs	harmful algal blooms
LPSs	lipopolysaccharides
MAPKs	mitogen-activated protein kinases
NSP	neurotoxic shellfish poisoning
OA	okadaic acid
PFP	pufferfish poisoning
PLTXs	palytoxins
PSP	paralytic shellfish poisoning
PTXs	pectenotoxins
qPCR	quantitative Polymerase Chain Reaction
ROS	reactive oxygen species
STXs	Saxitoxins
WHO	World Health Organization
YTXs –	Yessotoxin

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