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Global scanning of cylindrospermopsin: Critical review and analysis of aquatic occurrence, bioaccumulation, toxicity and health hazards

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Abstract

Cylindrospermopsin (CYN), a cyanotoxin produced by harmful algal blooms, has been reported worldwide; however, there remains limited understanding of its potential risks to surface water quality. In the present study, we reviewed available literature regarding the global occurrence, bioaccumulation, and toxicity of CYN in aquatic systems with a particular focus on fresh water. We subsequently developed environmental exposure distributions (EEDs) for CYN in surface waters and performed probabilistic environmental hazard assessments (PEHAs) using guideline values (GVs). PEHAs were performed by geographic region, type of aquatic system, and matrix. CYN was prevalent in North America, Europe, and Asia/Pacific, with lakes being the most common system. Many global whole water EEDs exceeded guideline values (GV) previously developed for drinking water (e.g., 0.5 $\mu g\ L^{-1}$) and recreational water (e.g., 1 $\mu g\ L^{-1}$). GV exceedances were higher in the Asia/Pacific region, and in rivers and reservoirs. Rivers in Asia/Pacific region exceeded the lowest drinking water GV 73.2% of the time. However, the lack of standardized protocols used for analyses was alarming, which warrants improvement in future studies. In addition, bioaccumulation of CYN has been reported in mollusks, crustaceans, and fish, but such exposure information remains limited. Though several publications have reported aquatic toxicity of CYN, there is a lack of chronic aquatic toxicity data especially for higher trophic level organisms. Most aquatic toxicity studies have not employed standardized experimental designs,

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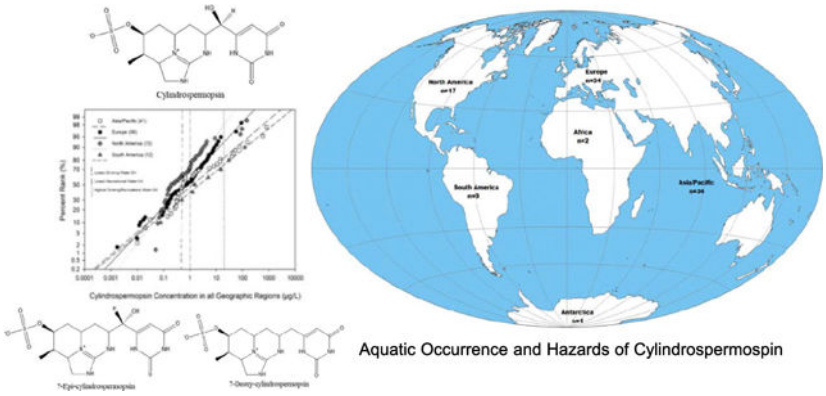
Conflicts of Interest

The authors declare no conflicts of interest.

failed to analytically verify treatment levels, and did not report purity of CYN used for experiments; therefore, existing data are insufficient to derive water quality guidelines. Considering such elevated exceedances of CYN in global surface waters and limited aquatic bioaccumulation and toxicity data, further aquatic monitoring, environmental fate and mechanistic toxicology studies are warranted to robustly assess and manage water quality risks to public health and the environment.

Graphical Abstract



Keywords

harmful algal blooms; cyanotoxins; cylindrospermopsin; probabilistic hazard assessment; water quality; public health

Introduction

Proliferation of harmful algae or harmful algal blooms (HABs) can severely impact water quality and present risks to public health (Brooks et al., 2016, 2017). Influenced by eutrophication, climate change, watershed modifications and other forcing factors (Brooks et al., 2016), HABs in inland waters appear to be increasing in magnitude, frequency and duration (Paerl et al. 2011, 2019). Concerns about inland HABs are commonly related to the cyanobacteria, which potentially produce undesirable secondary metabolites, including cyanotoxins. Exposure to cyanotoxins can lead to increased adverse health outcomes, and directly affect biodiversity and ecosystem services (Abeysiriwardena et al., 2018; Manganelli et al., 2012; Metcalf et al., 2018). Moreover, these environmental toxins can have significant socioeconomic consequences with impacts on fisheries and agriculture, degraded water quality for potable and recreational uses, and increasing odors effecting tourism (Carmichael et al., 2016; Blaha et al., 2009; Brooks et al., 2016; Gupta et al., 2013).

Naturally produced cyanotoxins include anatoxins, saxitoxins, L-beta-N-methylamino-L-alanine (BMAA), microcystins (MCs), saxitoxins, nodularins, cylindrospermopsins (CYNs), and others (Salmaso et al., 2017). Along with anatoxins and MCs, CYNs have emerged in the past few decades as a freshwater cyanobacterial toxin of increasing concern (Corbel et al., 2014). CYN is zwitterionic, relatively heat and pH stable, soluble in water, and

environmentally persistent (Chiswell et al., 1999). While this cyanotoxin was first recognized from a cyanobacterial strain of *Cylindrospermopsis raciborskii* (Ohtani et al., 1992), CYN is also known to be produced by at least *Anabaena sp., Aphanizomenon sp., Dolichospermum sp., Lyngbya sp., Raphidiopsis sp.* and *Umezakia sp.* (Preussel et al., 2006; Araoz et al., 2010; Schembri et al., 2001; Banker et al., 1997, Seifert et al., 2007; Harada et al., 1994; Li et al., 2001; Blahova et al., 2009; Pearson et al., 2010; Spoof et al., 2006; Niiyama et al. 2011; Messineo et al., 2010; McGregor et al. 2011; Kokocinski et al., 2013,2017).

Despite the widespread occurrence of CYN in surface waters of many countries including Australia (Al-Tebrineh et al., 2012; Everson et al., 2009; McGregor and Sendall 2015; Rasmussen et al., 2008), Germany (Fastner et al., 2007; Mantzouki et al., 2018; Rucker et al., 2007; Wiedner et al., 2008), the United States (Boyer et al., 2007; Howard et al., 2017; Loftin et al., 2016; Williams et al., 2006), and Brazil (Bittencourt-Oliveira et al., 2011, 2014; Lorenzi et al., 2018; Walter et al., 2018), it is challenging to effectively monitor and manage its incidence in the environment (Chiswell et al., 1999; Wormer et al., 2008; Norris et al., 2001; Duval et al., 2005). Cyanobacterial toxins including CYN are not typically routinely monitored in all parts of the world due to expensive availability of analytical equipment, training capacity, and the difficulty in culturing, harvesting, and preparing cells for analysis (Abeysiriwardena et al. 2018; Brooks et al., 2016, 2017; Lovin and Brooks 2019). In addition, it is difficult to manage HAB formation because proliferation of algal and cyanobacterial species and associated toxins can be influenced by diverse factors (Lurling et al., 2016; Al-Tebrineh et al., 2012), including nutrient availability (Grover et al. 2019; Wagner et al. 2019). Further, there are several standardized protocols that have been developed specifically for LC-MS/MS analysis of cyanotoxins, including CYN (Triantis et al., 2017a, b; Haddad et al., 2019), Because HAB monitoring efforts are inconsistent within and among countries (Brooks et al., 2016), it is useful to understand aquatic hazards and to identify where information is lacking in order to improve water quality assessment and management strategies.

Along with such worldwide prevalence of CYN in water bodies, its ability to potentially bioaccumulate in aquatic species can present ecological and public health risks. Aquatic bioaccumulation and biomagnification potential of various cyanotoxins including CYNs, anatoxins, and MCs have been reported; such observations are associated with ecological impacts (Al-Sammak et al., 2014; Ferrão-Filho and Kozlowsky-Suzuki 2011; White et al., 2005). For humans, the ingestion of CYN through contaminated drinking water or edible fish and shellfish can lead to several detrimental health effects (Abeysiriwardena et al., 2018; Adamski et al., 2014; Kalaitzis et al., 2010). CYN was originally characterized as hepatotoxic in the early 1990s (Ohtani et al., 1992), but not until recently has also been identified as potentially genotoxic, dermatotoxic, developmentally toxic, and carcinogenic (Armah et al., 2013), mostly based on findings from mammals. Several studies using human hepatic cells or rodent models have identified pathological and metabolic changes in the liver by CYN exposure (Falconer et al., 1999; Huguet et al., 2019; Terao et al., 1994; Seawright et al., 1999). In addition, CYN has been shown to cause oxidative stress, increase DNA strand breaks, and decrease natural cell apoptosis in mammalian hepatocytes or blood

lymphocytes (Hercog et al., 2017; Humpage et al., 2005; Straser et al., 2013; Zegura et al., 2011).

Here we critically reviewed published CYN data for aquatic occurrence, bioaccumulation, and toxicity in freshwater ecosystems. Along with CYN, we also reviewed the occurrence of two natural analogs, i.e., 7-epicylindrospermopsin (7-epiCYN) and 7-deoxycylindrospermopsin (7-deoxyCYN), which have also been identified and characterized in environmental samples (Fig. 1). A global scanning assessment for CYN and its relevant analogues was conducted using quantified data and information from previous peer-reviewed literature. Environmental exposure distributions (EEDs) were developed from ranked CYN concentrations and probabilistic hazard assessments were performed to identify the probability of exceeding GVs in surface waters (coastal systems, lakes, rivers, reservoirs) among various geographic regions. Additionally, bioaccumulation and aquatic toxicity data were examined to understand implications for water quality.

Methods

Literature Review for Environmental Occurrence, Bioaccumulation, and Aquatic Toxicity of CYN

Literature searches (Table S1 of Supplementary Materials for search details) were initially completed by June 2019 and then subsequently updated in October 2019, following previously reported methods by our group (James et al. 2011; Corrales et al., 2015; Kristofco et al. 2017; Saari et al, 2017; Kelly and Brooks 2018; Schafhauser et al. 2018; Mole and Brooks 2019; Lovin and Brooks 2019). We identified 97 refereed publications reporting worldwide CYN occurrence in surface waters, 7 publications studying its bioaccumulation in aquatic species, and 27 publications examining *in vivo* aquatic toxicity.

For environmental occurrences, we collated quantitative data on CYN based on study parameters including type of surface water system, geographic data (waterbody name, region, country), method of detection, year/season of collection, and the minimum detection limit of CYN (if stated). CYN can be produced and released extracellularly and/or released from intercellular production to water bodies through cell lysis, therefore, quantitative data on both intra- and extracellular CYN concentrations, or both from whole water samples, were identified along with data reporting levels by cyanobacterial cell mass. Surface water systems were categorized in four groups: coastal (including estuarine systems such as bays and lagoons), lacustrine (including lakes and ponds), rivers, and reservoirs (impounded lotic systems). Consistent with our previous approaches, only positive detection values were used in this assessment to examine hazards associated with occurrence of CYN (Corrales et al., 2015; Kristofco et al. 2017; Saari et al, 2017; Kelly and Brooks 2018; Schafhauser et al. 2018; Mole and Brooks 2019; Lovin and Brooks 2019).

Along with environmental occurrence data, aquatic bioaccumulation and toxicity was similarly collated. For aquatic toxicity studies, collected data were divided into two groups based on the type of endpoint: ecotoxicological data with common endpoints (e.g., survival, growth, reproduction, behavior), and toxicological data reporting sublethal responses (e.g., oxidative stress, hepatotoxicity, neurotoxicity). Because development of water quality

guidelines depends on information for aquatic species, experimental *in vivo* data for aquatic organisms were examined. For bioaccumulation studies, reported concentrations of CYN in aquatic organisms, including fish, invertebrates and amphibians, were also collected in a similar manner.

Environmental Exposure Distributions

In order to develop CYN EEDs, we utilized maximum environmental concentrations (MECs) and geometric means from specific systems reported in the peer-reviewed literature, again following previous approaches (Corrales et al., 2015; Kristofco et al. 2017; Saari et al, 2017; Kelly and Brooks 2018; Schafhauser et al. 2018; Mole and Brooks 2019; Lovin and Brooks 2019). MECs were chosen due to commonality in reviewed literature, whereas geometric means were used due to the nature of skewed data. Prior to construction of EEDs, geometric means of MECs were assigned Weibull rankings based on the following formula:

$$J = \left(i^{*}100\right)/(n+1)$$

where j is percent rank, i is the Weibull ranking assigned to each geometric mean of MECs and n is the number of detections. As previously mentioned in Posthuma et al., (2001), n+1 is included based on the assumption that there is one less than all occurrences measured. Linear regression analysis was performed using Microsoft Excel, and centile values were calculated from the following equation:

$$\text{Centile value} = \text{NORMDIST}\left(\left(b^{*}\log 10(x)\right) + a\right)$$

where a and b represent the slope and y-intercept, respectively. NORMDIST is used to provide a standard normal cumulative distribution function from a specific value. SigmaPlot 14 (Systat Software, San Jose, CA, USA) was used to graph the regressions.

Exceedances of Guideline Values (GVs)

To examine potential exceedances of common guideline values (GVs) for the developed EEDs, we initially summarized the GVs for CYN in drinking and recreational waters, which have been suggested worldwide (Table 1). Unlike other common cyanotoxins (e.g., microcystins), there are comparatively fewer GVs to support monitoring and management of CYN on a global scale. GV concentrations range from 0.5 μg L^{-1} to 20 μg^{-1} for drinking water and 1.0 μg L^{-1} to 20 μg L^{-1} for recreational water (Table 1). After identifying lowest and highest GVs, the lowest GV was chosen as a conservative estimate while the highest GV was also examined considering occurrence data was collected from various countries worldwide. For drinking water, we used 0.5 μg L^{-1} (Vermont, USA) and 20 μgL^{-1} (Ohio, USA), as the lowest and highest GVs, respectively (EPA, May 2019), for the probabilistic hazard assessments performed here. For recreational waters, 1 μg L^{-1} (California Caution Trigger Level, USA) for the lowest GV and 20 μg L^{-1} (Ohio, USA) for the highest GV were respectively used. It is important to note that all GVs used in the present study represent whole water concentrations consisting of both intra- and extra- cellular toxins. Toxin concentrations reported for samples of biomass only thus could not be compared with these

GVs. Further, hazard assessments were not performed for 7-epicylindrospermopsin and 7-deoxycylindrospermopsin, CYN analogues identified in environmental samples, due to lack of GVs for those particular analogues.

Results and Discussion

Environmental Occurrence by Geographic Region and Probabilistic Hazard Assessments for CYN

Environmental occurrence of CYN was first reported at Palm Island in Queensland, Australia by Ohtani et al., (1992). Since 2006, the number of studies reporting the detection of CYN in various freshwater sources have steadily increased (Figure 2). Using the occurrence data collected (Table S2 of Supplementary Materials), we developed whole water EEDs for CYN by geographic region (Figure 3). Most of the peer-reviewed publications detected CYN in surface waters in North America (n=17), Europe (n=34), and Asia/Pacific region (n=34), while limited information was available in South America (n=9), Africa (n=2), and Antarctica (n=1).

As shown in Fig. 4 and Table 2, we developed EEDs for CYN in four geographic regions including Asia/Pacific, Europe, North America, and South America by various aquatic system (e.g., coastal, lacustrine, reservoir, and river) and estimated exceedances of GVs. The only coastal data found was from Kleinteich et al., (2014) in Antarctica where several benthic CYN samples ranged from 0.00587– 0.157 μg g^{-1}. Compared to other geographic regions, exceedances of CYN GVs were elevated in Asia/Pacific. Specifically, CYN detections in the Asia/Pacific region exceeded the lowest drinking water GV by 62.4% (0.5 μg L^{-1}), 52.5% for the lowest recreational water GV (1 μg L^{-1}), and 15.2% of the time for the highest drinking and recreational water levels (20 μg L^{-1}) (Table 2). Water detections in Europe exceeded the lowest GVs by 49.19% and 38.6% of the time for drinking and recreational waters, respectively, and 7.27% for the highest drinking and recreational water levels (Table 2). North American detections exceeded these GVs by 45.5%, 32.1%, and 2.30%, respectively (Table 2); however, available information was limited to lacustrine systems.

When we examined occurrence data by aquatic system type, the 95th percentile value for CYN in lacustrine systems (15800 μg L^{-1}) was two times higher than rivers (812 μg L^{-1}), and nineteen times higher than reservoirs (82.2 μg L^{-1}). However, the median or 50^{th} centile value (Table 2) and the slope of EED (Fig. 4) curve were relatively similar among the three aquatic systems in the Asia/Pacific region. Percent exceedances for both the lowest drinking water GV and the lowest recreational water GV were also similar among the three aquatic system types, while the exceedances for highest drinking and recreational water GV in lacustrine (28.8%) and in river (30.5%) were higher than those from reservoir samples (13.6%). In Europe, detection of CYN was reported mostly from lacustrine (N=57) systems with a few data points from reservoirs (N=4). Based on the available European data, both the representative centile values and percentile exceedance of GVs were much higher in lacustrine systems than in reservoirs (Table 2). Unlike Asia/Pacific or Europe, there was less occurrence information for rivers and reservoirs of North and South America (Fig. 4 and Table 2).

Enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) were the two most commonly used detection methods for CYN, with 44% (n=81) of unique data points (including geometric means) used for analyses from ELISA assays, and 36% (n=65) from analyses specifically with LC-MS/MS (Table S3 and Figure F1 in Supplementary Materials). Percent exceedances were higher for lowest GVs for drinking water, lowest GVs for recreational waters and highest GVs for both drinking and recreational waters for systems analyzed by LC-MS/MS compared to ELISA at 61.5%, 52%, and 15.8%, respectively. In addition, ELISA assays were used for both qualifying and quantifying CYN in numerous studies. Although less expensive, this assay has been shown to be less accurate than other analytical methods (Al-Tebrineh et al., 2012; Fadel et al., 2014; Graham et al., 2010; Kokocinski et al., 2013; Loftin et al., 2016; Nguyen et al., 2017). Other methods, such as LC-MS/MS, require more preparation, equipment, and money to operate; however, offers multiple advantages (e.g., accuracy, precision) for quantitating CYN in environmental samples (Haddad et al. 2019). Additional analytical techniques have been used in the literature we critically examined here, including HRMS, LC-MS, UHPLC-MS/MS, HPLC-DAD and HPLC-PDA, which made up the other 20% of all unique data points (Table S4 of Supplementary Materials). Based on our review, several uncertainties exist in the various techniques and laboratory instruments used to determine CYN concentration throughout the various peer-reviewed literature, including those for extraction, purification, and quantification. Such uncertainties are associated with techniques, methodologies, accuracies, resources available, and in instrumentation used. Future environmental monitoring studies would benefit from employing isotope dilution LC/MSMS for environmental analysis to account for ion suppression and matrix effects (Haddad et al., 2019).

Global Occurrence and Exceedances of GVs by Matrix

Though the majority of peer-reviewed articles reported CYN concentrations in whole water samples (n=183), several studies also noted detection of intracellular (n=119) and extracellular (n=27) concentrations (Table S2). Detections of CYN in whole water by aquatic system type are presented in Figure 5. Table 3 shows centile values of EEDs for CYN in various matrices including whole water, intracellular, extracellular, benthic mats, and pelagic biomass by aquatic system with the estimated exceedance of proposed GVs.

CYN in whole water samples ranged from 0.00173 μg L^{-1} (Greer et al., 2016) to 815 μg L^{-1} (Li et al., 2001). The median and 95th percentile concentration was 0.898 μg L^{-1} and 24.8 μg L^{-1}, respectively. GVs of 0.5 μg L^{-1} (lowest drinking water), 1 μg L^{-1} (lowest recreational water) and 20 μg L^{-1} (highest drinking and recreational) were exceeded 52.6 %, 40.6 %, and 6.04 % of the time, respectively (Table 3). These representative centile values and percent exceedances of whole water samples for CYN were relatively similar to observations for extracellular CYN, but much higher than those reported for intracellular CYN. Along with the intracellular and extracellular matrices, detections of CYN in benthic mats or pelagic biomass were also reported (Table S2 of Supplementary Materials). CYN concentrations ranged from 0.00196 to 1580 μg g^{-1} in benthic mat biomass (Kleinteich et al., 2014; Van Colen et al., 2017) and 0.00072 to 917 μg g^{-1} in pelagic biomass (Mantzouki

et al., 2018; McGregor et al., 2011). Because there are no available GVs for biomass of CYN, we could not perform hazard assessments for these matrices.

For whole water samples of CYN, lacustrine systems, which make up ~87% of all occurrence data, exceeded the lowest drinking water GV 44.5% of the time, while a 35.8% exceedance was identified for the lowest recreational GV, and 9.03% for both highest GVs (Table 3). Though rivers and reservoirs have not been as heavily studied as lakes, these systems generally showed higher exceedances of GVs compared to lacustrine systems.

CYN Analog Detections

There was limited information of CYN analog detections in aquatic systems. Environmental concentrations of 7-deoxyCYN ranged from 0.05 to 1070 μg L^{-1} (Stitz et al., 2013; McGregor et al., 2011). Based on 7 available data points (R^2=0.97), 5th, 10th, 50th, and 95th centile values for 7-deoxyCYN in water samples were 0.0507, 0.197, 23.7, and 11100 μg L^{-1}, respectively. Although five publications reported deoxyCYN (Everson et al., 2009; Everson et al., 2001; Gaget et al., 2017; Li et al., 2001, 2001), an EED could not be developed due to limited data. Additionally, we did not identify any quantitative data on other CYN analogs such as 7-epiCYN, 7-deoxysulfide-CYN, and 7-deoxydesulfide-12-acetyl-CYN. 7-deoxysulfide-CYN and 7-deoxydesulfide-12-acetyl-CYN are synthetic analogs and thus are not known to naturally occur.

Bioaccumulation of CYN in surface waters

Although limited, CYN has previously been detected in mollusks, crustaceans, and fish (Table 4). Of the seven bioaccumulation studies, the maximum CYN detections ranged from 0.00007 to 4.3 μg g^{-1}, where the highest measurement of CYN from *C. raciborskii* was found in freeze dried hepatopancreas of the Redclaw crayfish, *Cherax quadricarinatus,* from an aquaculture pond in Australia (Saker and Eaglesham, 1999). Some of those studies have also suggested a bioaccumulation factor (BAF) of CYN ranging from 4 to 171, indicating the bioaccumulation potential of this toxin in aquatic species. In the bioaccumulation studies using fish, various tissues including liver, intestine, muscle, ovary, viscera, and eggs were examined (Greer et al., 2017; Messineo et al., 2010; Mohamed and Bakr 2018; Saker and Eaglesham, 1999). Berry et al., (2012) reported the detection of CYN in muscle tissues from *Bramocharax caballeroi, Cichlasoma uropthalmus, Heterandria jonesii, Oreochromis aureus, Rhamidia sp., Cichlasoma helleri, Vieja sp., V. finestrata,* and *D. mexicana* collected in a small tropical lake of Mexico. The bioaccumulation potential differed by the fish species despite the same collection site; for example, CYN was accumulated only 0.00009 μg g^{-1} in the muscle of *Oreochromis aureus* while it was found at 0.00126 μg g^{-1} for the same tissue of *Heterandria jonesii* (Berry et al., 2012). Therefore, due to limited information we could not identify potential differences in CYN bioaccumulation among aquatic trophic positions.

While toxicokinetic and toxicodynamic studies are scarce for CYN, a previous study using a mouse model suggested liver is the major target organ (Norris et al., 2001). Other animal cell studies have reported the active transport of CYN for intestinal absorption (Chong et al., 2002; Gutierrez-Praena et al., 2012; Pichardo et al., 2017) probably because of its relationship with human illness following the ingestion of conventionally treated drinking

water (De la Cruz et al., 2013). However, further information regarding the tissue distribution or metabolism of CYN for aquatic species is needed.

Similar to our review on environmental occurrence data (Table S2), more than 40% of detections were quantified by the ELISA method (Supplementary Materials Figure F1), identifying the need for future bioaccumulation studies of CYN and other cyanotoxins in biota, particularly given matrix effects recently reported by Haddad et al. (2019). Another important observation is that no bioaccumulation information was identified for CYN analogs. It is important to note that several accumulation studies were performed in laboratory experiments and not accumulation in the field. These studies were not included in Table 4 due to the focus of the current paper on environmental observations (Da Silva et al., 2018; Saker et al., 2004; White et al., 2006; White et al., 2007). These studies reported levels of CYN in mollusks (*Anodonta cygnea* and *Melanoides tuberculata),* a macrophyte (*Azolla filiculoides)*, several fish species (*Hoplias malabaricus, Mytilus galloprovincialis,* and *Melanotaenia eachamensis)*, and a terrestrial amphibian (*Bufo marinus*). Clearly aquatic bioaccumulation of CYN deserves future attention.

Aquatic toxicity of CYN

Acute or chronic effects of CYN have been reported in algae, protozoa, macrophytes, freshwater invertebrates, fish and amphibians (Table 5). In the refereed literature, however, a very limited number of studies have reported CYN ecotoxicity to higher trophic level aquatic organisms (Berry et al., 2009). Crude extracts or live culture of two cyanobacteria species, *A. ovalisporum* and *C. raciborskii,* and purified CYN have been used for experimentation, and different effect concentrations has been shown by these forms of CYN. For example, Jambrik et al., (2010) reported growth (frond number) no observed effect concentrations (NOEC) for *Wolffia arrhiza* of 100 μg L^{-1} for the crude *A. ovalisporum* extract, and 1000 μg L^{-1} for the purified *A. ovalisporum* extract. Most previous studies have focused on adverse effects of CYN on survival, growth, and behavior. Though many of these studies have investigated influences of CYN on growth, characterization of aquatic effects is inconsistent. In *Chlorella vulgaris*, Campos et al. (2013) reported significant growth inhibition following exposure to both crude extracts from *A. ovalisporum* and purified CYN, but increased growth rate was observed in a similar study by Pinheiro et al. (2013), which might be influenced by increased nutrients. Inhibited growth by CYN exposure was also found in macrophytes and amphibians (Jambrik et al., 2010; White et al., 2007). Decreased overall behavior in aquatic snail *Melanoides tuberculate* and toad *Bufo marinus* was also reported, but these results were not clear (Kinnear et al., 2007; White et al., 2007). Based on data here, the most sensitive ecotoxicity data was found in other cyanobacteria and algae. Purified CYN significantly lowered the cell number of *Microcystis aeruginosa* at 1 μg L^{-1} (Rzymski et al., 2014), implicating lower no observed effect concentration (NOEC) than this exposure concentration. Crude extracts from *A. ovalisporum* significantly increased growth rate of *Nannochloropsis sp.* at ≥ 25 μg L^{-1} where the growth NOEC was 5 μg L^{-1} (Pinheiro et al., 2013). Due to such limited information from a few species, we could not create species sensitivity distributions, which are necessary for developing water quality guidelines.

Though several papers have focused on mammalian toxicity due to its direct relevance to humans (Antal et al., 2011; Baker et al., 2001; Basu et al., 2018; Bazin et al., 2010; Chernoff et al., 2018; Fastner et al., 2003; Fonseca et al., 2014; Gacsi et al., 2009; Kittler et al., 2016), limited in vivo mechanistic toxicity work with aquatic species has been performed. Based on our literature review, eleven studies have reported mechanistic toxicity information for CYN exposure in aquatic organisms (Table 2 of Supplemental Materials). Most of these efforts have studied oxidative stress by assessing activity of antioxidant enzymes such as Glutathione-S-transferase (GST) and catalase (CAT) or by measuring the production of reactive oxygen species (ROS) (Balsano et al., 2017; Campos et al., 2013; Flores-Rojes et al., 2015; Lindsay et al., 2006; Santos et al., 2015). Whereas a few studies have investigated other molecular or histological changes such as neurotoxicity, genotoxicity, and hepatotoxicity, most of these studies did not report significant effects following CYN exposure (Guzman-Gillen et al., 2015; M-Hamvas et al., 2017; Kinnear et al., 2007). Considering the typical association of hepatotoxicity and protein inhibition with CYN, additional studies in aquatic organisms should be conducted focusing on endpoints linked to understanding mechanisms of action.

In addition to identifying the attributes of previous aquatic toxicity studies with CYN, we also examined the quality of this existing literature. Of the 27 examined publications, only five (~19%) analytically verified experimental treatment levels, and the majority of these studies (~62%) did not report and/or determine the purity of CYN employed. The most common methods for detection included HPLC, HPLC-MS/MS, and LC-MS/MS, and CYN purity, if stated, was ≥ 95%. Further, only a few of these publications (n=3) followed and explicitly stated known standardized experimental guidelines (e.g., EPA, OECD). We also found several *in vitro* studies using primary culture cells from fish species including *Prochilodus lineatus, Cyprinus carpio L.,* and *Hoplias malabaricus* (Liebel et al., 2011; Sieroslawska et al., 2015; Silva et al., 2017). Along with cytotoxicity, *in vitro* endpoints involved in oxidative stress, genotoxicity, and immunotoxicity were studied, similar to sublethal observations from *in vivo* studies.

It is clear, based on our review, that future research needs to be conducted to understand aquatic impacts and the mechanistic toxicology of CYN. Further, aquatic exposure and toxicity of CYN congeners is unknown. We identified large knowledge gaps regarding individual and population levels effects of CYN on diverse aquatic species. Such research priorities are particularly important given that increasing temperatures, a major factor in cyanobacterial growth, have led to an increase in HABs in temperate regions (Abeysiriwardena et al., 2018; Sinha et al., 2012). Furthermore, with increasing population growth and limited sewage treatment worldwide, there is a greater risk for contamination from watershed development (Catherine et al., 2013; Lurling and Roessink 2006). Such influences of climate change and increasing eutrophication are expected to further intensify HABs and water quality risks from cyanotoxins at the global scale (Aguilera et al., 2018), which highlights the importance of developing an advanced understanding to public health and the environment.

Conclusions

Here we examined global occurrence data for CYN and identified a lack of information from Africa and South America, two major geographic regions experiencing increased population growth and landscape development. This observation is particularly important because inland HABs have been identified as a priority research need to achieve more sustainable environmental quality in Latin America (Furley et al., 2018) and other regions (Fairbrother et al., 2019; Gaw et al., 2019). We further observed elevated exceedances of GVs in reservoirs (60.7% of the lowest drinking water GV) and rivers (58.9% of the lowest drinking GV), though lacustrine systems have received the majority of environmental monitoring attention. Due to limited quantity and quality of chemical analysis, aquatic bioaccumulation, and toxicological information, we could not perform a robust assessment of risks to aquatic life. Future research is needed to advance our understanding the aquatic toxicology of CYN, and centile information from the EEDs reported here should support such efforts to ensure environmentally relevant exposure scenarios are examined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CYN	Cylindrospermopsin
EC_{50}	Half maximal effective concentration
EED	Environmental Exposure Distribution
ELISA	Enzyme-Linked Immunosorbent Assay
GV	Guideline Value
HAB	Harmful Algal Bloom
HPLC	High Performance Liquid Chromatography
IC_{50}	Half maximal inhibitory concentration
LC_{50}	Half maximal lethal concentration
LC-MS	Liquid Chromatography-Mass Spectrometry
MECs	Maximum Environmental Concentrations
NOEC	No Observed Effect Concentration

UPLC- MS/MS	Ultra Performance Liquid Chromatography-tandem Mass Spectrometer

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Highlights

- We examined aquatic occurrence, bioaccumulation, and toxicity of cylindrospermopsin
- Exposure distributions were developed by aquatic systems and geographic regions
- Limited information from Africa and Latin America, and for reservoirs and rivers
- Surface water exceedances of guideline values were consistently observed
- Limited aquatic bioaccumulation and toxicity data, which requires future study

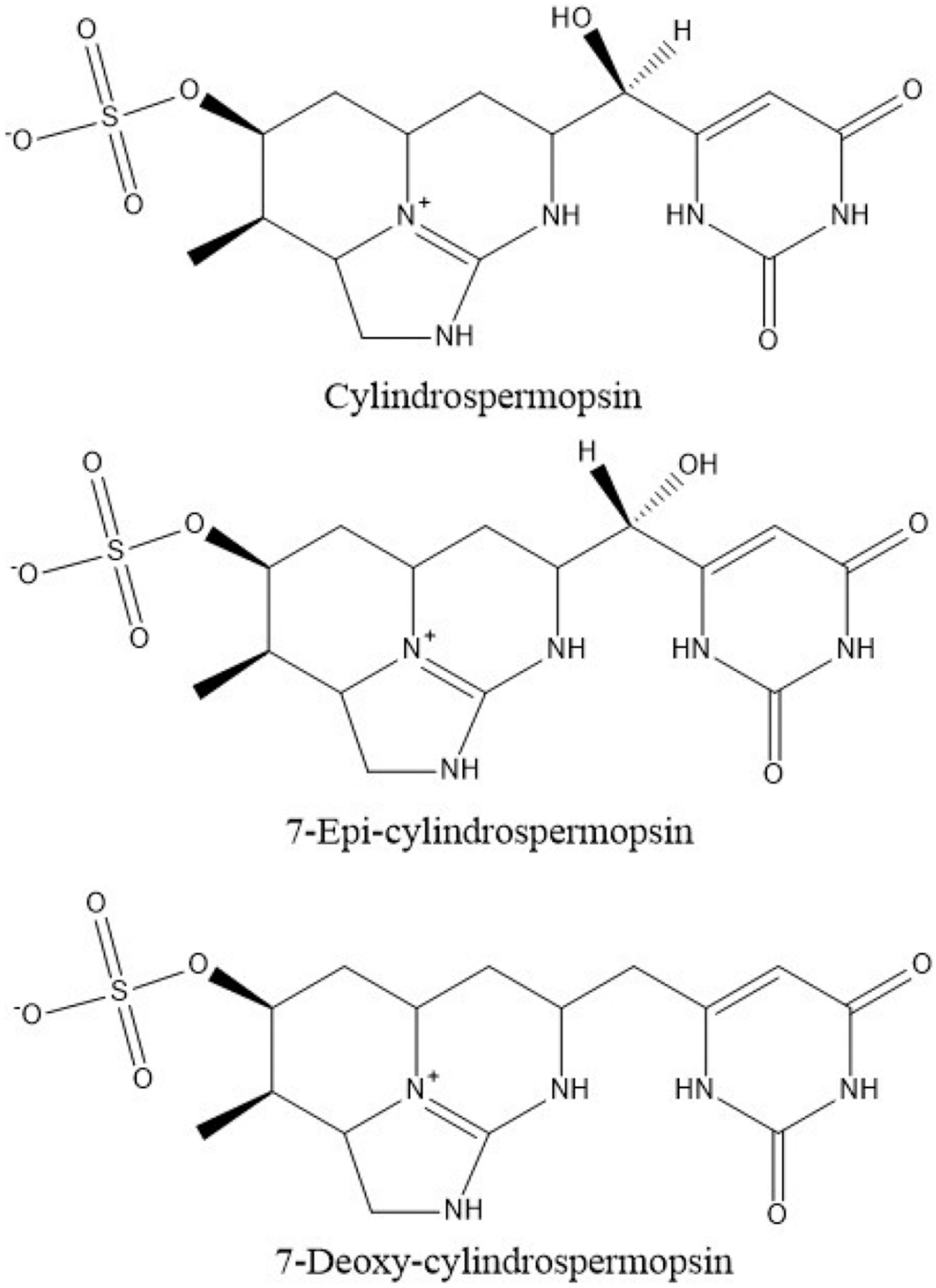

Figure 1.
Chemical structures of cylindrospermopsin and its analogues: Acylindrospermopsin; B= 7-epicylindrospermopsin; C= 7-deoxycylindrospermopsin.

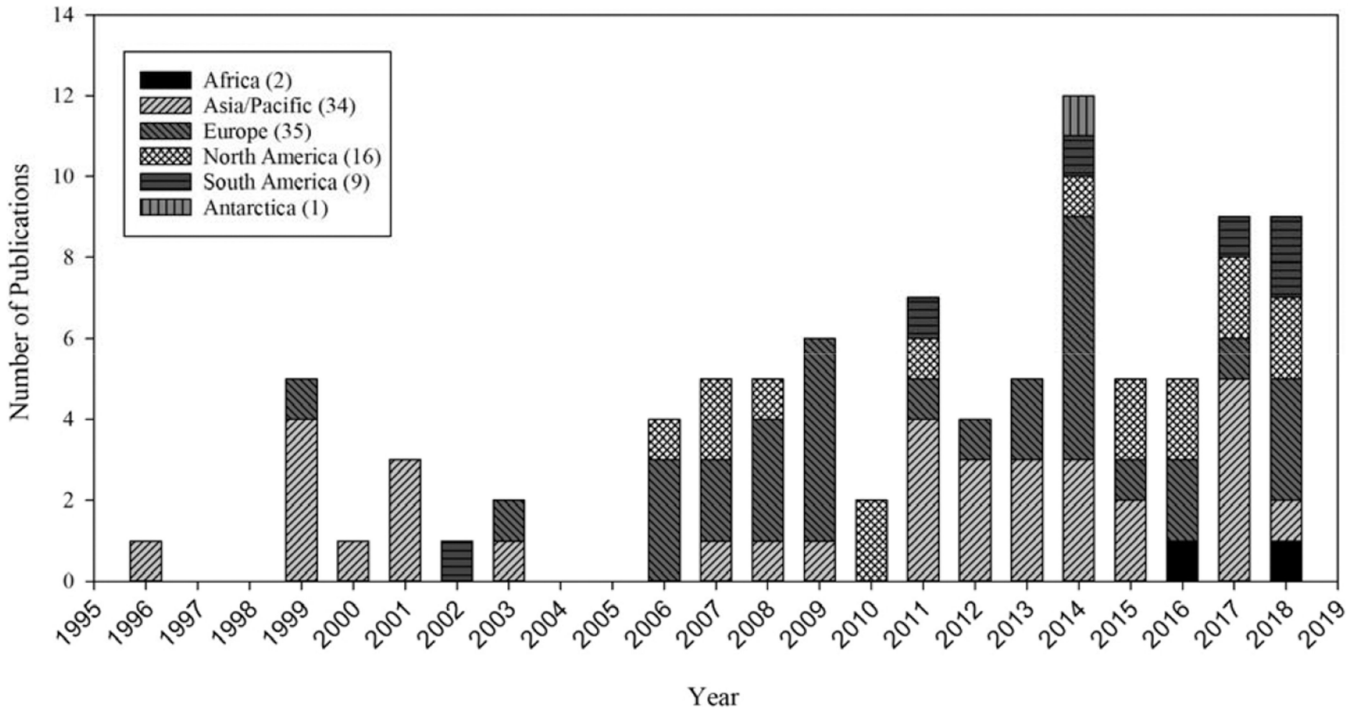

Figure 2.

The number of publications reporting positive and quantified detections of cylindrospermopsin in global surface waters from 1995–2019.

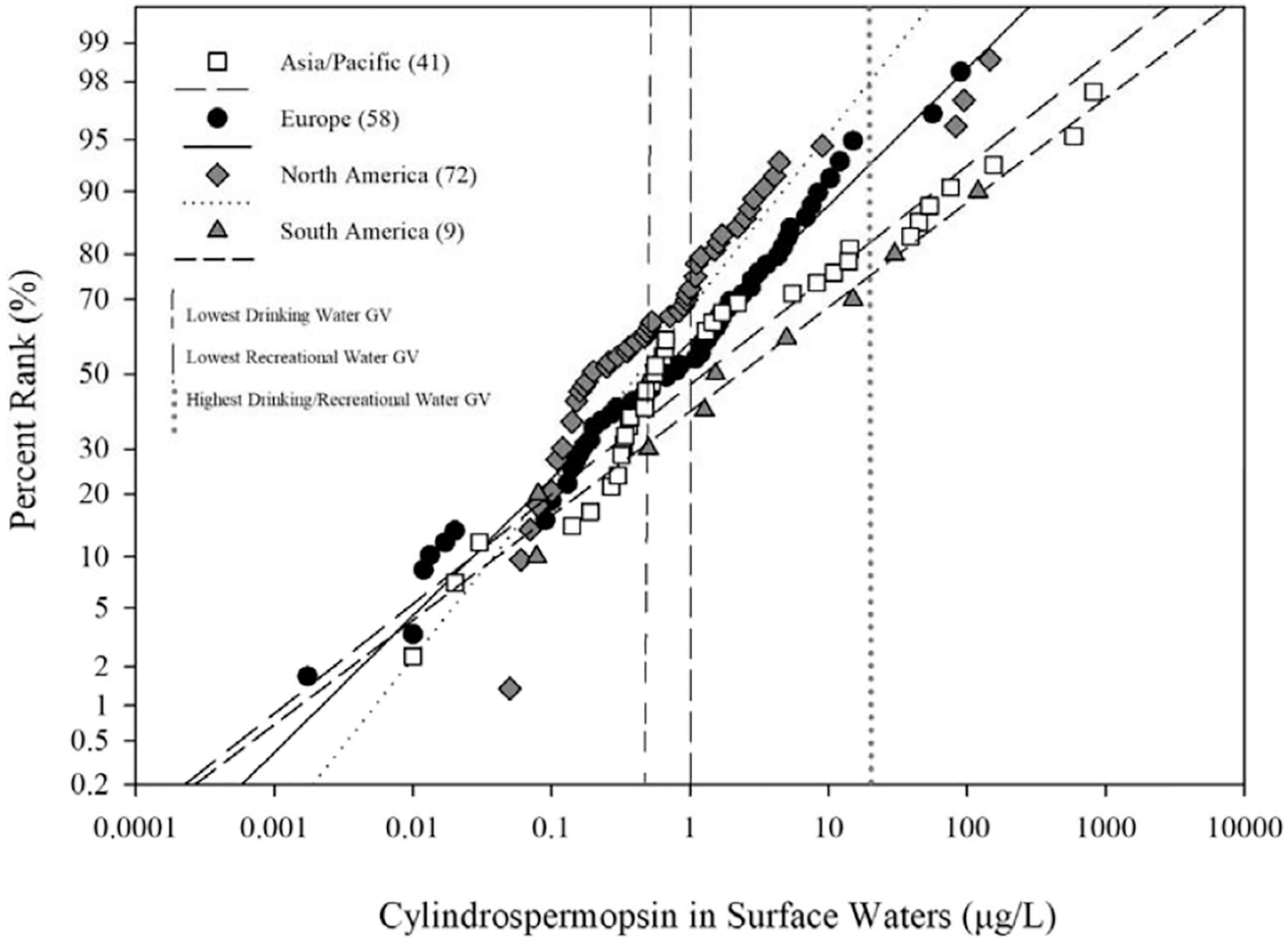

Figure 3.

Environmental exposure distribution of the geometric means of reported maximum environmental concentrations of cylindrospermopsin in whole water samples (including both intra and extracellular toxins) by geographic region. Numbers within parenthesis indicate the number of detections in each geographic region. Vertical dashed lines from left to right represent guideline values for lowest drinking water (0.5 µg/L), lowest recreational water (1 µg/L), and highest drinking and recreational water (20 µg/L), respectively.

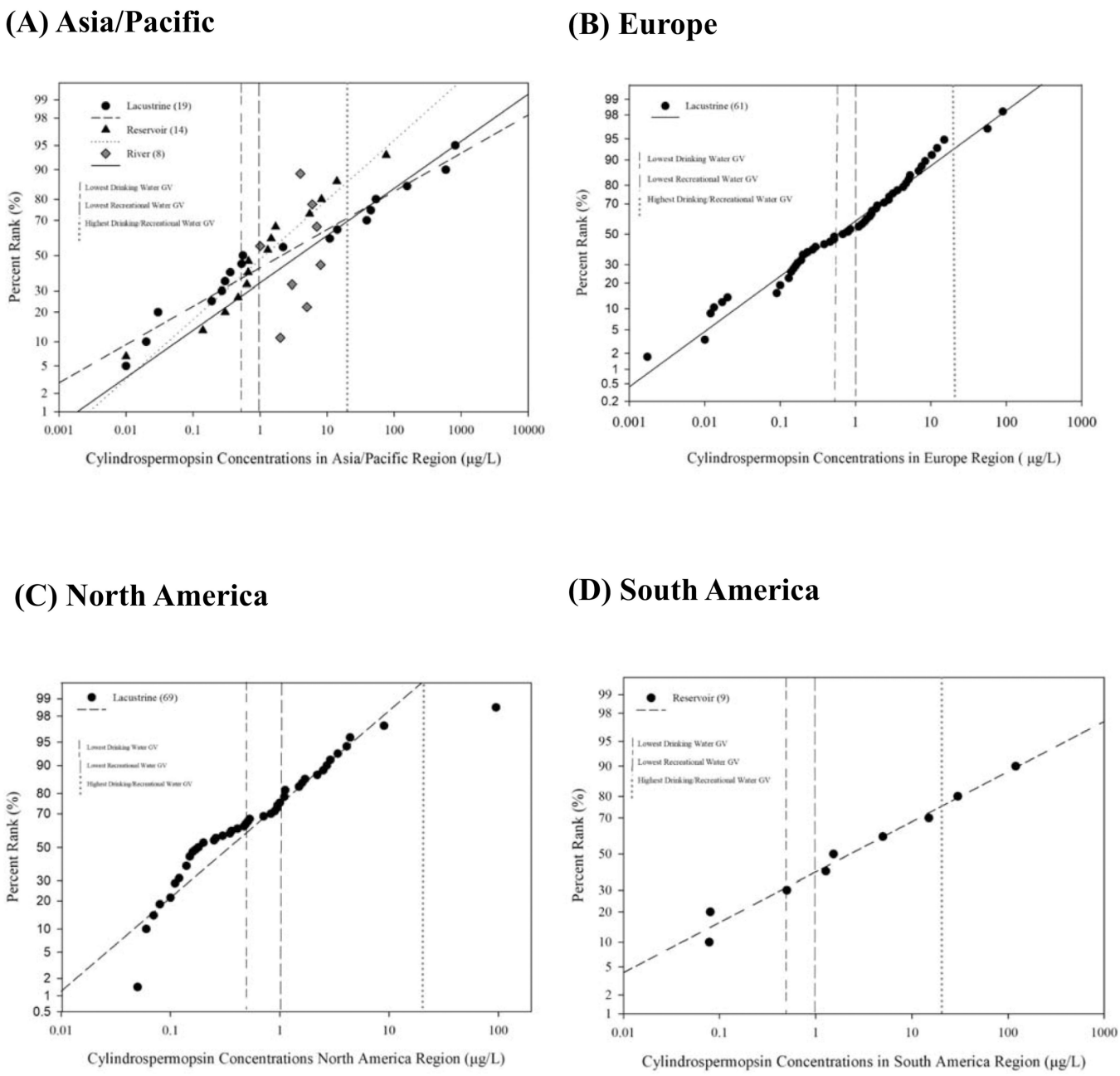

Figure 4.

Environmental exposure distribution of the geometric means of reported maximum environmental concentrations of cylindrospermopsin in whole water samples (including both intra and extracellular toxins) separated by aquatic system in (A) Asia/Pacific, (B) Europe, (C) North America, and (D) South America. Numbers within parenthesis indicate the number of detections in each geographic region. Vertical dashed lines from left to right represent guideline values for lowest drinking water (0.5 µg), lowest recreational water (1 µg/L), and highest drinking and recreational water (20 µg/L), respectively.

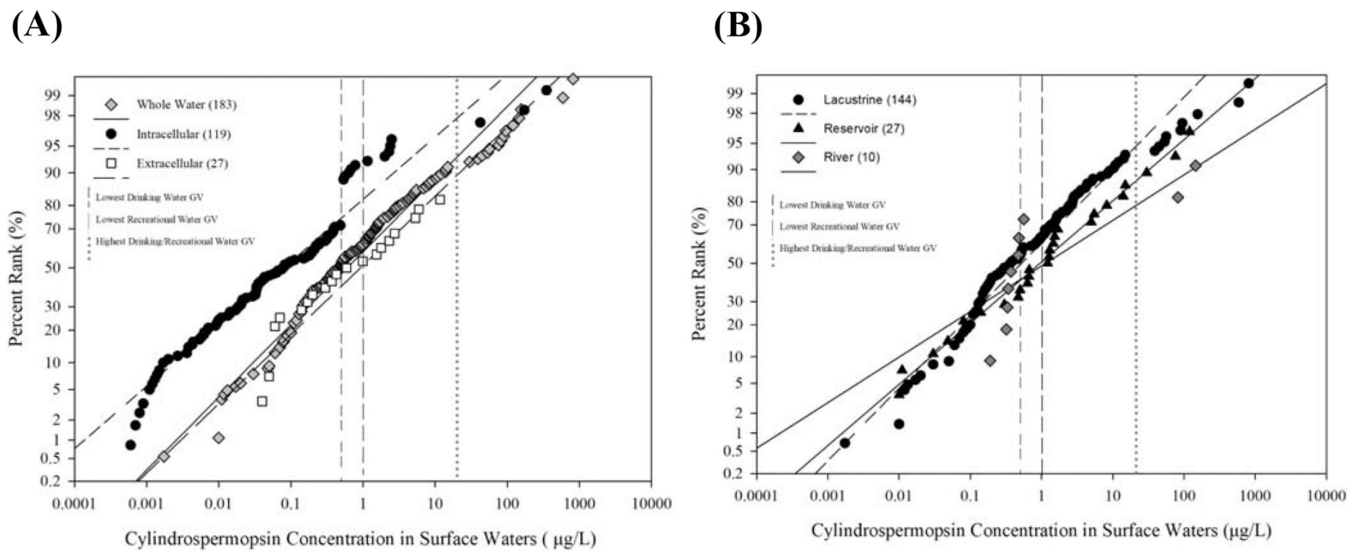

Figure 5.

Environmental exposure distribution of the geometric means of reported maximum environmental concentrations of cylindrospermopsin in whole water samples (including both intra and extracellular toxins) separated (A) by matrix and (B) by aquatic system. Numbers within parenthesis indicate the number of detections in each matrix or aquatic system. Vertical dashed lines from left to right represent guideline values for lowest drinking water (0.5 µg/L), lowest recreational water (1 µg/L), and highest drinking and recreational water (20 µg/L), respectively.

Table 1.

Global Guideline Values for cylindrospermopsin in drinking and recreational water uses.

Authority	Drinking Water (μg L^{-1})	Recreational Water (μg L^{-1})
International Criteria:		
Australia	1.0	-
Brazil	15	-
New Zealand	1.0	-
Unites States of America Criteria:		
California Warning Tier I, USA	-	4
California Danger Tier II, USA	-	17
Colorado, USA	-	7
Indiana Warning Level, USA	-	8
New Jersey, USA	-	8
Ohio State Department (< 6 years old, USA)	0.7[a]	-
Ohio State Department (Adults), USA	3[a]	5[b]
Ohio State Department, USA	20[b]	20[b]
Pennsylvania, USA	-	5
Vermont, USA	0.5	10
Washington, USA	-	4.5
Overall United States Guidance Values	3[c]	15[c]
United States Drinking Water Health Advisory (infants)	0.7	-
United States Drinking Water Health Advisory (children and adults)	3	-

[a] Do Not Drink.

[b] Do Not Use.

[c] Per 10 days.

Table 2.

Centile values of environmental exposure distributions for cylindrospermopsin and exceedance of GVs by geographic region. GV: guideline value.

Geographic Region	System	N	R^2	Centile Value (µg L^{-1})				Percent Exceedance of GVs (%)		
								Lowest Drinking Water	Lowest Recreational Water	Highest Drinking and Recreational Water
				5th	10th	Median (50th)	95th	(0.5 µg L^{-1})	(1 µg L^{-1})	(20 µg L^{-1})
Asia/Pacific	All	41	0.98	0.0130	0.0410	2.28	400.24	68.5	60.3	24.5
	Lacustrine	19	0.96	0.00276	0.0120	2.095	1587.66	63.9	57.3	28.8
	River	8	0.071	0.0174	0.0572	3.76	812.50	73.2	65.8	30.5
	Reservoir	14	0.94	0.0166	0.0424	1.17	82.2	62.8	52.4	13.6
Europe	All	61	0.98	0.0017	0.0217	0.499	27.89	49.9	38.8	6.57
	Lacustrine	57	0.98	0.0107	0.0259	0.576	30.8	52.3	41.00	7.13
	Reservoir	4	0.87	0.0004	0.0013	0.0663	9.97	25.4	18.7	3.05
North America[b]	Lacustrine	69	0.87	0.0261	0.0462	0.347	4.62	40.8	25.1	0.5
South America	Reservoir	9	0.98	0.0129	0.0406	2.28	400.23	68.5	60.3	24.5

[a]North America data for reservoirs and rivers were not sufficient enough to develop exposure distributions.

Table 3.

Centile values of environmental exposure distributions for cylindrospermopsin and exceedances of guideline values by aquatic matrix.

Matrix	Aquatic System	N	R^2 [a]	Centile Value (μg L^{-1} or μg g^{-1}) [b]				Percent Exceedance of GVs (%)		
								Lowest Drinking Water	Lowest Recreational Water	Highest Drinking and Recreational Water
				5th	10th	Median (50th)	95th	(0.5 μg L^{-1})	(1 μg L^{-1})	(20 μg L^{-1})
Whole Water	All	186	0.967	0.0132	0.0307	0.613	28.5	53.5	41.7	6.76
	Lake	144	0.96	0.012	0.0268	0.521	23.5	50.7	38.9	5.76
	River	10	0.627	0.00264	0.0101	1.15	497	58.9	51.5	21.9
	Reservoir	32	0.985	0.0140	0.0361	1.01	72.8	60.7	50.2	12.6
Intracellular	-	119	0.96	0.000886	0.00239	0.0799	7.21	25.1	17.8	2.18
Extracellular	-	27	0.94	0.0160	0.0391	0.923	53.3	59.8	48.7	10.6
Benthic Biomass	-	6	0.87	0.00000058	0.0000129	0.732	925501	-	-	-
Pelagic Biomass	-	29	0.96	0.000383	0.00314	5.25	71881	-	-	-

GV: guideline value.

[a] R^2 in a linear regression model constructing EED.

[b] Units for Whole water, Intracellular, and Extracellular are in μg L^{-1}, and μg g^{-1} in both Benthic and Pelagic Biomass samples.

Table 4.

Summary of aquatic bioaccumulation information for cylindrospermopsin in the field.

Taxonomic Group	Location	Date of collection	Species	Tissue Type	Sample Size	Detection Method	Maximum CYN concentration μg g^{-1} fresh weight)	BAF[a]	Reference
Invertebrate (crustaceans)	Lake Catemaco, Mexico	Oct. 2009	*Pomacea patula catemacensis*	Whole snail	-	HPLC and LC-MS	0.00335	157	Berry and Lind (2010)
	Veracruz, Mexico	Oct. 2009	*Copepods sp.*	Whole snail	n=1	ELISA	0.00104	49	Berry *et al.,* (2012)
			Pomacea patula catemacensis	Whole snail	n=2	ELISA	0.00158	74	
	Lake Eacham, Townsville, Australia	Aug. 1997	*Cherax quadricarinatus*	Hepat opancreas (pooled)	n=2	HPLC	0.54 (μg g^{-1} freeze dried weight)	-	Saker and Eaglesham (1999)
					n=2	HPLC	4.3 (μg g^{-1} freeze dried weight)	-	
				Muscle	n=2	HPLC	0.12 (μg g^{-1} freeze dried weight)	-	
					n=2	HPLC	0.9 (μg g^{-1} freeze dried weight)	-	
Invertebrate (mollusk)	Veracruz,Mexico	Oct. 2009	*Vaughtia fenestrata*	Muscle[b]	n=1	ELISA	0.00081	81	Berry *et al.,* (2012)
	Awoonga Dam, Australia	-	*Alathyria pertexta pertexta*	Whole body	-	Unknown	0.56	-	Anderson *et al.,* (2003)
Fish	Albano Lake, Central Italy	Sep. 2006	*Salmo trutta*	Viscera	n=2	ELISA	0.0027	-	Messineo *et al.,* (2009)
			Salmo trutta	Muscle	n=2	ELISA	0.0008	-	
			Salmo trutta	Ovary	n=1	ELISA	0.00007	-	
	Veracruz, Mexico	Oct. 2009	*Bramocharax caballeroi*	Muscle[b]	n=2	ELISA	0.00081	38	Berry *et al.,* (2012)
			Cichlasoma uropthalmus	Muscle[b]	n=1	ELISA	0.00026	12	
			Heterandria jonesii	Muscle[b]	n=1	ELISA	0.00126	59	
			Oreochromis aureus	Muscle[b]	n=2	ELISA	0.00009	4	
			Rhamidia sp.	Muscle[b]	n=2	ELISA	0.00024	11	
			Cichlasoma helleri	Muscle[b]	n=2	ELISA	0.00015	7	
			Vieja sp.	Muscle[b]	n=1	ELISA	0.00042	20	
			V. finestrata	Muscle[b]	n=1	ELISA	0.00081	38	
			D. mexicana	Muscle[b]	n=2	ELISA	0.0008	38	
	[c]Southeast Asia	-	*Oreochromis niloticus*	Liver	n=1	UPLC-MS/MS	0.1034	171	Greer *et al.,* (2017)

Taxonomic Group	Location	Date of collection	Species	Tissue Type	Sample Size	Detection Method	Maximum CYN concentration µg g^{-1} fresh weight)	BAF[a]	Reference
		-		Eggs	n=1	UPLC-MS/MS	0.0469	-	
	Lake Eacham, Townsville, Australia	Aug. 1997	*Melanotaenia eachamensis*	Viscera	n=5	HPLC	1.2 (µg g^{-1}freeze dried weight)	-	Saker and Eaglesham (1999)
	Sohaq province, Egypt	Oct. 2010-Sep. 2013	*Oreochromis niloticus*	Intestines	n=24	ELISA and HPLC	0.417	-	Mohamed and Bakr (2018)
				Liver	n=24	ELISA and HPLC	1.5	-	
				Muscle	n=24	ELISA and HPLC	0.280	-	

ELISA, Enzyme-linked immunoassay; HPLC, High Performance Liquid Chromatography; UPLC-MS/MS, Ultra Performance Liquid Chromatography- tandem Mass Spectrometer.

[a]Bioaccumulation Factor.

[b]Muscle below dorsal fin on left side of fish.

[c]Sampling location is not specified.

Table 5.

Aquatic toxicity information for cylindrospermopsin.

Taxonomic Group	Test Type	Test Organism	Form of CYN	Exp. Duration	Endpoint	Parameter	Effect Conc. (μg L^{-1})	Analytical verification	Purity	Temp(°C)	pH
Algae	Acute	*Chlamydomonas reinhardtii*	Crude extracts from *A. Ovalisporum*	4 days	Growth	IC_{50}	= 2,310	HPLC	N/A	25	-
				7 days	Growth	IC_{50}	= 2,220	HPLC	N/A	25	-
		Chlorella vulgaris	Crude extracts from *A. Ovalisporum*	4 days	Growth	IC_{50}	= 2,440	HPLC	N/A	25	-
				7 days	Growth	IC_{50}	= 2,280	HPLC	N/A	25	-
		Nannochloropsis sp.	Crude extracts from *A. Ovalisporum*	4 days	Growth	IC_{50}	= 2,330	HPLC	N/A	25	-
				7 days	Growth	IC_{50}	= 1,430	HPLC	N/A	25	-
	Chronic	*Chlamydomonas reinhardtii*	Crude extracts from *A. Ovalisporum*	4 days	Growth, stimulation	NOEC	= 50	HPLC	N/A	25	-
				7 days	Growth, stimulation	NOEC	= 50	HPLC	N/A	25	-
			Purified CYN	4 days	Growth, stimulation	NOEC	= 4,400	HPLC	100%	25	-
				7 days	Growth, stimulation	NOEC	= 8,500	HPLC	100%	25	-
		Chlorella vulgaris	Purified CYN	4 days	Growth, stimulation	NOEC	= 8,500	HPLC	N/A	25	-
				7 days	Growth, stimulation	NOEC	< 16,700	HPLC	100%	25	-
			Crude extracts from *A. Ovalisporum*	4 days	Growth, stimulation	NOEC	= 250	HPLC	N/A	25	-
				7 days	Growth, stimulation	NOEC	= 50	HPLC	N/A	25	-
			Purified CYN	3 days	Growth	NOEC	< 5	HPLC	98%	-	-
				7 days	Growth	NOEC	= 18.4	HPLC	98%	-	-
			Crude extracts from *A. Ovalisporum*	3 days	Growth	NOEC	= 32	HPLC	98%	-	-
				7 days	Growth	NOEC	< 32	HPLC	98%	-	-
		Microcystis aeruginosa	Purified CYN	3 days	Growth	NOEC	< 1	HPLC	>95%	21	-
		Nannochloropsis sp.	Crude extracts from *A. Ovalisporum*	4 days	Growth	NOEC	= 5	HPLC	N/A	25	-
				7 days	Growth	NOEC	= 5	HPLC	N/A	25	-
			Purified CYN	4 days	Growth	NOEC	= 4,400	HPLC	100%	25	-
				7 days	Growth	NOEC	> 16,700	HPLC	100%	25	-

Taxonomic Group	Test Type	Test Organism	Form of CYN	Exp. Duration	Endpoint	Parameter	Effect Conc. (μg L^{-1})	Analytical verification	Purity	Temp(°C)	pH
		Parachlorella kessleri	Crude extracts from *A. Ovalisporum*	14 days	Growth	NOEC	> 150	HPLC	N/A	-	-
Microorganism	Chronic	*Tetrahymena thermophila*	Purified CYN	24 hr.	Growth	IC_{50}	= 480	No	N/A	30	-
Macrophyte	Chronic	*Azolla filiculoides*	Crude extracts from *A. Ovalisporum*	7 days	Growth	NOEC	= 500	HPLC	N/A	25	-
		Hydrilla verticillata	Whole cell extracts of *C. Raciborskii*	14 days	Growth, stimulation	NOEC	> 400	HPLC	N/A	-	-
		Lemna minor L.	Crude extracts from *A. Ovalisporum* (BGSD-423)	5 days	Growth (fond number)	NOEC	= 100	HPLC	N/A	21	-
				5 days	Growth (fresh weight)	NOEC	= 1000	HPLC	N/A	21	-
			Purified CYN	5 days	Growth (fond number)	NOEC	< 10	HPLC	N/A	21	-
				5 days	Growth (fresh weight)	NOEC	= 1000	HPLC	N/A	21	-
		Wolffia arrhiza	Crude extracts from *A. Ovalisporum* (BGSD-423)	5 days	Growth (fond number)	NOEC	= 1000	HPLC	N/A	21	-
				5 days	Growth (fresh weight)	NOEC	= 1000	HPLC	N/A	21	-
			Purified CYN	5 days	Growth (fond number)	NOEC	= 10	HPLC	N/A	21	-
				5 days	Growth (fresh weight)	NOEC	< 10	HPLC	N/A	21	-
Invertebrate (crustaceans)	Acute	*Artemia salina*	Extracts from water samples in the Nuwara Wewareservoir (Environmental)	24 hr.	Survival	LC_{50}	= −694,970 to −118.080	No	N/A	28	8.43–8.60
			Extracts from water samples in the Nuwara Wewareservoir (Cultured)	24 hr.	Survival	LC_{50}	= −157,490 to 3,216,840	No	N/A	28	-
			Purified CYN	24 hr.	Survival	LC_{50}	= 4480	HPLC-PDA	N/A	23	-
				48 hr.	Survival	LC^{50}	= 2860	HPLC-PDA	N/A	23	-
				72 hr.	Survival	LC^{50}	= 710	HPLC-PDA	N/A	23	-
		Brachionus thermophila	Purified CYN	24 hr.	Immobilization	EC_{50}	> 4000	No	N/A	-	-
		Daphnia magna	Purified CYN	24 hr.	Survival	LC_{50}	> 4,000	No	N/A	20	-

Taxonomic Group	Test Type	Test Organism	Form of CYN	Exp. Duration	Endpoint	Parameter	Effect Conc. (μg L^{-1})	Analytical verification	Purity	Temp(°C)	pH
				24 hr.	Immobilization	EC_{50}	> 4,000	No	N/A	20	-
				48 hr.	Survival	LC_{50}	= 890	No	N/A	20	-
				48 hr.	Immobilization	EC_{50}	= 890	No	N/A	20	-
			Crude extracts from *A. Ovalisporum*	3 days	Survival	LC_{50}	= 86.96	HPLC-MS/MS	N/A	19	
			Crude extracts from *C. raciborskii*	24 hr.	Survival	LC_{50}	= 109.26	HPLC-MS/MS	N/A	19	
			Live culture of *C. raciborskii* (Maranha˜o Reservoir in Portugal)	192 hr.	Survival	LC_{100}	= 3.6 × 10^6 cells mL^{-1}	No	N/A	19	-
			Live culture of *C. raciborskii* (aquaculture pond in Townsville, Autralia)	72 hr.	Survival	LC_{100}	= 1.3 × 10^6 cells mL	HPLC-MS/MS	N/A	19	-
		Thamnocephalus platyurus	Purified CYN	24 hr.	Survival	LC_{50}	= 270	No	N/A	25	-
Invertebrate (gastropod)	Chronic	*Melanoides tuberculata*	Whole cell extracts of *C. Raciborskii*	14 days	Behavior	NOEC	> 400	No	N/A	-	-
				14 days	Reproduction (number of hatchlings)	NOEC	> 400	No	N/A	-	-
			Live culture of *C. raciborskii*	14 days	Behavior	NOEC	> 50%	No	N/A	-	-
				14 days	Reproduction (number of hatchlings)	NOEC	> 50%	No	N/A	-	-
Fish	Acute	*Danio rerio* (2–5 hpf)	Crude 30% MeOH extracts from *A. ovalisporum* (isolate: APH OVAL)	24 hpf	Survival	EC^{100}	= 143 μg biomass mL^{-1}	HPLC-MS/MS	>95%	28	-
			Crude 30% MeOH extracts from *C. raciborskii* (isolate: 4899, MARAU, CAIA, 4799, BRAZ, LJ, AQS)	24 hpf	Survival	EC_{100}	= 143 μg biomass mL^{-1}	HPLC-MS/MS	>95%	28	-
			Crude CHCl3 extracts from *C. raciborskii* (isolate: 4899, MARAU, CAIA, 4799, LJ, AQS)	24 hpf	Survival	EC_{100}	= 71.5 μg biomass/mL	HPLC-MS/MS	>95%	28	-
			Purified CYN (microinjection)	5 dpf	Survival	LC^{50}	= 8.765	HPLC-MS/MS	>95%	28	-

Taxonomic Group	Test Type	Test Organism	Form of CYN	Exp. Duration	Endpoint	Parameter	Effect Conc. (μg L^{-1})	Analytical verification	Purity	Temp(°C)	pH
			Purified CYN (immersion)	5 dpf	Survival	NOEC	> 50,000	HPLC-MS/MS	>95%	28	-
Terrestrial Amphibian	Acute	*Bufo marinus (juvenile)*	Whole cell extracts of *C. Raciborskii*	7 days	Survival	NOEC	> 400	HPLC-MS/MS	N/A	23.5 +/− 1	8.5–8.9
				7 days	Behavior	NOEC	> 232	HPLC-MS/MS	N/A	23.5 +/− 1	8.5–8.9
				14 days	Behavior	NOEC	> 400	HPLC-MS/MS	N/A	23.5 +/− 1	8.5–8.9
				7 days	Growth	NOEC	> 400	HPLC-MS/MS	N/A	23.5 +/− 1	8.5–8.9
			Live culture of *C. raciborskii*	7 days	Survival	NOEC	> 400	HPLC-MS/MS	N/A	23.5 +/− 1	-
				7 days	Growth	NOEC	> 232	HPLC-MS/MS	N/A	23.5 +/− 1	8.5–8.9
				7 days	Behavior	NOEC	> 180	HPLC-MS/MS	N/A	23.5 +/− 1	8.5–8.9

IC_{50}, half maximal inhibitory concentration; NOEC, no observed effect concentration; LC_{50}, half maximal lethal concentration; EC_{50}, half maximal effective concentration.