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Review

Health and Environmental Impacts of Cyanobacteria and Cyanotoxins from Freshwater to Seawater

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Abstract: Cyanobacterial harmful algal blooms (cyanoHABs) are a natural phenomenon produced mainly by the interaction between natural and anthropogenic events. CyanoHABs are characterized by the production of cyanotoxins that can have harmful effects on different species within the food web and even affect human health. Among the most prevalent toxin groups worldwide are microcystins (MCs), anatoxins (ATXs), cylindrospermopsins (CYNs) and nodularins (NODs), which are characterized as toxins with hepatotoxic, neurotoxic, and cytotoxic effects. This review summarizes and analyzes research on the influence of cyanoHABs, the main toxin-producing cyanobacteria and the most prevalent cyanotoxins in freshwater and marine bodies, highlighting their global occurrence, toxicology, and bioaccumulation dynamics in vectors of the food web, and the main cases of acute and chronic intoxications in humans. This review is useful for understanding the dynamics of cyanoHABs' interaction with the ecosystem and their impact on human health, and how the implementation of a surveillance and management framework for cyanobacteria and cyanotoxins could generate vital information for stakeholders to establish health guidelines on the risks and hazards of cyanoHABs for the ecosystem and humans.

Keywords: cyanobacteria; cyanotoxins; bioaccumulation; health risk; human; ecosystem; microcystin; anatoxins; cylindrospermopsins; nodularins; stakeholders

Key Contribution: This review article provides an update on the current status of the impact of cyanobacteria and cyanotoxins on the trophic web and their impact on public health. The advantages, limitations, and future directions are also discussed.

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1. Introduction

Cyanobacteria are phytoplanktonic, prokaryotic, and photoautotrophic (Gram-negative) microorganisms, and have been producers of atmospheric oxygen on Earth for about 3.5 billion years, a period in which they have adapted to different climatic, geochemical, and anthropogenic changes [1–3]. These blue-green algae represent the primary producers in aquatic ecosystems, being considered natural inhabitants of rocks, soils, and diverse environments such as freshwater, estuaries, and marine waters [4]. Their intense proliferative capacities tend to produce biomass, which causes turbidity, discoloration of the water, and, sometimes, foam formation, processes known as blooms [5–11].

Blooms, specifically related to cyanobacteria, are defined as "the increase of biomass in a waterbody (chlorophyll-α concentration) over a relatively short period of time (between a few days and 1 to 2 weeks) and characterized by the predominance (>80%) of a single species or a few species within the phytoplankton community" [12–14]. Through this process, cyanobacteria can reach concentrations of more than 10^6 cells per liter of water [15].

The last century has been marked by a constant and excessive increase in the levels of greenhouse gases and nutrient inputs. These pollutants end up in freshwater courses such as lakes and rivers, resulting in eutrophication processes, defined from a natural point of view as an excessive increase in primary production derived from a high rate of photosynthesis, which is triggered by the natural discharge of nitrogen and phosphorus, which are carried away by rain and surface waters that erode Earth's surface [16,17].

In addition, anthropogenic activities associated with high agricultural activity, high levels of industrial waste, and the demographic growth of cities have caused gradual alterations in the physical–chemical state of lentic and lotic water bodies, causing the alteration of their trophic states (Figure 1) [3], generating the decomposition of organic matter and a decrease in the concentration of dissolved oxygen in the water, and consequently causing the death of different species associated with the aquatic ecosystem, such as benthic invertebrates and fish [6,18,19].

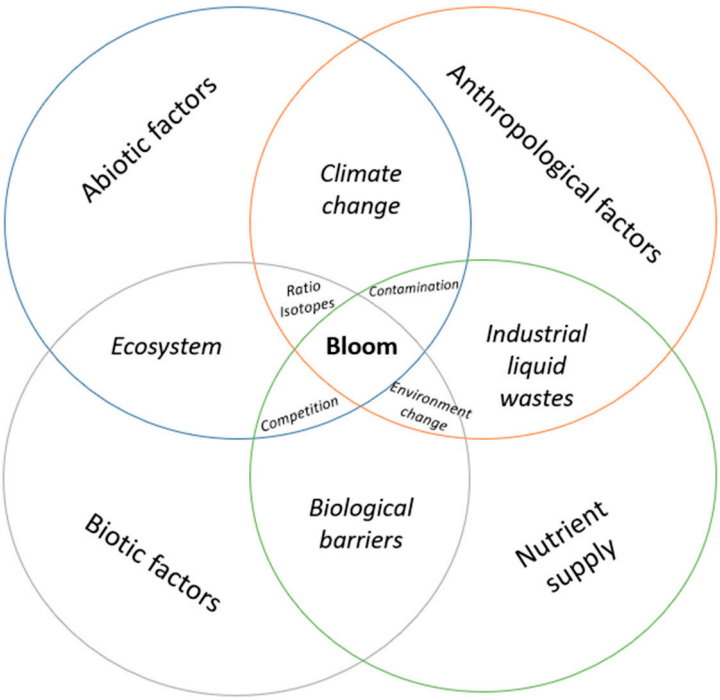

Figure 1. Diagram of factors influencing incidence of cyanoHABs.

Blooms tend to occur seasonally, usually in spring and summer, and are the result of excessive nutrient enrichment, particularly nitrogen and phosphorus [19,20]. This, together with favorable conditions of temperature, light penetration in the water column, water pH, conductivity (salinity), water turnover time in lotic zones, food web variability, and carbon dioxide availability, favors the displacement of the phytoplankton community towards cyanobacteria, which can form dense and recurrent blooms [4–6,18–22]. The sum of these factors plus climatic variability have allowed certain taxa of freshwater cyanobacteria to become more frequent at different latitudes and/or in specific sectors or regions of most countries, and their incidence has tended to increase due to global changes generated by anthropogenic activities (Figure 2) [1,12,23–30].

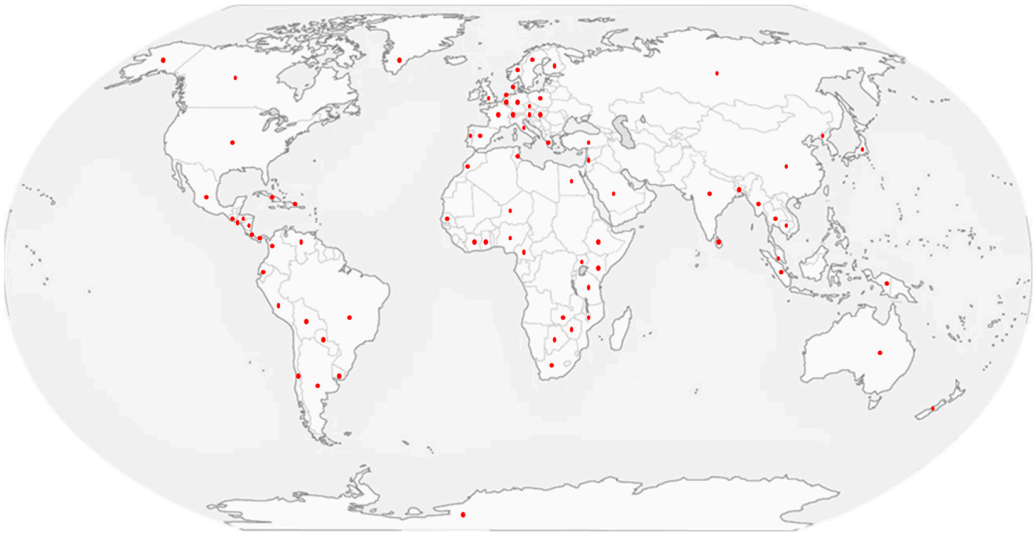

Figure 2. Map of global distribution of cyanoHABs (denoted by red dots).

The greatest danger associated with cyanobacteria is that under certain conditions, cyanobacteria produce bioactive metabolites called cyanotoxins. Because cyanotoxins pose risks to aquatic organisms and humans, blooms that produce these chemicals are called "cyanobacterial harmful algal blooms" (cyanoHABs) [12,14,31,32].

About 3000 species of cyanobacteria are currently known; however, not all of them produce toxins [19,33], since the dynamics between physicochemical parameters, genetic factors between species, and the physiological state of cells can affect/alter cyanotoxin synthesis (cell quota), thus allowing an interaction between toxic and non-toxic genotypes to occur environmentally [34–36]. However, paleolimnological analyses allow us to determine that both the abundance and toxicity of cyanoHABs date back millennia [37–41].

From an environmental point of view and according to biotic and abiotic interaction conditions, it is possible that cyanobacteria alternate their life cycle between the benthos and the pelagic zones, allowing inoculation to promote flowering or to settle in the sediment (seed bank) until the right conditions for growth are in place [42–48]. This process is key to cyanotoxin content, as cyanotoxins are not passively excreted by cyanobacteria and are usually released into the aquatic environment during cell death and lysis. However, some species of cyanobacteria can release toxins into the water without rupturing or dying (e.g., *Cylindrospermopsis* sp.) [3,49].

The global impacts of cyanoHABs and their toxins generate high socioeconomic and ecological costs, affecting without limitation drinking water sources, lake and marine resources, agriculture, transportation, tourism, trade, the food web, and ecosystems [50,51]. For these reasons, the World Health Organization (WHO) has developed guidelines based on the densities and toxicities of cyanoHABs in water, establishing that different types of exposures can pose a significant risk to human health [33,52,53].

Although there is important scientific information on the subject, there are still questions regarding the following: How are toxins assimilated at different trophic levels? Are they events that only affect inland water bodies? Is there any relationship between cyanoHABs and marine vectors? How relevant is the impact of cyanoHAB exposure on human intoxication? How can decision makers be guided to understand the risks and hazards of cyanoHABs to the environment and public health?

The main objectives of this paper are to examine and establish the dynamics of cyanoHABs and cyanotoxins in freshwater and estuarine bodies of water, including the

trophic network, in order to propose actions that will allow the application of quality control and management methods in inland water bodies.

For this review, we compiled data from published scientific studies investigating the occurrence of the most prevalent cyanobacteria/cyanotoxins worldwide, their toxicology, the assimilation and interaction between trophic networks in freshwater and marine species, the main cases of intoxication in humans, and the risks and hazards associated with cyanoHABs and cyanotoxins. A wide range of environmental, toxicological, and other scientific literature was explored via the Scopus database, which includes PubMed, Web of Science, and ScienceDirect.

2. Cyanotoxins

Cyanotoxins correspond to secondary metabolites, i.e., they are intermediates or metabolic products that do not play a vital role in the growth, development, and/or reproduction of cyanobacteria; therefore, it is suggested that they have an auxiliary purpose of responding to environmental stress, or that they are synthesized to act as a defense mechanism against the threat of other microalgae species competing for light, nutrients, and habitats [12,54–56].

The detection of cyanotoxin concentrations in processes associated with cyanoHABs depends primarily on four factors: (1) species abundance; (2) the abundance of genotypes (toxigenic); (3) the type(s) of toxin(s) that can be produced by the taxon; and (4) the cellular quota of toxins [57–59]. Thus, cyanotoxins that are preferentially found intracellularly can be detected in the water, which will be favored according to the chemical nature of the toxins and the stage of bloom development, this process being more characteristic in stages of the senescence or decline of blooms [59–63].

This release of cyanotoxins into the environment can have significant effects on aquatic species, including decreased survival rates, altered development, larval mortality, reduced feeding, and death [12,64]. Harmful effects may be enhanced, since some cyanobacterial taxa can produce a wide variety of cyanotoxins and may even produce different groups of toxins [12,65]. These variables favor the possibility that cyanotoxins can bioaccumulate (process by which toxins enter the food web by building up in individual organisms) in different aquatic vectors, favoring their transfer through the trophic network until they reach people, which can cause different clinical pictures of acute or severe intoxication [12,36,66–68].

2.1. Hepatotoxins

2.1.1. Microcystins (MCs)

Microcystins correspond to a group of cyclic heptapeptides which have seven amino acids (ciclo-(D-alaninel-X2-DMeAsp3-Z4-Adda5-D-glutamato6-Mdha7)) (M.W. 881–1360 Da) (Figure 3a) [69]. Methylations, hydroxylations, epimerizations, and amino acid substitutions give rise to structural diversity. So far, more than 300 different analogs have been identified in lakes or cell cultures, the most prevalent analogs being MC-LR, MC-RR, and MC-YR, with MC-LR standing out for its high toxicity (Figure 3a) [70–75].

MCs are stable, non-volatile, water-soluble molecules produced as secondary metabolites by different genera of cyanobacteria at levels of up to 1% by mass (Table 1) [67,70,76].

This group of cyanotoxins is characterized by having different types of toxic levels according to the analog detected (LD_{50} MC-LR y-RR 50 μg/kg and 600 μg/kg b.w., respectively) [76–78]. *Microcystis aeruginosa* is the dominant producer of MCs; however, it has also been detected in taxa such as *Anabaena* sp., *Oscillatoria* sp., and *Planktothrix* sp. (Table 2) [79,80].

At the cellular level, MCs cause specific damage to liver cells by inhibiting protein phosphatases (PP1 and PP2A), resulting in the hyperphosphorylation of cellular proteins [81].

This occurs because the amino acid ADDA is covalently bound to the cysteine residue that both enzymes have in their catalytic center, Cys-266 in the case of PP1 [82–84] and Cys-273 in the case of PP2A [85]. Thus, it is the amino acid ADDA that defines the toxicity of MCs [71,86–89].

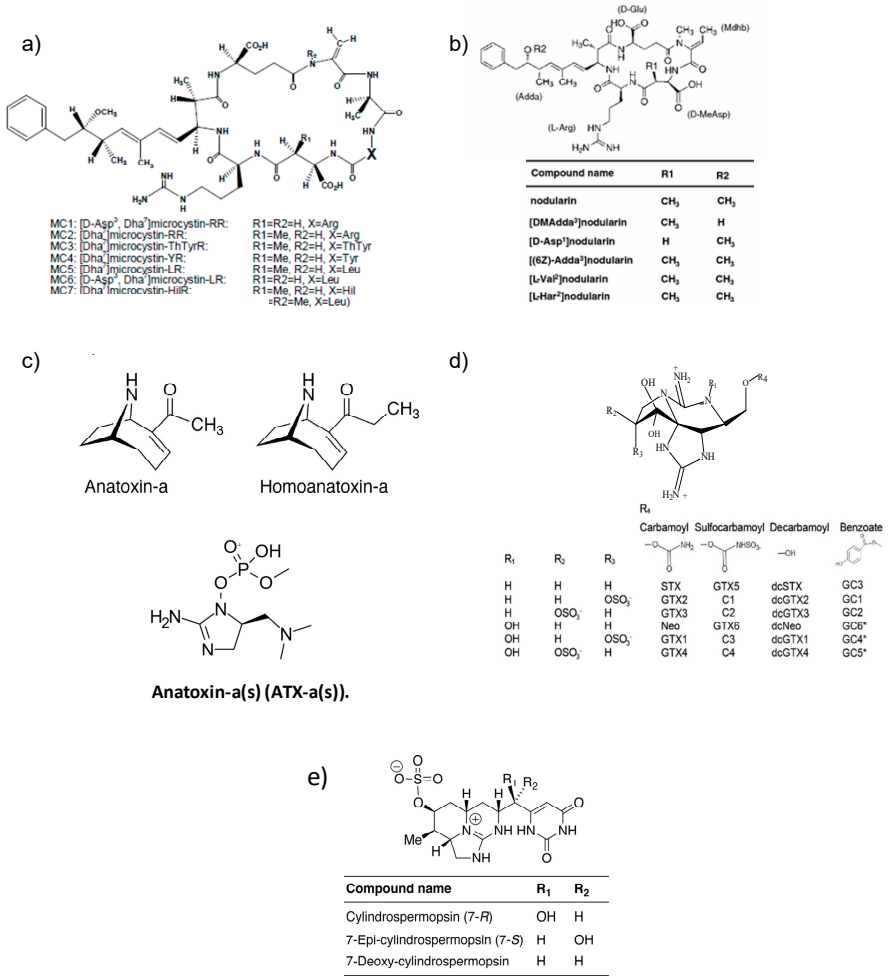

Figure 3. Structure of cyanotoxin groups. (**a**) Microcystins (MCs); (**b**) nodularins (NODs); (**c**) anatoxins (ATXs); (**d**) saxitoxins (STXs); (**e**) cylindrospermopsins (CYNs).

Table 1. Characteristics of freshwater cyanobacteria and cyanotoxins and their toxic effects.

Cyanotoxin	Cyanobacterial-Producers	Cell Quota	Toxic Effects	Cyanotoxin-Producers	References
Microcystins (MCs)	*Aphanizomenon* *Dolichospermum* *Limnothrix* *Microcystis* *Nostoc* *Oscillatoria* *Phormidium* *Planktothrix* *Gloeotrichia* *Hapalosiphon* *Radiocystis*	<150 to 850 fg/cell	diarrhea, vomiting, stomach cramps, nausea, acute liver failure, chronic kidney disease, respiratory symptoms, abdominal pain, sore throat, dry cough, blistering at the mouth, headache, flulike symptoms, irritation and rashes (colorectal cancer). [1]	*Microcystis* spp., *M. aeruginosa*, *M. viridis*, *Dolichospermum* sp., *Anabaena flos-aquae*, *A. subcylindrica*, *A. variabilis*, *Oscillatoria (Planktothrix) agardhii*, *Nostoc* sp., *Nostoc spongiaeforme*, *Anabaenopsis* sp., *Hapalosiphon* sp., *Gloeotrichia echinulata*, *Plectonema boryanum*, *Phormidium corium*, *Phormidium splendidum*, *Rivularia biasolettiana*, *R. haematites*, *Tolypothrix distorta*, *Arthrospira fusiformis*.	[12,90–92]
Nodularins (NODs) [2]	*Nodularia Noctoc*	60–500 fg/cel	Allergic reactions, skin rashes, gastrointestinal illness, nausea, liver damage, bleeding.	*Nodularia spumigena*, *Nostoc* sp.	[2,12,91]
Cylindrospermopsins (CYNs)	*Anabaena* *Cylindrospermopsis* *Aphanizomenon* *Chrysosporum* *Raphidiopsis* *Umezakia*	<1.9 to 196 fg/cell	Nausea, vomiting, diarrhea, stomach cramps, hepatomegaly, kidney dysfunction.	*Cylindrospermopsis raciborskii*, *Aphanizomenon ovalisporum*, *Dolichospermum* sp., *Anabaena lapponica*, *Raphidiopsis curvata*, *Umezakia natans*.	[12,90,91]
Anatoxin-a (ATX)	*Anabaena* *Aphanizomenon* *Cylindrospermum* *Microcystis* *Oscillatoria* *Phormidium* *Planktothrix*	0.1–500 fg/cell	Convulsions, fatigue, paralysis, respiratory failure.	*Arthrospira fusiformis*, *Anabaena* spp., *Aphanizomenon* sp., *Phormidium* sp., *Anabaena flos-aquae*, *Anabaena planktonica*, *Cylindrospermum* sp., *Oscillatoria* sp., *Raphidiopsis mediterranea*, *Phormidium formosum*.	[90,91]
Saxitoxins (STXs)	*Cuspidothrix* *Dolichospermum* *Microseira* *RaphidiopsisPlanktothrix Oxynema*	120–1300 fg/cell	Tingling sensation around the lips, convulsions, headaches, dizziness, nausea, vomiting fatigue, paralysis, respiratory failure.	*Aphanizomenon flos-aquae*, *Microseira* sp. *Dolichospermum circinale*, *Cylindrospermopsis raciborskii*, *Planktothrix* sp.	[90,91]

[1] Several human epidemiological studies from China have reported an association between liver or colon cancer and the consumption of drinking water from surface waters containing cyanobacteria and microcystins. In these studies, individuals with liver cancer were also exposed to aflatoxins and hepatitis, both risk factors for liver cancer. The results from this work demonstrate a possible association, but do not directly determine a link between microcystin exposure and liver cancer. [2] No epidemiological studies have explicitly investigated the relationship between NOD exposure and health outcomes at the population level.

Table 2. Toxicity of cyanotoxins.

Cyanotoxin	Primary Toxicity	Mode of Action	Lifetime Drinking Water (µg/L)	Short-Term Drinking Water (µg/L)	Recreational Water (µg/L)	LD_{50}	TDI (µg/kg/day)	NOAEL (µg/kg bw/day)	LOAEL (µg/kg bw/day)	Classification	References
Microcystins	Hepatotoxicity	Inhibition of protein phosphatases	1.0	12.0	24.0	5.0–10.9 (oral; µg/kg)	0.04	40.0	50.0	Group 2B—possibly carcinogenic to humans.	[2,53,87,93–95]
Nodularins	Hepatotoxicity	Inhibition of protein phosphatases	1.0	12.0 [1]	n.d.	50.0 (intraperitoneal; µg/kg)	0.04	100.0	n.d.	Group 3—not classifiable as to its carcinogenicity to humans.	[50,53,93,96]
Cylindrospermopsin	Hepatotoxicity	Inhibition of protein phosphatases	0.7 (0.01)	3.0	6.0	4.4–6.9 (oral; µg/kg)	0.03 [2]	30.0	150.0	n.d. (potential for carcinogenicity)	[52,53,97,98]
Anatoxin-a	Neurotoxicity	Nicotinic acetylcholine receptor agonists	1.0	30 [3]	60.0	>5000.0 (oral; µg/kg)	0.1 [2]	98.0	n.d.	n.d.	[52,53,97,99]
Anatoxin-a(s)	Neurotoxicity	Inhibition of acetylcholinesterase	1.0	n.d.	n.d.	20.0–40.0 (intraperitoneal; µg/kg)	n.d	n.d	n.d	n.d.	[52,100–102]
Saxitoxins	Neurotoxicity	Blocking of sodium channels	3.0	0.3	30.0	35.0 (oral; µg/kg)	0.05 [2]	0.5	1.5	n.d.	[52,53,97,101,103]

[1] Sufficient toxicological data are lacking for the derivation of a guideline value (GV) for nodularins. Tentatively, the microcystin GV can be applied due to the structural and toxicological similarity between microcystins and nodularins. [2] Oregon Health Authority (OHA). [3] Valore referential short-term and lifetime exposure GVs were not developed, and short-term exceedances of the acute GV should not be permitted. n.d.: not detected.

Exposure to these toxins has caused significant effects and deaths at the trophic level, including small planktonic invertebrates, fish, other fish species [104,105], and vertebrates (dogs, cows, sheep, otters, and horses) [1,106–108]. The main route of toxic action is through ingestion, although it has been proposed that inhalation may be another route of absorption of MCs [109–111].

The major source of exposure to MCs for humans is from drinking water, although other pathways, such as food, interaction with recreational waters, and nutritional supplements, may be significant [76,90]. These cyanotoxins, when ingested, are transported throughout the body, where they enter the cells through organic anion transport polypeptides (OATP) present in the membranes. The main target of action is the liver [112]; however, MCs can also affect other tissues such as the kidneys, colon, brain, lungs, and heart [2,50,113,114]. In addition, MC-LR modulates the expression of tumor necrosis factor α (TNF-α) and proto-oncogenes such as *c-jun*, *jun B*, *jun D*, *c-fos*, and *c-myc* [2,14].

The World Health Organization (WHO) has established a tolerable daily intake (TDI) in drinking water of 1.0 µg/L for MC-LR, while for recreational activities, a level of 20 µg/L MC-LR (value according to an intake volume of 0.2 L per day) has been set (Table 3) [90]. These levels have been accepted in most countries, with MC-LR being classified as "possibly carcinogenic to humans" in 2010 [57,101,115].

2.1.2. Nodularins (NODs)

This group of toxins corresponds to cyclic peptides consisting of five amino acids, including the characteristic amino acid ADDA, which assigns the structural feature to NOD toxins [116]. Structural variations have given rise to at least 10 variants of NODs being described (Figure 3b) [69,117]. Nodularin is the most common pentapeptide (M.W. 825 Da) of general structure cyclo-(D-MeAspl-L-arginine2-Adda3-D glutamate4-Mdhb5), and Mdhb is 2-(methylamino)-2-dehydrobutyric acid [34,118,119]. The most common analog corresponds to NOD-R, cycle (-D-erythro-b-methylAsp (iso)-L-Arg-Adda-D-Glu (iso)-2-(methylamino)-2-(Z)-dehydrobutyric acid), where ADDA stands for 3-amino-9-methoxy-2,6,8-tri-methyl-10-phenyldeca-4 (E), 6 (E)-dienoic acid [120]. The most characteristic NOD-producing species is *Nodularia spumigena*, which is typical of brackish waters (estuaries), whose blooms have been detected mainly in Europe, South Africa, Canada, Australia, the United States, and New Zealand [50,65,121,122].

NODs share a similar chemical structure to MCs, allowing them to have the same level of toxic action, i.e., inhibit PP1/2A [74,123–127].

Experimental data (i.p. in mice) have established that NODs accumulate mainly in the liver; however, it is possible to detect significant levels in the blood and intestines, where they enter via diffusion through non-specific organic anion transporters, using the bile acid transport system as a pathway [65,91]. Their toxicity at the hepatic level is characterized by causing disorganization of the cytoskeleton, lipid peroxidation, loss of membrane integrity, cellular vesicle formation, cell disruption, necrosis, intrahepatic hemorrhage, and apoptosis, all of which provide the ideal scenario for death by hemorrhagic shock. Additionally, NODs induce oxidative stress and produce reactive oxygen species (ROS), causing damage such as lipid, protein, and DNA peroxidation [65,126].

Although several studies have shown that NODs induce the expression of TNF-α and proto-oncogenes, this group of cyanotoxins has been classified by IARC as "animal carcinogenic but not classifiable as to its carcinogenicity to humans" [3,69].

NOD-associated blooms have caused extensive hemorrhaging and deaths in animals, but to date, there are no epidemiological data that can be associated with human intoxication [12]. However, different countries have established health regulations that set

maximum limits for both cyanobacteria in recreational waters and levels of cyanotoxins in water intended for human consumption (Table 2) [3,57,86].

2.2. Neurotoxins

2.2.1. Anatoxins (ATXs)

Anatoxin-a (ATX, M.W. 165 Da) and homo-anatoxin-a (HTX, M.W. 179 Da) represent the most characteristic bicyclic alkaloids of this group (Figure 3c) [97]. These toxins are produced by cyanobacteria of different genera (Table 1) [12,128–130]. The prevalence of this group of cyanotoxins is low; however, ATX has been detected in blooms at levels of ≈154 µg/L, but like other toxic groups, the release of cyanotoxins to the medium occurs only at senescence stages of the bloom [76,131].

Their chemical characteristics confer high solubility and stability in darkness, and they possess a half-life of ≈1–2 h in the presence of high light intensity [99] and ≈14 days under normal light conditions at basic pH [60,132]. However, once released into an aqueous medium, these cyanotoxins can be weakly adsorbed on sandy sediments and more strongly on sediments rich in clay and organic matter, the latter being characterized as promoters of toxin sorption (ATX-a) [56,133].

ATXs bind irreversibly to acetylcholine receptors, causing depolarization of post-synaptic neuronal cells [102,134]. Symptoms produced by ATX (LD_{50} 260 µg/kg b.w.) include convulsions, limb spasms, and eventual paralysis, leading to death in ≈7 min (Table 1) [74,101,135].

One of the most widely described analogs currently corresponds to anatoxin-a(s) ($ATX_{(s)}$), a neurotoxic alkaloid (M.W. 252 Da), whose chemical characteristic is that it is an N-hydroxyguanidine methylphosphate ester that causes the irreversible inhibition of acetylcholinesterase [12,136], causing symptoms in animals such as convulsions, urinary incontinence, respiratory distress, and hypersalivation, this being the characteristic symptom that assigns the term "s" to the analog [56,137–141].

To date, no epidemiological data have been recorded associating human poisoning with this group of cyanotoxins [76], but it has been detected in water bodies in the U.S.A. and Canada, where toxicosis has been observed in dogs, pigs, and poultry, with time to death ranging from 5 to 30 min [50].

2.2.2. Saxitoxins (STXs)

The saxitoxin group (STX-group) corresponds to polar chemical compounds constituted by a unit called imidazoline, which, according to the modification of some of its functional groups, allows them to be divided into three characteristic groups: carbamoyl-toxins, N-sulfocarbamoyl-toxins, and descarbamoyl-toxins. These neurotoxins possess high affinity for voltage-dependent sodium channels, causing muscle paralysis by blocking the nerve impulse [103,142,143]. (Figure 3d).

STX-group toxins are characterized by being mainly associated with harmful algal bloom events (HABs) in the sea (dinoflagellates) [144] and also by having a high prevalence in marine hydrobiological resources, specifically gonyautoxin analogs (GTX; GTX3/GTX2 and GTX4/GTX1), which tend to predominate in the toxin profile in shellfish (75–85%) [144–146]. However, these toxins have also been identified in different cyanobacterial genera (*Cylindrospermopsis*, *Dolichospermum*, *Aphanizomenon*, *Planktothrix*, and *Lyngbya*) (Table 1) [74,147,148].

The half-life of saxitoxin (STX) depends on pH and temperature; they are stable at 25 °C and neutral pH, and can be detected in water intended for irrigation and in rivers in the range of ~9 to 28 days post-bloom [56,149]. They exhibit high chemical stability at acidic pH (~2–4), and high degradation at extremely alkaline pH [150–153].

These toxins have been detected and associated with intense blooms, reaching levels of 193 μg/L in water and with toxicities in different vectors of approximately 4466 μg STX equiv/g dry weight [12,101,154–157], conducive to the ideal scenario for human exposure through vector consumption and/or recreational activities.

Toxic events associated with intoxication in humans by STX-group toxins have demonstrated a high rate of biotransformation of the analogs [144,156–160]. The identification of STX analogs is regulated by international regulations only in products for consumption of marine origin, but not in freshwater vectors [161]. However, some countries (Australia, Brazil, and New Zealand) have established a maximum permissible level of 3.0 μg/L for drinking water (Table 3) [101,162,163].

2.3. Cytotoxin

Cylindrospermopsins (CYNs)

This group of cyanotoxins is characterized as tricyclic alkaloids consisting of a tricyclic guanidine group combined with a hydroxyethyl uracil [98]. Cylindrospermopsin (CYN, M.W. 415.43 Da) is the most prevalent analog detected and has been classified as a cytotoxin, since it can affect both the liver (hepatotoxic) and the nervous system (neurotoxic) [2,76]. Modifications in specific groups produce toxic variants such as 7-epi-CYN, 7-deoxy-CYN, 7-deoxy-sulfo-CYN, and 7-deoxy-sulfo-12-acetyl-CYN (Figure 3d) [69,164–166].

Cylindrospermopsin raciborskii corresponds to the most studied species of this group, and is characterized by being associated with subtropical and tropical habitats; however, it has been classified as an invasive species due to its identification in other latitudes worldwide [74]. Additionally, this species has been associated with STX-group production [3,167].

This group of analogs, as well as other cyanotoxins, are characterized by being water-soluble, highlighting that the areas associated with blooms are characterized by high levels of extracellular toxins, detected in an average range of 20–95% of net production [61,168–172].

The main target organ is the liver, although toxic effects have been described in kidneys, lungs, heart, and thymus [74,173–176]. The molecular structure of CYN confers hydrophilic characteristics; therefore, its intestinal absorption and incorporation into hepatocytes is mediated by active transport systems, such as the bile acid transport system [12,177,178].

In vitro studies have demonstrated the mutagenicity of CYN [179–181]. However, no information is available on the carcinogenicity of this group in humans, nor has tumor-initiating activity been established [166,182–184].

Environmentally, toxic levels of CYN have been reported in surface waters at concentrations of ~173 μg/L [12] and sometimes with the coexistence of MCs [70]. These high environmental levels have suggested that this group of cyanotoxins possess the capacity to disrupt the antioxidant system and/or cause oxidative stress in a wide variety of aquatic animals [36].

To date, only New Zealand and Cuba have developed monitoring guidelines for risks associated with benthic toxic blooms, even though toxin concentrations are not detailed, given the constant spatial and temporal variation in blooms [185–187].

Table 3. Drinking and recreational water guidelines of different cyanotoxins worldwide.

Country/Organization	Cyanotoxin	Maximum Concentration in Drinking Water	Maximum Concentration in Recreational Water	References
WHO	Microcystin-LR	1.0 µg/L	24.0 µg/L	[188]
	Cylindrospermopsin	0.7 µg/L	6.0 µg/L	
	Saxitoxins	3.0 µg/L	30.0 µg/L	
	Anatoxin-a	3.0 µg/L	60.0 µg/L	
USEPA	Microcystin	0.3 µg/L [1] 1.6 µg/L [2]	<8.0 µg/L	[189–192]
	Cylindrospermopsin	0.7 µg/L [1] 3.0 µg/L [2]	<15.0 µg/L	
	Saxitoxins	0.3 µg/L [1] 1.6 µg/L [2]	8.0 µg/L	
	Anatoxin-a	0.7 µg/L [1] 3.0 µg/L [2]	15.0 µg/L	
EU	Microcystin-LR	1.0 µg/L		[192]
China	Microcystin-LR	1.0 µg/L [4]	ND	[190]
Australia	Microcystin	1.3 µg/L	≤10.0 µg/L	[191]
	Nodularin	1.3 µg/L	≤10.0 µg/L	
	Cylindrospermopsin	0.9 µg/L	ND	
	Anatoxin-a	3.1 µg/L	ND	
	Saxitoxins	3.1 µg/L	ND	
Brazil	Microcystin	1.0 µg/L	ND	[193]
	Cylindrospermopsin	15.0 µg/L	ND	
	Saxitoxins	3.0 µg/L (STX equiv.)	ND	
	Nodularin	1.0 µg/L	ND	
Canada	Microcystin-LR	1.5 µg/L [3]	10 µg/L	[194]
Denmark	Microcystin	1.0 µg/L [3]	20 µg/L	[195]
Belgium and Luxembourg	Microcystin-LR	1.0 µg/L [3]	20 µg/L	[196]
France	Microcystin-LR	1.0 µg/L [3]	≤25.0 µg/L 13.0 µg/L	[197]

Table 3. *Cont.*

Country/Organization	Cyanotoxin	Maximum Concentration in Drinking Water	Maximum Concentration in Recreational Water	References
Finland	Microcystin	<1.0 µg/L [3]	ND	[198]
Germany	Microcystin	<1.0 µg/L [3]	<10.0 µg/L	[199]
Greece	Microcystin-LR	1.0 µg/L [3]	ND	[200]
Italy	Microcystin	ND [3]	< 25.0 µg/L	[201]
Poland	Microcystin-LR	1.0 µg/L [3]	20.0 µg/L	[202]
Czech Republic	Microcystin-LR	1.0 µg/L [3]	ND	[203]
Portugal	Microcystin-LR	1.0 µg/L [3]	ND	[204]
Netherlands	Microcystin	1.0 µg/L [3]	<20.0 µg/L	[205]
New Zealand	Microcystin	1.0 µg/L	≤12.0 µg/L	[206]
	Cylindrospermopsin	1.0 µg/L	ND	
	Saxitoxins	3.0 µg/L	ND	
	Anatoxin-a	6.0 µg/L	ND	
	Anatoxin-a(s)	1.0 µg/L	ND	
	Homoanatoxin-a	2.0 µg/L	ND	
	Nodularin	1.0 µg/L	ND	
Singapore	Microcystin	1.0 µg/L [4]	ND	[207]
Spain	Microcystin	1.0 µg/L [4]	ND	[208]
Turkey	Microcystin-LR	1.0 µg/L [3]	<25.0 µg/L	[209]
	Cylindrospermopsin	1.0 µg/L	ND	
Uruguay	Microcystin-LR	1.0 µg/L	20.0 µg/L	[210]
	Cylindrospermopsin	0.5 µg/L	ND	
	Saxitoxins	3.0 µg/L	ND	
South Africa	Microcystin-LR	ND	<10.0 µg/L	[211]
Perú	Microcystin-LR	1.0 µg/L [4]	ND	[212]
Argentina	Microcystin-LR	1.0 µg/L [4]	ND	[213]
Mexico	Microcystin-LR	1.0 µg/L [4]	ND	[214]
Costa Rica	Microcystin-LR	1.0 µg/L [4]	ND	[215]
Paraguay	Microcystin-LR	1.0 µg/L [4]	ND	[216]
Panama	Microcystin-LR	1.0 µg/L [4]	ND	[217]

ND: not determined. [1] Infants and pre-scholar children. [2] School-age children and adults. [3] European Union guidelines. [4] WHO guidelines.

3. Food Web Transfer

Given the developmental characteristics of cyanoHABs in aquatic ecosystems, it can be established that they can have varied effects on different aquatic organisms. The first assimilation pathway corresponds to the direct filtration of cyanobacteria by primary consumers (zooplankton, crustaceans, and bivalves), even when the food is considered of poor quality for this trophic segment, as it lacks polyunsaturated fatty acids (PUFA) and essential sterols [138,218,219].

Subsequently, during the cyanoHAB decay phase, the stage of cyanotoxin disposal to the aqueous medium begins, a stage in which all organisms that are part of the food web are directly exposed, in different magnitudes, to the toxins, i.e., from undetected levels to levels of >7000 µg MCs/L; 180 µg CYN/L; 42,300 µg NOD/L; and 1750 µg ATX-a/L [217,220]. This scenario promotes a second pathway, corresponding to the direct filtration of diluted cyanotoxins in the water column. Most toxins are characterized by high hydrophilicity, which apparently favors their distribution in the tissues of the species. However, it is important to note that cyanotoxins do not passively penetrate cell membranes, as they require specific transporters for cellular assimilation [3,70].

3.1. Freshwater Vectors

For the first trophic level (primary consumers), which is characterized by the presence of different species of zooplankton and crustaceans, there are data obtained from an environmental point of view associated with cyanoHABs. In fact, species of this trophic level preferentially assimilate senescent cyanobacteria at the bottom of lotic or lentic water bodies, filtering cyanotoxins that may be in different types of sediments. Thus, the types of analogs assimilated can be very diverse according to the chemical stability that toxins can present in the ecosystem. Several studies have established that MCs produce alterations in the development of some zooplankton species. The exposure of MC-LR (10.2 ng/mg b.w.) on *Daphnia* sp. tends to produce alterations in growth rates, as well as to decrease the survival rate of larvae, in addition to the high incidence of deformations in individuals during their development [119,221–223].

Likewise, in the case of crustaceans (*Pacifastacus lenisculus*), it has been experimentally established that the species presents high tolerance to exposure to *Microcystis* sp. and that they can also assimilate low levels of MCs without showing toxic effects. However, in species such as *Chasmagnatus granulatus*, gill damage has been observed with concomitant inhibition of Na^+ K^+ ATPases and an increase in antioxidant capacity [224].

Regarding CYN exposure, preferential distribution in hepatopancreas and muscle tissues has been experimentally detected in *Cherax quadricarinatus*, with no toxic effects observed [225]. In the case of anatoxin-a, there are few studies on its accumulation in species of this trophic level.

Another important group of affected species is bivalves, benthic invertebrates that represent the most direct connector between cyanoHABs and the food web. These organisms, under normal environmental and physiological conditions, filter an average of 2–3 L/h of water because they are omnivorous organisms, and according to their densities in the water body, they can have an important influence on planktonic species, suspended organic matter, and cyanoHABs [226–228]. These freshwater vectors are mainly characterized by ingesting and accumulating cyanotoxins through cell filtration during cyanoHABs. However, certain patterns can modulate the assimilation and filtration process selectively, such as taxon type, cell size, cell morphology, colony formation or a lack thereof, toxicity, and the types of cyanotoxins. Additionally, bivalves may excrete some types of cyanobacteria as pseudofeces, a process that also appears to influence the density of cyanobacteria in the water column (Table 4) [228].

Table 4. Occurrence of cyanotoxins in food web transfer.

Typical Species					
Species		**Cyanotoxins**	**Toxin Accumulation**	**Method of Detection**	**References**
Bivalvia					
Freshwater					
Bivalve	*Alathyria pertexta*	CYN	130.0–560.0 μg CYN/kg	HPLC	[229]
	Anodonta cygnea	CYN	2.9–61.5 μg/g DW	HPLC	[230]
	Anodonta woodiana	MC	12.6 μg/kg DW	HPLC	[231]
	Cristaria plicata	MC-LR/YR/RR	0.07 μg/g DW	LC-MS/MS	[232]
	Unio douglasiae	MC	420.0 μg/kg DW	HPLC	[231]
	Corbicula fluminea	STX	0.4–0.6 μg/g DW	HPLC	[233]
Seawater					
Bivalve	*Alanthyria condola*	STX	0.8–6.2 μg/g DW	HPLC	[234]
	Macoma balthica	NOD	0.16–30.0 μg/g DW	LC-ESI-MS	[235]
	Macoma balthica	NOD	320.0 μg/kg DW	HPLC-DAD	[236]
	Magallana gigas	NOD	24.1–397.3 μg/kg	LC-MS/MS	[237]
	Mytilus edulis	NOD	0.28–13.8 μg/g DW	LC-ESI-MS	[236]
	Mytilus edulis	NOD	2200.0 μg/kg DW	ELISA-LC-MS	[238]
	Mytilus edulis	NOD	400.0–1100.0 μg/kg DW	LC-MS/MS	[239]
	Mytilus galloprovinciales	MC-LR/YR/RR	0.7–53.9 ng/g	ELISA/UHPLC-HRMS	[71]
	Mytilus galloprovinciales	ATX	6.6 ng/g DW	HPLC	[240]
	Mytilus galloprovinciales	MC-LR	45.0–141.5 ng/g	ELISA	[241]
	Mytilus trossulus	MC-LR/LA/LW	1.9–32.3 μg/kg DW	LC-MS/MS	[242]
Gastropoda					
Freshwater					
Crayfish	*Paranephrops planifrons*	NOD	9.7–225.3 μg/kg WW	LC-MS	[243]
Lobster	*Cherax quadricarinatus*	CYN	0.54–4.3 μg/g	HPLC	[244]
Snail	*Bellamya aeruginosa*	MC-LR	6.61 μg/g DW	LC-MS/MS	[245]
	Bellamya aeruginosa	MC-LR/RR	1.06–7.42 μg/g DW	LC-MS	[246]
	Helisoma trivolvis	MC	37.0 μg/g DW	HPLC	[231]
	Hippeutis complanatus	MC	1223.26 ng/g FM	HPLC	[247]
	Lymnaea stagnalis	MC-LR	0.26 μg/g DW	ELISA	[248]
	Margaria melanoides	MC	0.40 μg/g DW	ELISA	[249]
	Melanoides tuberculata	CYN	ND–250.0 μg/g DW	HPLC	[240]
	Physa acuta	MC	1325.45 ng/g FM	HPLC	[250]
	Physa gyrina	MC	129.0 μg/g DW	HPLC	[231]
	Planorbis planorbis	MC	548.33 ng/g FM	HPLC	[250]
	Pomacea patula catemacensis	CYN	3.35 ng/g	LC-MS/MS	[251]
	Pomacea patula catemacensis	STXs	1.04–21.34 ng/g	ELISA	[251]
	Sinotaia histrica	MC-LR	9.03 μg/g DW	HPLC	[252]

Table 4. *Cont.*

Typical Species					
Species		**Cyanotoxins**	**Toxin Accumulation**	**Method of Detection**	**References**
Shrimp	*Mysis relicta (Decapoda)*	NOD	0.5–0.74 μg/g DW	ELISA/PP1	[253]
Seawater					
Crayfish	*Callinectes sapidus*	MC	105.0 μg/L	ELISA	[254]
	Cherax quadricarinatus	CYN	0.9–4.3 μg/g DW	HPLC	[244]
Shrimp	*Macrobrachium nipponensis*	MC-LR	0.24 μg/g DW	LC-MS/MS	[245]
Snail	*Vaughtia fenestrata*	CYN	0.8 ng/g	ELISA	[255]
Prawn	*Penaeus monodon*	NOD	6.0–80.0 μg/kg DW	ELISA-LC-MS	[256]
Actinopterygii					
Freshwater					
Fish	*Anguilla australis*	NOD	24.0 μg/kg	LC-MS/MS	[250]
	Anguilla reinhardtii	NOD	58.6 μg/kg DW (liver)	LC-MS/MS	[251]
	Bramocharax caballeroi	CYN	0.81 ng/g	ELISA	[255]
	Ctenopharyngodon idellus	MC-LR/YR/RR	0.04 μg/g DW	LC-MS/MS	[246]
	Carassius auratus	MC-LR	150.0 ng/g DW	LC-ESI-MS	[257]
	Cyprinus carpio	ATX-a	30.0 ng/g DW	GC/MS	[258]
	Cyprinus carpio	MC-LR/YR/RR	0.10 μg/g DW	LC-MS/MS	[257]
	Gasterosteus aculeatus L.	NOD	2.8–700.0 μg/kg	LC-MS/MS	[259]
	Geophagus brasiliensis	STX	1.22–1.97 μg STX equiv/100 g	HPLC-FLD	[260]
	Hypophthalichthys molitrix	MC	1.16–17.8 μg/kg DW	HPLC	[231]
	Hypophthalmichthys molitrix	MC-LR/YR/RR	0.08 μg/g DW	LC-MS/MS	[257]
	Lates niloticus	MC-LR/YR/RR/LA	0.7 μg/kg DW	LC-MS/MS	[261]
	Melanotaenia eachamensis	CYN	1.2 μg/g DW	HPLC	[262]
	Oncorhynchus mykiss	MC-LR	90.66 ng/g DW	LC-MS/MS	[263]
	Oreochromis niloticus	MC-LR/YR/RR/LA	0.6–15 μg/kg DW	LC-MS/MS	[261]
	Oreochromis niloticus	CYN	0.417 μg/g DW	ELISA/HPLC	[264]
	Perca flavescens	MC	130.0 μg/g DW	ELISA	[265]
	Perca fluviatilis L.	MCs	50.0 μg/g	HPLC-UV	[266]
	Rastrineobola argentea	MC-LR/YR/RR/LA	23.4 μg/kg DW	LC-MS/MS	[261]
	Rutilus rutilus	NOD	900.0 μg/kg DW	ELISA/LC-MS/MS	[267]
	Silurus glanis	MC-RR	0.14 μg/g DW (muscle)	HPLC	[259]
	Salmo trutta	NOD	125.0 μg/kg DW	ELISA	[268]
	Tilapia rendalli	MC	2.9–67.8 μg/g PS	HPLC/ELISA	[269]

Table 4. *Cont.*

Typical Species					
Species		**Cyanotoxins**	**Toxin Accumulation**	**Method of Detection**	**References**
Seawater					
Fish	*Ariosoma mellissii*	MC-LR	28.1 µg/kg DW	ELISA	[270]
	Clupea harengus	NOD	6.5 µg/kg DW	ELISA	[259]
	Clupea harengus membras L.	NOD	0.0–90.0 µg/kg	LC-MS/MS	[252]
	Gadus morhua	NOD	0.05 µg/g DW	LC-MS/MS	[238]
	Melanotaenia eachamensis	CYN	1.2 µg/g DW	HPLC	[244]
	Mugil cephalus	NOD	32.3–56.8 µg/kg DW	LC-MS/MS	[271]
	Osmerus eperlanus	MCs	874.0 µg/g DW	HPLC-DAD	[266]
	Platichthys flesus	NOD	1.0 µg/kg DW	ELISA	[272]
	Platichthys flesus	NOD	100.0–600.0 µg/kg WW	LC-MS/MALDI-TOF-MS	[273]
	Platichthys flesus	NOD	22.0–557.0 µg/kg	HPLC	[274]
	Salmon salar	NOD	5.0–10.0 µg/kg	ELISA/LC-MS/MS	[252]
	Vieja sp.	CYN	0.42 ng/g	ELISA	[255]
Atypical Species					
Species		**Cyanotoxins**	**Toxin accumulation**	**Method of Detection**	**References**
Humans					
Human	Homo sapiens-sapiens.	MC	2.03 µg daily MC intake	HPLC	[275]
	Homo sapiens-sapiens.	MC-LR/YR/RR	2.2–3.9 µg daily MC intake	LC-MS/MS	[232]
	Homo sapiens-sapiens.	MC	2.2 ng/mL	ELISA	[276]
	Homo sapiens-sapiens.	MC	7.1–31.4 ng/mL	LC-MS/MS	[277]
	Homo sapiens-sapiens.	MC	0.16–0.96 ng/mL	ELISA	[278]
Mammals					
Cow	*Aberdeen angus*	MC-LR	7100.0 µg/L (rumen)	LC-MS/MS	[279]
	Bos Taurus	MC	5.7 ± 0.5 mg/L	ELISA	[280]
Buffalo	*Bison bison*	MC	9.7 ± 1.4 mg/L	ELISA	[237]
Deer	*Capreolus capreolus*	MC-YR/LR/RR	1.36 µg equiv MC-LR/g	LC-MS	[281]
Dog	*Canis lupus familiaris*	MC	100.0 mg/g DW	ELISA–LC-MS/MS	[282]
	Flat-coat Retriever	ATX	1.04 µg/g	LC-HRMS	[283]
	Golden retriever	dihydroanatoxin-a (dhATX)	974.88 ng/g DW	LC-HRMS	[284]
	Labrador	Homo-ATX-a	9.5 µg/g DW	LC-MS/MS	[285]
	Yorkshire terrier	ATX-a	0.6 mg/g (liver)	HPLC-UV-LC-MS/MS	[286]
	Canis lupus familiaris	ATX	357.0–785.0 mg/kg	LC-HRMS	[287]
Dolphin	*Tursiops truncatus*	MC/NOD	14.3 ± 5.6 ng/g DW	ELISA-LC-MS/MS	[288]
Pig	*Sus scrofa domesticus*	MC-LR	26.4 µg/g DW	LC-MS/MS	[289]
Sea Otter	*Enhydra lutris*	MC-RR	1.36–104.46 µg/g	LC-MS/MS	[106]

Table 4. *Cont.*

Typical Species					
Species		**Cyanotoxins**	**Toxin Accumulation**	**Method of Detection**	**References**
Amphibians					
Bufo marinus	*Rhinella marina*	CYN	895.0 µg free-CYN/kg FW	LC-MS/MS	[290]
Bullfrog	*Lithobates catesbeianus*	MC	1 µg/L	ELISA	[291]
Rana eperotica	*Pelophylax epeiroticus*	MC	0.26–0.47 µg/g DW	PP2/ELISA	[290]
Reptiles					
Turtle	*Emys orbicularis*	MC-LR	0.001–37.2 µg/g DW	PP2A/Limieux-GC-MS	[292]
	Mauremys leprosa	MC-LR, -RR, -YR	0.02–1.193 µg/g DW	PP2A/Limieux-GC-MS	[292]
	Pelodiscus sinensis	MC	0.011–0.021 µg/g DW	LC-ESI-MS	[257]
Birds					
Black-crowned night heron	*Nycticorax nycticorax*	MCs	10.0 ng/g DW gonad	LC-ESI-MS	[257]
Chicken	*Gallus gallus domesticus*	MC-LR	20.0 µg/kg	Bioassay	[293]
Domestic duck	*Anas platyrhynchos*	MC	0.031 µg/g DW (liver)	HPLC	[231]
	Anas platyrhynchos	MCs	15.0 ng/g DW muscle	LC-ESI-MS	[257]
Duck	*Somateria mollissima*	NOD	3.0–180.0 µg/kg DW	LC-MS/MALDI-TOF-MS	[294]
Flamingo	*Phoeniconaias minor*	ATX-a	7.62 µg/g DW	LC-MS/MS	[295]
	Phoenicopterusruber	MC	625.0 µg equiv MC-LR/mL	ELISA	[296]
Plant Kingdom					
Apricot	*Prunus armeniaca* L.	MC	7.20 ± 0.85 µg/kg DW	ELISA	[232]
Grape	*Vitis vinifera* L.	MC	0.10 ± 0.02 µg/kg DW	ELISA	[232]
Lettuce	*Lactuca sativa* L.	MC	8.31–177.8 µg/kg FW	LC-MS/MS	[233]
Plum	*Prunus domestica* L.	MC	7.17 ± 0.39 µg/kg DW	ELISA	[232]
Aquatic plant	*Ceratophyllum demersum*	MC	0.1–0.2 µg/L	HPLC	[297]
	Myriophyllum spicatum	MC	0.5 µg/L	HPLC	[297]
Chordata					
Tunicate	*Microcosmus sabatieri*	ATX-a	193.7–1240.2 µg/kg	LC-MS/MS	[298]

DW: dry weight. WW: wet weight. FW: fresh weight. FM: fresh muscle.

In the case of MCs, the different accumulation rates detected in bivalves are related to the specific assimilation capacities, the developmental stages of each species, and the predominant analog associated with the bloom, which is why the most identified and studied analog is MC-LR [70,101]. However, it has been determined that bivalves show high resistance to the accumulation of MCs and that the degree of accumulation is clearly associated with physiological aspects and vertical distribution in the stratum. Thus, different species in the same body of water can accumulate varying concentrations (0.07–420 μg/g) without showing toxic effects (*Anodonta woodiana*, *Cristaria plicata* and *Unio douglasiae*), while in other vectors (gastropods), exposure may result in the death of the species [231].

Once the toxins are filtered, they are preferentially accumulated in the digestive glands (hepatopancreas), tissue in which the stages of bioconversion and distribution of the analogs are initiated. The bioconversion phase is through GST (*Dreissenia polymorpha* and *Diplodon chilensis*), without consideration of the fact that some analogs are not metabolized, in order to initiate the process of purification of the metabolized analogs (*Diplodon chilensis* > 60%), and also of the non-metabolized fraction [119,299–301]. This process predisposes sandy-bottom-habitat species (clams) to leach and accumulate a mixture of free and metabolized toxic analogs, favoring low retention rates and the bioconversion and distribution of cyanotoxins in visceral and non-visceral tissues [119].

The World Health Organization (WHO) has established a tolerable daily intake (TDI) for MCs in seafood of 24 μg/kg wet weight based on a 60 kg person consuming 100 g of seafood per day [302,303].

Regarding CYNs, the levels of these types of cyanotoxins in benthic organisms are very low (*Alathyria pertexta*), with toxicities in the range of 130–560 μg/kg, following the trend of other types of toxins, i.e., with preferential accumulation in the digestive glands with low bioconversion rates [229]. Meanwhile, in other species, variable toxicities have been detected, such as in snails (3.35 ± 1.90 ng/g) and shrimp (0.1–4.3 μg/g) [12,68,251].

The next trophic level comprises different types of fish, which are usually classified as secondary consumers. However, their classification can be refined according to diet; thus, in freshwater bodies, we can find detritivorous, omnivorous, herbivorous, and carnivorous fish, which establishes that the assimilation and transfer of cyanoHABs and their toxins seem to be highly specific according to the predominant type of species in the ecosystem [304]. Several studies have determined that, in the case of MCs, they tend to be transferred into the trophic chain, reaching variable concentrations according to the type of fish feeding. Once ingested, MCs tend to bind covalently to the proteins of different tissues, which allows us to understand the dynamics of the prevalence and interaction of toxins in some tissues. MCs tend to be mostly detected in the liver, intestines, kidneys, and gonads and, to a lesser extent, in muscle (<20 times) [101,248,289,304,305]. Miles et al. [306] establishes that post-exposure MCs have a dual action, being classified as toxic (free) analogs, which are not covalently bound to any protein, and non-toxic analogs, covalently bound to any structure. However, the latter fraction can be released, generating toxic action in a secondary way when circulating in the system. Thus, MCs, according to their molecular mode of action, can generate liver and gill diseases as a consequence of exposure (via PP2A inhibition) [222].

Complementarily, the toxic effects are dependent on the developmental stages of the fish (larvae/juveniles/adults). MCs, in early stages, tend to generate greater alterations in larval development: they decrease growth rates, generate malformations, and produce important alterations in antioxidant capacity, which tends to alter the number of individuals in a specific habitat. In adult individuals, assimilation depends directly on the feeding route (direct vs. vectorial), which, added to the high development of their epithelial layer,

their greater metabolic capacity, and their high mobility in the aquatic environment, makes them more resistant [12,307].

Detritivorous, omnivorous, and herbivorous fish feed directly on cyanobacteria and may indirectly ingest cyanotoxins. Thus, after environmental exposure to cyanoHABs, the route of interaction of fish with toxins and cyanoHABs (MCs) is mainly by oral ingestion and secondarily by absorption through the gill epithelium [3,308]. Therefore, the toxic capacity depends largely on the stage of development of the bloom, which will define the type of toxin availability. In the early stages, more intracellular toxins will be available, while in the senescence stage, the toxin availability will be diluted in the water, generating a lower toxic effect. Thus, the route of MC exposure is decisive for its toxic effects in fish, since exposure through the medium would generate a lower effect without causing mortality compared to the oral route [88].

Environmental evaluations of the effect of MCs on different types of fish have determined that omnivorous species such as tilapia (*Oreochromis niloticus*, 0.6–15 μg/kg DW) and silver carp (*Hypophthalamichtys molitrix*, 1.16–17.8 μg/kg DW) have low toxin accumulation rates, since they are characterized by selective feeding, generating the option to exclude themselves from the effects of the bloom of toxic taxa. Complementarily, when comparing omnivorous species (*Perca* sp., 50–130 μg/kg DW) with carnivorous species (*Oncorhynchus* sp., 90.66 ng/g DW), it has been determined that some omnivorous species tend to be more sensitive, which is directly related to their low metabolic capacity (Table 4) [309,310].

Given the incidence of certain species of cyanoHABs in freshwater bodies, concentration data in fish tend to be preferentially oriented towards MCs and to a lesser extent towards CYNs. Thus, data related to CYNs are scarce, but it has been environmentally established that this group of toxins accumulates preferentially in the digestive system and at low concentrations in the muscle. Toxicities also depend on the type of fish and its diet (0.081, 0.42, and 1.2 μg/g in *Bramocharax caballeroi*, *Oreochromis nilaticus*, and *Melanotaenia eachamensis*, respectively) [244,264,311].

Regarding ATX-a, there are few studies on its assimilation and accumulation in fish. However, toxicities have been detected in omnivorous fish (*Cyprinus carpia*) in the range of 0.030–0.768 μg/g [249].

In addition, there is little information regarding the environmental impact of NODs on freshwater organisms, mainly because this type of toxin is preferentially found in estuaries, where the waters are slightly brackish, or in coastal lakes with saline characteristics [65]. However, it has been possible to establish NOD transfer in different fish species in the range of 24–700 μg/kg [119,259,271,312].

Therefore, it can be established that in aquatic ecosystems (lentic and lotic), fish play an important role in the assimilation of cyanoHABs through direct feeding or through the food web [228]. However, although these species are directly and indirectly exposed to the different types of cyanotoxins, the data evidence that their accumulation in tissues in adult individuals is low, a plausible proposal being the high capacity of metabolization and detoxification of most of the ingested cyanotoxins via GTS (MCs, NOD), Cytochrome P450/GST (ATX and $ATX_{(s)}$), and Cytochrome P450 (CYN), thus favoring less toxic and more-water soluble metabolites [138].

However, different levels of cyanotoxin (MCs/CYN) accumulation in biota cannot be predicted based on trophic level, as concentrations depend on several interactions, including the organism's consumption rate, digestive capacity, and time since exposure. Berry et al. [311], through an evaluation of different types of fish, established a higher concentration of MCs in phytoplanktivorous fish compared to omnivorous and zooplanktivorous fish, suggesting that the accumulation of these toxins varies according to the direct interaction with cyanoHABs and not according to biomagnification processes [311]. Ferrão-

Filho et al. [138], through a meta-analysis in species of different trophic levels, confirmed that the ecological data point to a process of biodilution (a decrease in the concentration of a pollutant with a corresponding increase in the trophic level in a body of water) of cyanotoxins (MCs) to the detriment of biomagnification (the process by which toxins are passed from one trophic level to the next within a food web) [138].

Undoubtedly, the high-water solubility of cyanotoxins (MC-LR, CYN and ATX) and the high detoxification capacity in adult individuals are factors that promote the biodilution of toxins in the food web, greatly hindering biomagnification [313]. However, the capacity of some cyanobacterial species to produce more than one type of toxin (MCs/STXs; MCs/CYNs) could affect the metabolic activity of some aquatic species, leading to the biomagnification of some types of specific cyanotoxin analogs, thus constituting a threat to public health [3,138,314]. In addition, it is important to note that a key factor contributing to biodilution is that most primary consumers are omnivores (especially filter feeders), as they consume a mixed diet composed of allochthonous and autochthonous organic matter, which would explain the differences in cyanotoxin bioaccumulation in trophic networks [313].

3.2. Marine Vectors

Countries with regulatory norms regarding cyanobacteria and their toxins set sanitary and regular controls in freshwater bodies. However, given the flow dynamics of certain lentic and lotic bodies, it is possible to transfer these microorganisms through currents to the sea, and there are species of cyanobacteria that, under environmental conditions, increase their prevalence in brackish water (*Nodularin* sp.), which allows them to contribute toxins more constantly to the shoreline [41,315]. From this perspective, it is evident that osmotic variation affects the integrity of cyanobacteria, leading to cell lysis with the concomitant release of cyanotoxins into the aqueous medium. Thus, the accumulation of different cyanotoxin analogs in benthic and planktonic marine species is plausible [49,106,316].

In the last 20 years, different investigations have focused on determining the transmission of cyanotoxins from freshwater to marine products, which has allowed the detection of different analogs in bivalve tissues. MCs have been detected in native and cultured mussels, establishing a coherent dispersal dynamic in the freshwater → estuary → seawater transect, which has been corroborated by demonstrating the presence of *Microcystis* sp. taxa with *mcyB* gene expression [69,317–319].

The mode of interaction is preferentially through the direct filtration of cyanotoxins, removing the option of the rejection or generation of pseudofeces by marine bivalves, since direct contact with cyanoHABs is very low (>5%). Thus, assimilation, like for other toxins, would follow the same dynamics as in freshwater species, filtration→assimilation→distribution→metabolization→elimination, with the retention and bioconversion capacity of the new toxic analogs generated varying in each species. Thus, different types of cyanotoxins (MCs, CYNs, ATXs, and NODs) have been identified in bivalves from different habitats (rocky stratum and sandy bottom)—such as *Macona blathica* (≥80–320.0 μg/kg), *Mytilus edilus* (0.28–1110 μg/kg), *Mytilus galloprovinciales* (0.7–141.5 ng/kg), and *Mytilus tronssulus* (1.9–32.3 μg/kg) (Table 4) [237,238,241,320].

The accumulation of cyanotoxins could follow a dynamic related to the periods of higher incidence of cyanoHABs, corresponding to spring–summer, which would allow, in some cases and according to the periodicity of blooms, for varied and constant contributions to be made to marine species, allowing filtration to be cumulative in some marine species that stand out for having a high filtration rate (e.g., *Mytilus* sp.). This does not rule out that during the summer period, some species may show complete or partial detoxification/purification processes for some analogs of the different groups of

cyanotoxins [236,273,303]. It should be noted that this detoxification/purification process is not definitive and that it is also species-specific, which may mean that in some percentage ranges, there is distribution of toxins to the non-visceral tissues (muscles) of filter feeders. This is the case for CYN, which has been detected in mussels at levels of ~3 mg/kg [317].

Amzil et al. [49], through the EMERGTOX program implemented in France since 2018, showed that it was possible to detect a wide group of unregulated toxins in seafood products (mussels and gastropods), including spirolides, pinnatoxins, gymnodimine, brevetoxins, microcystins, anatoxin, and cylindrospermopsin, among others. In this study, MCs and CYN were detected at concentrations of 9.0 and 18.0 µg/kg, respectively, and ATX was detected for the first time in mussels from the coast of France. In addition, it was possible to determine that the greatest concentrations were found in *Microcystis* sp. The study even identified that the most assimilated toxins corresponded to the dmMC-RR and MC-RR analogs, establishing favorable bioconversion to dmMC-RR in the tissues of plovers [49].

Regarding NODs, these cyanotoxins tend to be more prevalent in seafood products, since they are produced by species with more estuarine habitats, allowing animals inhabiting these environments to tolerate a constant supply of toxins up to a limit that has not been well established (upstream). Species such as mussels and clams can steadily assimilate NODs (7.0–397 µg/kg in Sweden), which, even given the constant input of NODs, could promote, in some species, a more efficient detoxification dynamic (~70%, 72 h) [65,119,236,237].

The major turning point is represented by the STX-group, as these analogs have been described as being produced by some cyanobacterial genera (Table 1) [56,321–323], in addition to the dinoflagellate genera that produce them in marine environments (*Alexandrium* sp.) [241,324,325]. These toxins in a marine environment have a high prevalence in the food web ($\geq$800 µg STX equiv/kg) due to annual blooms preventing total detoxification in some species of bivalves and gastropods [326–328]. Thus, to delimit the prevalence of toxins from the concentrations of cyanoHABs and HABs, it is necessary to carry out constant monitoring of both types of blooms, as well as analyze toxins from the cyanoHABs and HABs, since the incidence of these toxins in marine hydrobiological organisms may not be associated with HABs [144].

Likewise, most species in the sea stand out for having a high rate of bioconversion and detoxification of the STX-group (Phase I, CYP450, and Phase II via GST), which tend to broaden the toxin profile towards more toxic analogs [144,329]. However, it is possible that some species—when first exposed to cyanoHABs and/or HAB toxins—may experience harmful effects through oxidative stress or accumulation of the toxins in their tissues (feet), leading to paralysis and, consequently, stranding of the species on marine coasts [144,330,331].

Simultaneous events of filtration and accumulation of cyanotoxins and marine toxins have been confirmed by Anderson et al. [332], who detected the occurrence of MCs and domoic acid (DA) in estuaries in the U.S.A. This is due to blooms of *Pseudo-nitzschia* spp. contributing DA and MCs (intracellular + extracellular) from freshwater bodies, whose dynamic dispersion is favored by environmental factors (wind and temperature) [332].

Additionally, within the marine trophic network, secondary and tertiary consumers stand out significantly, most of which are fish, which, given the dynamics of the distribution and stability of cyanotoxins, make biomagnification determinations complex [333]. Ferrão-Filho et al. [138] established that in freshwater fish, the bioaccumulation factor is species-specific, reaching a value of < 3.5. This factor could be further simplified in a marine environment, where the possibility of bioaccumulation could be restricted and linked to NODs, given the habitat from which they originate [334]. Stewart et al. [271] detected different levels of NOD in different species representative of different levels of the food web, establishing that the bioaccumulation dynamics of the toxins was explained according to the

chemistry of the toxin and the dynamics of the different types of fish species in the sea. Thus, fish such as *Platichthys flesus*, characterized by a mainly bottom-dwelling diet (crustaceans, mollusks, and annelids) have been found to possess NOD levels of >100 µg/kg, which are assimilated and absorbed mainly through browsing on the sandy bottom. *Salmo salar*, a carnivorous species whose diet is mostly composed of small fish, has a low capacity for the bioaccumulation of toxins, with concentrations of approximately <10 orders of magnitude, so according to the data, the part of the food web involving carnivorous fish is more related to the biodilution of toxins than to biomagnification, which is enhanced given their low exposure to toxins and the high metabolic capacity they possess [217,271,335]. Similarly, a general bioaccumulation trend of the different groups of cyanotoxins is prevalent in the digestive tissues, kidneys, gonads, and gills of fish, and to a lesser extent in their brains and muscle tissue, which can also exert damage to different organs according to the level of action that characterizes the group of toxins, leading to growth inhibition, behavioral changes, alterations in the antioxidant system, and mortality [3,138,336]. It should be noted that MCs have also been detected in seawater at concentrations ranging from 0.003 to 19.8 ng/L (Amvrakikos Gulf) [241] and that accumulation of the different groups of cyanotoxins has been identified in species such as *Anguilla* sp., *Clupea harengus*, *Osmerus eperlanus*, *Salmo salar*, and *Vieja* sp., among others (Table 4) [266,270,273,311].

3.3. Non-Traditional Vectors

The evaluation of cyanoHABs shows that most of the toxic events escape the logic of interaction within a trophic network, evidencing a direct route of exposure through the ingestion of cyanobacteria/cyanotoxins. Several articles have shown intoxications in sheep, cattle, dogs, fish, invertebrates, and other organisms, including higher plants [119,176,337,338].

The first scientific evidence of these poisoning cases was recorded in Australia, where a bloom of *Nodularia* sp. caused the death of sheep, horses, dogs, and pigs, and later, similar events were recorded in Europe (Table 4) [271]. Complementarily, in Canada and the U.S.A., blooms associated with *Microcystis aeruginosa* have caused the death of birds, in which concentrations of *Microcystis aeruginosa* were detected at ~6000 µg MCs/L [185]. While in Spain, the death of flamingos has been linked to blooms of *Microcystis aeruginosa*/*Anabaena flos-aquae*, in this case, the analyses correlated the deaths with the bioaccumulation process with respect to the levels of cyanotoxins detected in the water, corresponding to ~10 µg/mL MC, in relation to the content detected in the crops and livers of the birds (600 µg/mL and 440 µg/mL, respectively) [304].

Cyanotoxins in Crops

In view of this dynamic interaction of freshwater courses with cyanoHABs events, a high risk of using lentic and lotic waters for the development of hydroponic crops, or for the direct irrigation or sprinkling of soils intended for growing crops, such as lettuce, radishes, arugula, dill, parsley, alfalfa, broccoli, and cabbage, has been demonstrated. From this perspective, different studies have determined the bioaccumulation of CYN in different types of vegetables, such as spinach and lettuce, where the toxin has been detected in the roots and leaves [68,69,339,340].

Regarding crops, it has also been suggested that a constant supply of cyanotoxins (CYN, MCs, or NODs) can have toxic effects in plants that result in a decrease in seed germination, a reduction in photosynthetic yield, oxidative stress, and the alteration of plant growth and development (e.g., wheat, corn, peas, and lentils) [50,68,341,342]. In lettuce leaves, MC concentrations have been detected ranging from 0.094 to 2.487 µg MC-LR/g [343]. Concentrations exceeding 2.0 µg/g per day have also been reported,

surpassing the regulatory levels established for drinking water [53]. Similarly, MCs are the most prevalent cyanotoxins detected in species such as apricot, grape, orchid, and plum, with toxicity levels varying between 0.1 and 177 μg/kg, depending on the species (Table 4) [344,345].

To understand this assimilation pathway, ref. [31] established that irrigation processes can have physical effects on cyanoHABs, which, combined with microorganism-mediated decomposition, gradually release intracellular cyanotoxins (MCs) into the environment. This allows the constant assimilation of toxins through the roots, stems, and leaves of plants, resulting in a clear bioaccumulation process. However, the direct application of MCs shows that soil microorganisms degrade these toxins, leading to a reduction in toxin availability and, consequently, a decrease in the rate of assimilation and accumulation by plants [31,341].

Thus, the consumption of stems, leaves, and edible crops can be considered an important vector, as their intake at concentrations > 0.04 μg MC/kg body weight/day may have harmful effects in extreme age groups (<10 or >65 years) [341]. The washing and rinsing process for certain plant species can help reduce cyanotoxin concentrations in leaves, but is less effective in stems. Nevertheless, it still lowers cyanotoxin levels to amounts that may not pose a risk to human health [2,61].

4. Human Exposure to Cyanotoxins

In freshwater bodies (lentic and lotic), cyanoHABs and their cyanotoxins are the main organisms that, in the last 20 years, have undergone an increase in their incidence and prevalence in various freshwater sources worldwide, becoming a public health problem [52] in many cases. Their negative effects in terms of human impacts mainly translate into interruptions in water supplies, closures of recreational areas, and poisoning [217,338,346,347].

The identification of cyanoHAB episodes is generally a straightforward process, as they can sometimes change the hue of the water source to a characteristic green color with the formation of dense scum masses, sometimes coupled with the production of an unpleasant odor [348]. However, to obtain an approximation of their real health impact, as a first step, it is necessary to identify the species responsible for the bloom, which in many cases may be mixed with toxic and non-toxic taxa, and simultaneously determine the densities of cyanobacteria in water bodies (cells/mL); however, the main problem and challenge lies in analyzing and quantifying the concentrations of cyanotoxins present in the water [304]. Consequently, multiple countries have adopted regulatory policies on the levels and densities of cyanobacteria in water, informing monitoring and alerts; in addition, some countries monitor the cyanotoxins in water according to reference values established by the WHO, while others monitor them according to their experiences, given that the risk is exposure to cyanotoxins (Table 3) [30,52,69,98].

Australia has set the maximum limit for recreational water use to a density of cyanobacteria of ≥40,000 cells/mL, and New Zealand has set the maximum limit for the consumption of drinking water to a cyanobacteria level of ≥1.0 μg/L of MCs [101].

The main routes of exposure to cyanotoxins tend to occur accidentally through the ingestion of water or contaminated food (water, saline, and vegetable vectors), the inhalation of contaminated particles (aerosols), or skin contact with contaminated water [3,52,349]. It is important to understand that exposure occurs because cyanotoxins are released into the water by different cyanoHAB degradation processes, among which photolysis, hydrolysis, and bacterial degradation stand out, and that according to the chemical properties of each group of cyanoHABs, they can persist actively for a long time following dilution [170,350].

The toxic symptoms related to cyanotoxins in humans are limited; evidence from proven cases allows us to establish that the initial symptoms associated with intoxication

tend to be common to other clinical conditions (gastroenteritis, nausea, vomiting, diarrhea, allergies, etc. (Table 1), which somewhat hinders the first steps of anamnesis in hospitals or emergency centers [50].

Animal studies have determined that the main target tissue is the liver, tissue in which the first stage of detoxification occurs. In the case of MC-LR, the first stage involves an oxidation reaction that produces MC-LR-GSH (~60% in liver) to then favor cysteine conjugation and produce MC-LR-Cys, a metabolite that can promote the elimination of cyanotoxins through urine [231,289,351,352].

Among the most important and relevant cases of cyanotoxin exposure recorded to date is one that occurred in Brazil in 1996 (Caruaru), in which 116 patients from a dialysis center developed a clinical picture with symptoms that included headache, eye pain, blurred vision, nausea, and vomiting. Of the intoxicated patients, the conditions of ~100 were aggravated by the development of severe liver problems related to indicators of liver cell injury, including elevated serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) concentrations. Seventy-six people died, and the presence of MCs and CYN in the water was identified as responsible for the problem. Subsequent analyses determined the presence of MCs in the serum of intoxicated patients at levels of up to 28.8 μg/L, while in asymptomatic patients, levels ranging from 0.2 to 0.96 μg MCs/L were detected. Thus, it could be established that the highest toxic effects and deaths that occurred in individuals were directly linked to intravenous exposure to MCs [101,127,276–278].

Subsequently, a similar event occurred in 2001 in Rio de Janeiro (Brazil) in which 44 patients from a dialysis center under similar procedures experienced identical clinical pictures [278].

Although what happened in Brazil is one of the best studied cases, in 1979, an outbreak in Australia led to the poisoning of 149 people, who experienced clinical symptoms that included fever, headache, vomiting, profuse bloody diarrhea, hepatomegaly, and renal damage. Subsequent epidemiological and ecological studies allowed the event to be associated with the presence of *Cylindrospermopsis raciborskii* in water bodies [338,353,354], and subsequently, it was possible to associate the poisoning with the presence of CYN in water [74,165]. CYN is characterized by inhibiting liver function as well as protein and glutathione synthesis, leading to cell death, and could explain this clinical picture.

To complement data on the concentration of toxins in water, Mchau [355] conducted a cross-sectional study using 432 people (~69% farmers) to determine the levels of exposure and risk of ingesting cyanotoxins through water consumption (Ukerewe in Mwanza, Tanzania). As a result, it was determined, through the UPLC-MS/MS technique, that the water samples collected showed toxicities ranging from 5.0 to 58.4 μg/L, while in the serum samples of the people, CYN-, NOD-, and MC-related analogs were identified. The concentration of CYN detected ranged from 0.02 to 0.15 ng/mL; concentrations of MC-LR, MC-RR, and dmMC-LR were detected at levels of 0.2–0.11 ng/mL (MC-RR < 0.02 ng/mL and dmMC-LR < 0.05 ng/mL), while the concentration of NOD was <0.05 ng/mL. These toxicities were found to be consistent with the regular symptoms presented by individuals (~50%), among which stomach upset, eye irritation, diarrhea (32%), vomiting (9%), and throat irritation (10%) were prominent [355]. However, to date, no incidents specifically attributed to NODs have been reported.

Among the groups most exposed to cyanoHABs and their toxins are children and adolescents, whose characteristics include smaller size (mass) and a greater tendency to ingest water and stay longer in the water during recreational activities (~2 h periods) [220]. In July 2002, a case was reported of several adolescents who, after playing in a pond with cyanobacteria (Wisconsin, USA), began to develop mild and severe clinical pictures,

with common symptoms of nausea and diarrhea. The most severe symptoms occurred in the group that reported drinking the water; of those affected, one died after 48 h due to heart failure. Toxicological analyses of their feces and stomach contents were positive for the toxin anatoxin-a and the cyanobacterium *Anabaena flos-aquae*; despite this, chemical analyses were inconclusive in linking the death to cyanotoxins [356].

Another particular case was reported in 2007 in Argentina (Salto Grande), in which an adolescent, while riding a jet ski, fell into an area containing a bloom of *Microcystis* spp. Their exposure to the bloom lasted approximately 2 h before they were rescued. Four hours after exposure, the patient presented a clinical picture with characteristic symptoms of nausea, abdominal pain, and fever (duration between 48 and 72 h), which became more complex over the course of 3 days, with the presence of dyspnea and respiratory distress, at which point the patient was hospitalized with a diagnosis of atypical pneumonia. At this stage, renal failure, decreased platelets, increased leukocytes, and the development of hepatotoxicosis were also identified, with an evident alteration in markers related to liver damage (ALT, AST and γGT). Ecological evaluations and analyses related to the event identified the species *Microcystis aeruginosa* (~3080–4100 cells/mL) in the water body at concentrations ~48.6 μg/L contributed to by the MC-LR analog. Full recovery of the adolescent occurred 20 days after the incident [357].

Perhaps the most dramatic case associated with poisoning occurred in 2015 in Montevideo, Uruguay. A few hours after recreational activities on a beach in the area, a family began to present gastrointestinal symptoms, which for one of them (a 20-year-old) began to be more limiting (diarrhea, vomiting, fatigue, and jaundice). These symptoms aggravated the patient's situation, which, according to a laboratory analysis, evidenced a picture of anemia, coagulopathy, and increased serum levels of ammonium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. After five days, the patient began to present acute liver failure, which triggered autoimmune hepatitis type II (AH-II). Their clinical picture finally led to liver transplantation surgery. In parallel, water samples from the area determined MC levels between 2900 and 8200 μg/L. An analysis of the MCs in the liver extracted from the patient identified the presence of MC-LR and [D-Leu1]MC-LR at concentrations of 2.4 and 75.4 ng/g tissue. These results, when linked to ecological data from the area, estimated that the person may have ingested ~1.78 L of the water [358].

Another relevant pathway for cyanotoxin ingestion is through food webs, which increases the risk of human exposure through the consumption of vectors (bivalves or fish) from water bodies with high prevalence of cyanoHABs or cyanoHABs and/or cyanotoxin receptors. Thus, exposure from fish consumption is critical, as fish have been shown to accumulate toxins in their livers and may eventually accumulate them in their muscles; bivalves can also accumulate cyanotoxins for periods longer than 6 months, with cyanotoxins possessing the ability to be biotransformed into more toxic analogs, which could result in lower clearance rates for certain analogs [304]. One study identified MCs in the serum of fishermen, probably related to the ingestion of MCs through water and the consumption of contaminated fish. Alterations in blood biochemical parameters (ALT, AST, LDH, and ALP) related to hepatocellular damage correlated with likely MC infection through water consumption at levels of ~1.31 μg MC-LR per day (2 L per day), and that through fish consumption (intake of ~100–300 g per day) could correspond to ~0.86–2.57 μg MC-LR, exceeding the total TDI of 2.4 μg for an adult of ~60 kg [232,289].

Another route of exposure occurs through the inhalation of cyanotoxins produced by the aerosol produced in waves. However, studies conducted involving the collection and analysis of aerosols over 4, 12, and 24 h have shown that their concentrations do not constitute a direct danger to people, with risks limited only to extreme age groups or to people with prevalent respiratory diseases (asthma) [2].

Empirical data related to cyanotoxin intoxications are very limited, and only those of greater consequence have adequate data traceability. Bloch et al. [359] conducted an epidemiological study on cases related to cyanoHABs exposure in the U.S.A. The data showed that of the total cases reported of environmental exposure in watercourses, only ~20% were related to cyanoHABs. Most of the cases were characterized by acute symptoms, among which the most frequently reported clinical symptoms were diarrhea, vomiting, nausea, skin rash, and abdominal pain, and in some cases, symptoms such as fever, throat irritation, and cough were reported. In those cases, linked to water ingestion, the most common symptoms were diarrhea, vomiting, abdominal pain, and nausea. Of the total number of cases analyzed, only 2% presented severe symptoms, with no evidence of death [359]. However, other studies have reflected significant cases linking incidents of cyanoHABs to acute and chronic gastrointestinal diseases through exposure [360]. It should be noted that MCs do not enter the human body through dermal exposure due to the size of the molecules and their chemical nature, in addition to the fact that their clinical effects are associated with the ingestion or aspiration of water or food containing cyanobacterial cells and/or cyanotoxins, which are then distributed to target tissues through active transport mechanisms. This possibility can be extrapolated to NODs, considering that they share a similar chemical structure to MCs, which allows them to have the same level of toxic action, although it is important to point out that there are not enough epidemiological data linked to human cases [304,361].

From a chronic point of view, epidemiological studies (~80 years) have established a direct relationship between the high prevalence of primary liver cancer and the ingestion of water contaminated with MCs in China and Croatia [92,362].

According to the data presented, the most common routes of exposure may be through dermal exposure; inhalation in recreational (sports), professional (fishing), or domestic (showers) activities; ingestion through vectors; or the absorption of cells and toxins ingested with water, generally unintentionally and parenterally (accidental) [53]. The level of severity of intoxications will largely depend on the route of intoxication, toxicity levels, and duration of exposure, which is complemented by physiological capacities that link the absorption, detoxification, and excretion capacity of cyanotoxins [61].

5. Risks of cyanoHABs

At present, toxic cyanobacteria are recognized as the group of organisms primarily responsible for cyanoHAB-related events. They are becoming increasingly complex and persistent, producing longer bloom periods, with the consequent transfer of multiple types of cyanotoxins to the food web, leading to a wide range of public health effects [363].

Cyanotoxins correspond to a set of secondary metabolites produced by different genera and species of cyanobacteria, which, through interaction and assimilation with the trophic network, can contaminate different species. Cyanotoxin exposure via these routes has been linked to various hepatotoxic, cytotoxic, and neurotoxic effects in humans, resulting in acute and chronic poisoning [304,332]. The increased incidence in areas of Central and South America has established important challenges in the areas of taxon classification, laboratory cultures, and the determination of strain toxicity, whereby cyanoHAB events and the cyanotoxins involved represent a potential risk to human and animal health, given their wide range of toxicities arising from the different toxin groups, in which the risks of chronic exposure to human health are unknown in some groups (STXs) [50,232,245,364].

To determine the environmental and public health risks, it is necessary to evaluate the concentrations of cyanotoxins observed in the environment and the toxicity levels established in different experimental studies. This allows the risks associated with the different taxa of cyanoHABs to be assessed, including the evaluation of the variability of

naturally synthesized analogs and those linked to biotransformation processes in vectors coming from different aquatic ecosystems and trophic levels. This makes it possible to assess the risk of simultaneous cyanoHAB events involving the possibility of exposure to a mix of analogs which could lead to the potentiation of effects by exceeding toxicity thresholds, making them a risk to public health [16,50,52,204,365].

To understand and avoid these circumstances, international organizations have created and proposed norms that establish limits for exposure to cyanoHABs and cyanotoxins [53,103], which are referential and which, despite the exposure and seafood poisoning in Central and South America, are not yet considered within sanitary regulatory norms.

From this perspective, some countries use guideline reference values for cyanobacterial biomass (low risk < 20,000; moderate 20,000–100,000; high 100,000–10,000,000; very high > 10,000,000 cells/mL); pigment concentrations (low risk < 10; moderate 10–50; high 50–5000; very high > 5000 chlorophyll-α); and cyanotoxin concentrations (low risk < 10; moderate 10–20; high 20–2000; very high > 2000 μg/L MC-LR) [30,53]. Densities of 11,500 cells m/L of *Microcystis aeruginosa* can produce MC-LR toxicity of 2.3 μg/L [201].

In order to fill the gaps and be able to respond adequately to benchmark indicators, national health agencies must establish and have the necessary tools to allow for adequate risk management; among them, the following stand out: the technical and professional capacity for the taxonomic identification of cyanobacteria (toxic and non-toxic); the analytical capacity to identify cyanotoxin groups in freshwater bodies and estuaries (MCs, ATXs, CYNs, STXs, and NODs); the capacity to develop detection and quantification methods in different biological matrices to determine the level of bioaccumulation and/or biomagnification in different species; the acquisition of analytical standards for the identification of groups of cyanotoxins; the constant training of work teams and dissemination of technical data to decision makers (authorities, mayors, governments, medical services, etc.) [61].

From the point of view of effects, toxicity assessment involves an analysis of the amounts or doses of a chemical substance ingested by a person or an animal that causes adverse health effects [304]. Thus, the acute reference dose (ARfD) is defined as an estimate of the amount of a substance present in food or drinking water that can be ingested in a period of 24 h or less, without an appreciable risk to human health (expressed as a function of body weight), and which derives from the no-observable-adverse-effect level (NOAEL) [142,317]. Meanwhile, the total daily intake (TDI) allows the risk to be assessed through the average food intake over a lifetime [317].

Thus, the WHO has established a TDI for MC-LR < 0.04 μg per kg body weight, considering the reference limit in drinking water of MC-LR < 1 μg/L (NOAEL MC-LR 40 μg/kg/day). Based on this, it has been proposed that if a person in recreational swimming activities ingests ~100 mL of water, the exposure limit corresponds to 24 μg of MC-LR per liter of bathing water (Table 2) [52,87,95].

Additionally, a TDI for MCs in seafood of 24 μg/kg wet weight has been established based on a 60 kg person consuming ~100 g of seafood per day. For fish consumption, the established limits are based on the consumption and mass of children and an adults, with the reference values being 4.0 μg/kg and 8.0 μg/kg, respectively [87,232,302,303].

In relation to the STX-group, the EU has established a limit for this group of toxins in bivalve mollusks corresponding to 800 μg STX-2HCl equiv/kg of meat. This limit is intended to protect consumers from acute risks; in fact, 144–304 μg of STX/person has been found to produce acute intoxication in humans. Toxicities > 450 μg of STX/person can produce severe intoxications, and >1000 μg of STX/person leads to death [157]. These data cannot be used to assess chronic risks from repeated exposure to STX, as no information is available [157].

However, several studies consider that the toxicities of some groups of cyanotoxins may underestimate the risk, since calculations have been made on the basis of some toxic analogs, and it has been found that the ratio of free and covalently bound toxins to tissues may vary over time (MCs) so that the toxic capacity of the analogs during the digestion process is increased [70,366,367]. Likewise, the risk of human intoxication may increase, especially when people consume freshwater or saltwater vectors (estuaries) contaminated with cyanotoxins. A relevant point is that cooking processes do not destroy or denature cyanotoxins, but can promote the conversion of analogs, increasing the toxin profile, and some post-cooking toxic groups may increase in toxicity by being free from tissues (MCs) [12,368]. Hence, it is important to implement frequent monitoring of cyanobacteria and cyanotoxins in water reservoirs [119].

Currently, many countries have not implemented standards or the WHO guidelines, and warnings about cyanoHABs are only carried out when a bloom is evident and has a visual impact or impacts tourism, but without reporting on toxicities and toxin profiles involving water bodies [361].

Eutrophication and high climatic variability are related to cyanoHABs, promoting their frequency and sometimes determining profiles from increasingly toxic taxa in freshwater bodies and sometimes producing subacute/subchronic exposure through recreational activities [61]. Additionally, high water flow (lotic zones) allows the expansion of cyanoHABs and cyanotoxins towards estuarine and marine areas, which favors the dispersion and consequent accumulation of cyanotoxins in marine resources, which can have serious effects on public health due to intoxication through vector consumption [52,369,370].

Thus, for an adequate evaluation of water bodies intended for recreational activities (fishing and bathing), it is necessary to carry out regular monitoring, which will generate relevant information on the dynamics of the cyanobacterial community and its toxicity (including types of toxins and the relationships between analytes), which is complemented by relating them to the trophic status of the water bodies (Universal, Carlson and TRIX). Critical variables such as a chlorophyll concentration > 1.0 μg/L and the identification of potentially toxic cyanobacteria at densities > 20,000 cells/mL can be considered the first step in establishing a monitoring level in affected areas. Densities of 20,000 cells/mL, of *Microcystis aeruginosa* can yield 2–4 μg/L or up to 10 μg/L in the case of particularly toxic taxa [61,365]. In terms of risk, in this instance, monitoring should be complemented with molecular techniques that allow the toxic potential of cyanobacteria to be defined (duration of 4 h) along with an ELISA test for the determination of toxicities (duration of 2 h), since at this point, the consideration only of cell counts can cause an overestimation when the proportion of toxic versus non-toxic individuals is low; likewise, toxicity can be underestimated if the bloom is in the senescence phase, the period in which toxicity is higher in water. From this point, communication with local health authorities, tourism authorities, and decision makers is necessary for future actions to be taken.

Persistence of the bloom (1–2 weeks) can produce densities between 20,000 and 100,000 cells/mL (90 μg/L of Chlorophyll-a), which has been associated with ocular mimicry in bathers, and the maximum limit in the case of *Microcystis* spp. can generate 20 μg/L of toxin [363]. Therefore, it is essential to complement the data with LC-MS/MS analysis to determine the profile and concentrations of cyanotoxins in cells and water, which, according to the established levels, could warrant a level 1 alert. Worsening of these data (cyanobacterial density, chlorophyll concentration, toxicities in water) warrants a level 2 alert, which is established by complementing the analyses in vectors obtained through sports activities and in marine species of habitual consumption or commercial interest (Figure 4). For these two alert levels, relevant decisions are required, such as the precautionary closure of recreational areas, the prohibition of bathing (people and pets) and

of vector extraction (fish and bivalves), and the prohibition of water use for consumption or use for irrigation in agricultural production and, eventually, the consumption of seafood products [12]. Lotic synthems can transfer cyanoHABs and cyanotoxins to marine areas, where species characteristic of the ecosystem can leach and accumulate cyanotoxins (MCs, NODs, and STXs) in their tissues [49].

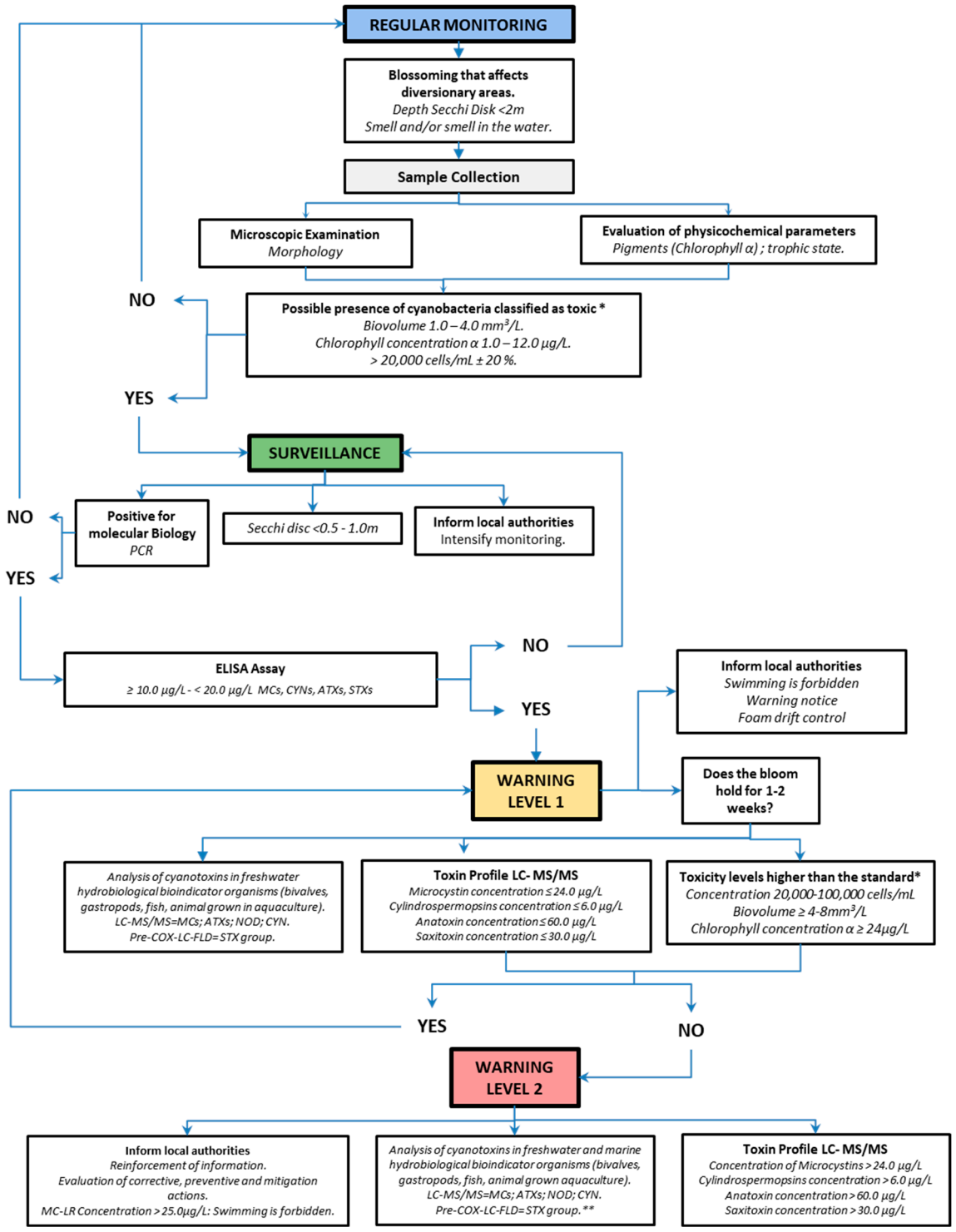

Figure 4. Framework for monitoring and managing cyanobacteria and cyanotoxins in recreational water bodies. * WHO, 2021. ** European Union, 2017.

Thus, in order to establish a logical framework, it is essential to identify biomarkers of exposure in order to conduct appropriate biomonitoring studies, which will allow for constant re-evaluation of the risks and hazards [69].

6. Discussion

Aquatic ecosystems are made up of photosynthetic organisms such as macrophytes, microalgae, and benthic/planktonic cyanobacteria, which fix carbon, produce oxygen, and form the basis of food webs [371,372]. The interaction of multiple environmental factors contributes to and favors the growth of different microalgae in the sea, lakes, and rivers. These factors correspond to light intensity, water temperature, pH, carbon dioxide concentration, nutrient availability (nitrogen, phosphorus, iron, and molybdenum), the physical characteristics of the water (shape and depth), the stability of the water column, water flow (rivers), and the structure and function of aquatic ecosystems [143,373].

CyanoHABs correspond to natural events; however, in the last 60 years, as a consequence of human development and the increase in agricultural, urban, and industrial activities, there have been important changes in the environments of lakes and rivers (eutrophication) leading to a higher incidence and prevalence of cyanoHABs worldwide [57,374], which has been attributed to the process of climate change [163,375,376]. It has therefore been proposed that a synergistic interaction between increased eutrophication and climate change has led to the development of new events associated with cyanoHABs in lentic and lotic zones [57,377]. The Intergovernmental Panel on Climate Change (2019) [378] has established that the incidence of harmful algal blooms, their toxicity, and the consequent risk to natural and human systems will continue to increase in direct relation to global warming, which will reach 1.5 °C over the next 20 years, in addition to the increase in CO_2 emissions in the 21st century [7,378].

Rigosi et al. [29], evaluating pollutants that contribute to the determination of the trophic state in water bodies, determined that high biomasses of cyanobacteria are characteristic of oligotrophic water bodies, with nutrient input being the major factor; in mesotrophic lakes, the temperature factor showed a more direct relationship with an increase in bloom. In eutrophic and hypereutrophic lakes, a significant interaction between nutrients and temperature was observed [29].

By evaluating isolated components, it can be established that microalgae show a strategy of adaptation to extreme temperature changes. *Microcystis aeruginosa* exhibits seasonal succession with temperature changes, producing blooms in summer (ideal temperature ~20 to 25 °C); in autumn, it sinks in the water, and in winter, it tends to inhabit the surface layer of the sediments without losing viability, progressively returning to the system through the water column in spring by regulating its gas vesicles, which allows it to float (benthic–planktonic phase) [28,379,380]. This process is also related to *mcyB* gene expression and MC content, since high temperatures (>20 °C) tend to increase MC production, while low (<4 °C) and very high (>35 °C) temperatures decrease it [46,381,382].

Nevertheless, cyanoHAB events occur in the face of a biotic–abiotic interaction, in which the stoichiometric relationship is difficult to establish and forecast. Thus, climatic variability in terms of rainfall (intense or intermittent rainfall) may lead to the interruption of blooms in summer periods, after which proliferation of the same species or other potentially toxic species in the ecosystem is possible. This raises the possibility that for certain communities, the frequency, duration, and intensity of cyanoHABs may increase in certain water bodies [6,52].

From an ecological and environmental perspective, the effects of current and probably continuous climate variability in the long term will lead us to a scenario of climate change that includes modifications in the patterns of precipitation and temperatures in

different regions of the world. Thus, climate change and human impact (nutrient inputs) may trigger future variations in the magnitude, frequency, and length of the period of cyanoHABs [383–386]. Therefore, cyanoHABs are a problem in aquatic ecosystems and, subsequently, through different exposure pathways, can alter public health [261,387–389].

This represents a major risk scenario from a marine point of view. Several studies have already established the real possibility that, through currents, cyanoHABs can be distributed from lotic ecosystems (MCs) to estuaries and/or from estuaries (NODs) to the sea. During this pathway, the physicochemical interactions of the aquatic environment favor cell lysis, which allows cyanotoxins to efficiently dispose of the medium, which can be filtered, accumulated, biotransformed, and removed from highly efficient organisms in the sea (mussels). This is a major challenge, since cyanotoxins are not included in permanent monitoring programs for their detection and quantification, leading to the possibility of intoxication in people, mostly in extreme age groups (children and the elderly), or generating subtoxic levels that lead to the chronic consumption of some groups of cyanotoxins, especially those classified as possibly carcinogenic [49,229].

In addition, the high chemical variability among the different groups of cyanotoxins brings an important challenge in the identification and quantification of the different analogs and especially of the new chemical variants that are detected and characterized every year from different geographical areas, which is also related to identifying and properly tabulating the cyanobacteria producing-groups of cyanotoxins and understanding their stages of toxin production in relation to nutrient inputs, temperature, and/or rainfall [318,390].

In recent years, the human population has experienced rapid growth, especially post-pandemic, in which there has been a migration of the urban population to rural areas, generating a drastic change in land use and demographically modifying areas that were historically used for agriculture. This has resulted in a considerable impact on lake areas, where water use has been altered, leading to the implementation of new irrigation systems, which have begun to generate significant inputs of anthropogenic organic waste, contributing to and favoring the incidence of cyanoHABs [228,391].

The different scenarios studied in the literature clearly demonstrate that cyanoHABs will intensify worldwide, creating a major challenge for water resources, tourism, health, and political administrations. The vast majority of countries do not consider the option of implementing the Guidelines for drinking-water quality and Guidelines for safe recreational water environments [53,392], which translates into a major problem in the generation of databases on the prevalence and incidence of cyanoHABs and, at the same time, represents a challenge for stakeholders in the face of events of great magnitude and impact involving the ingestion of cyanotoxins through drinking water or the consumption of contaminated shellfish and/or fish [229,393]. Therefore, it is important that in those countries where cyanoHAB events are increasing in incidence and prevalence, stakeholders establish international agreements in their respective countries and complementarily allocate and/or manage economic resources to increase the technical capabilities of experts for the proper identification of cyanoHAB-producing taxa through microscopic (Utermöhl technique) and molecular (RT-qPCR technique) techniques. Based on standardized procedures, records can be made to establish the place and time in which blooms occur, allowing relationships to be established between identified species and the densities, pigment types, biovolume, and trophic status of water bodies [385]. These involve bioconversion processes of cyanotoxins through various vectors (fish and shellfish) which, together with recreational activities as well as drinking water consumption, can cause significant public health problems. Therefore, the WHO has proposed limits for the different groups of cyanotoxins for both recreational activities and drinking water consumption (Table 2) [50,198].

The implementation of these technical proposals will help to direct preventive monitoring towards regular monitoring, which will allow the development of a database and, thus, through this information, the adequate evaluation of health problems, the mitigation proposals, and the comparison of harmonized data between countries. In this way, regional or global decision making is favored, which can be translated into optimized guidelines or international standards for each of the groups of cyanotoxins that are already known or those yet to be identified.

7. Conclusions and Future Challenges

CyanoHABs constitute an increasingly relevant threat to freshwater aquatic ecosystems, where environmental (abiotic–biotic) and anthropogenic interactions, such as global warming and the eutrophication of water bodies, provide the ideal scenario for an increase in their incidence and prevalence on a global level, through alterations in the community and diversity of microorganisms with a concomitant deficiency in water quality.

Direct (water) or indirect (vectors) contact with cyanoHABs/cyanotoxins causes adverse reactions, organ damage, and even death in humans. The cases produced and/or registered in relation to human health show the deficiency in high-quality and timely information for health professionals, generating a barrier to taking quick and adequate action when facing serious poisoning situations. Anatomopathological and epidemiological evaluations have helped us to understand this problem, reflecting the lack of information and training on the subject at this level.

Once sustainable monitoring programs are established, those with responsibility for maintaining waterbodies (e.g., for use as drinking water sources or for recreation) could use the historical results from these programs to develop guidelines for acceptable levels of cyanotoxins.

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