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Review

A review of microcystin detections in Estuarine and Marine waters: Environmental implications and human health risk

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ABSTRACT

Toxin production by harmful cyanobacteria blooms (CyanoHABs) constitutes a major, worldwide environmental threat to freshwater aquatic resources that is expected to expand in scale and intensity with global climate change. Extensive literature exists on the most frequently encountered cyanotoxin, microcystin, in freshwater environments. Yet, the expansion of microcystin producing CyanoHABs and the transport of contaminated inland waters to estuarine and coastal marine waters has only recently received attention. This paper synthesizes information on the salinity tolerance of microcystin producing cyanobacteria and summarizes available case reports on microcystin presence in estuarine and coastal waters. We highlight a potential food-borne exposure route to humans by reviewing the growing body of evidence that shows microcystins can accumulate in coastal seafood. These cases reinforce the importance of freshwater nutrient reduction and the need for freshwater management efforts to look beyond lacustrine and riverine systems. Events reviewed here likely only represent a small proportion of cases where microcystins affect estuarine and coastal waters. We strongly suggest increased monitoring and research efforts to understand, react to, and prevent ecological and health problems associated with the growing problem of toxic CyanoHABs in coastal environments.

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1. Introduction

Harmful cyanobacteria blooms (CyanoHABs) are comprised of naturally occurring photosynthetic prokaryotes found in a wide variety of aquatic environments and capable of producing toxic secondary metabolites (cyanotoxins). CyanoHABs can thrive under a wide range of environmental conditions and are especially prolific and competitive under high nutrient conditions often associated with eutrophic waters. Although nutrient loading is a strong risk factor for bloom promotion, no single environmental or anthropogenic factor has been identified to cause bloom formation. Nonetheless, large scale ecological disturbances associated with urbanization, rising agricultural activities, and introduction of invasive species (Bykova et al., 2006), combined with climate change have escalated the intensity, frequency and geographic distribution of CyanoHABs (Carey et al., 2012; Paerl and Huisman, 2009; Paerl and Paul, 2012; Visser et al., 2016). For example, in the United States, CyanoHABs previously affected only a few regions, but major blooms now impact lakes, rivers, wetlands, estuaries and nearshore marine waters across the country (Glibert et al., 2005). Proliferation and dominance of CyanoHABs have been observed worldwide, with approximately 75% of cyanobacteria blooms known to be toxic (Chorus et al., 2000). The myriad of water quality, fisheries, recreational, animal and human health problems associated with cyanotoxins are expected to rise as CyanoHABs increase in severity (Falconer and Humpage, 2005).

Hepatotoxic microcystins (MCs) are the most common cyanotoxins, with over 100 known variants (Vesterkvist et al., 2012). MCs are small, monocyclic peptides composed of seven amino acids connected via peptide bonds with the general structure cyclo(D)-Ala-X-(D)-*erythro*-β-methyl-*iso*-Asp-Y-Adda-(D)-*iso*-Glu-*N*-methyldehydro-Ala (Fig. 1); X and Y represent positions occupied by the variable L-amino acids (Codd et al., 2005; Welker and von Döhren, 2006). The unusual Adda amino acid, unique to MCs, is often associated with toxicity of the molecule (Dawson, 1998).

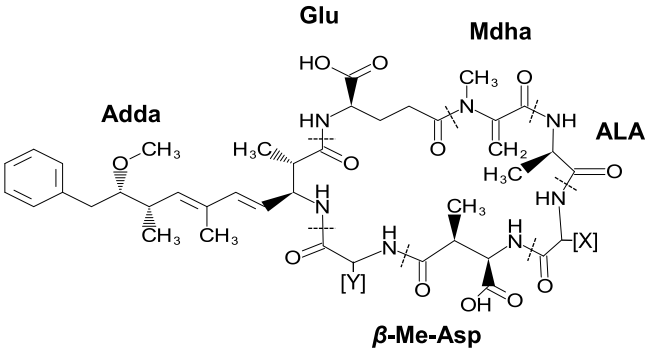

Fig. 1. Structure of the peptide hepatotoxin, microcystin.

MCs are potent inhibitors of the serine threonine protein phosphatases (PPs) PP1 and PP2A (MacKintosh et al., 1990). Inhibition of protein phosphatase can lead to accumulation of phosphorylated proteins in the liver causing cell necrosis, massive hemorrhage and death (Bhattacharya et al., 1997; Merel et al., 2013). Acute or chronic MC exposures may cause permanent liver damage (Li et al., 2011), and promote tumors (Nishiwaki-Matsushima et al., 1992; Grosse et al., 2006; Fujiki and Suganuma, 2011). Due to the toxicological effects from MCs, exposure to the toxins presents a health hazard and numerous MC poisonings have been documented in pets, livestock, wildlife, and humans (Mez et al., 1997; Azevedo et al., 2002; Merel et al., 2013; Backer et al., 2013; Hilborn et al., 2014).

MCs are commonly produced by the genera, *Anabaena* (*Dolichospermum*), *Aphanizomenon, Microcystis, Planktothrix* and more rarely by *Anabaenopsis, Aphanocapsa, Cylindrospermopsis, Fischerella, Gleotrichia, Gomphosphaeria*, *Hapalosiphon, Nodularia, Nostoc, Oscillatoria, Phormidium, Pseudanabaena, Synechococcus* (Sivonen and Jones, 1999; Chorus et al., 2000; Mohamed and Carmichael, 2000; Paerl and Otten, 2013; EPA, 2015). Cyanobacteria of the genus *Microcystis* are among the most common producers of freshwater blooms on every continent except Antarctica (Carmichael, 1992) and some level of toxins are frequently associated with these blooms (Carmichael, 1995). A recent review found documentation confirming *Microcystis* blooms from 108 countries and territories; MCs were found in 79 of these locations (Harke et al., 2016).

Reports of CyanoHABs in brackish waters are on the rise (Paerl and Paul, 2012), yet MCs remain under-investigated in estuarine and marine waters. Since coastal watersheds support more than half of the world's population (NOAA, 2012; Ache et al., 2013), it is critical to better understand MC dynamics in saline environments. Other than the review by Vareli et al. (2013) emphasizing MC production by marine phytoplankton, there is little summary literature on MC-producing CyanoHABs in marine and estuarine systems or on delivery of MC-contaminated freshwaters polluting nearshore environments. Because of their high potential for human health impacts, a review of MCs in brackish and saline environments is particularly appropriate and timely. This review summarizes: 1) known effects of salinity on MC producing cyanobacteria, 2) MC-producing CyanoHABs in estuarine and nearshore coastal environments, 3) case studies documenting transfer of MCs from freshwater to coastal ecosystems and 4) MC accumulation in estuarine and marine seafood, emphasizing organisms consumed by humans.

2. Salt tolerance of CyanoHABs

A wide range of environmental variables including salinity, temperature, nutrient and light availability, residence time, turbulent mixing and grazing, can influence CyanoHAB formation

and toxin production (Paerl and Huisman, 2009; Davis et al., 2009; O'Neil et al., 2012; Visser et al., 2016). Although most freshwater cyanobacteria cannot survive for extended periods in saline waters, some genera have a relatively high salt tolerance. Several common MC-producing genera (*Anabaena, Anabaenopsis, Microcystis* and *Oscillatoria*) may even display rapid growth rates in saline environments (Robson and Hamilton, 2003; Ross et al., 2006; Tonk et al., 2007; Miller et al., 2010). For example, *M. aeruginosa* has one of the highest salt tolerances of all cyanophytes (Otsuka et al., 1999; Orr et al., 2004; Verspagen et al., 2006) and can continue to both grow and produce MCs in saline environments (Tonk et al., 2007).

Studies on the salinity tolerance of *M. aeruginosa* show highly variable results, with conflicting reports for salinity thresholds and tolerance between strains within the same species (Fig. 2; Otsuka et al., 1999). For example, *M. aeruginosa* in the Potomac River lost photosynthetic ability at salinities of 1–2, resulting in cell density declines (Sellner et al., 1988). In contrast, others found the specific growth rate of *M. aeruginosa* was unaffected by salinity up to 10 or approximately 30% of seawater salinity (Verspagen et al., 2006; Tonk et al., 2007; Lewitus et al., 2008; Tolar, 2012).

Literature reports generally agree that *M. aeruginosa* has a salt tolerance of $\leq$10, but a few studies indicate survival at higher salinities. For instance, one laboratory study showed *M. aeruginosa* could survive salinities up to 17.5 for nine days (Tonk et al., 2007). Another laboratory experiment found *M. aeruginosa* growth rate only declined to zero growth at a salinity of 25 (Robson and Hamilton, 2003). The colonial form of *M. aeruginosa* has been shown to survive for extended periods of time in the San Francisco Bay Estuary at salinities from 0.1–18 (Lehman et al., 2005). Only one known study has demonstrated that *Microcystis* spp. can survive in seawater (average salinity of 35). Miller et al. (2010) found *Microcystis* spp. could survive in an experimental setting for about 48 h when grown in seawater from Monterey Bay, California.

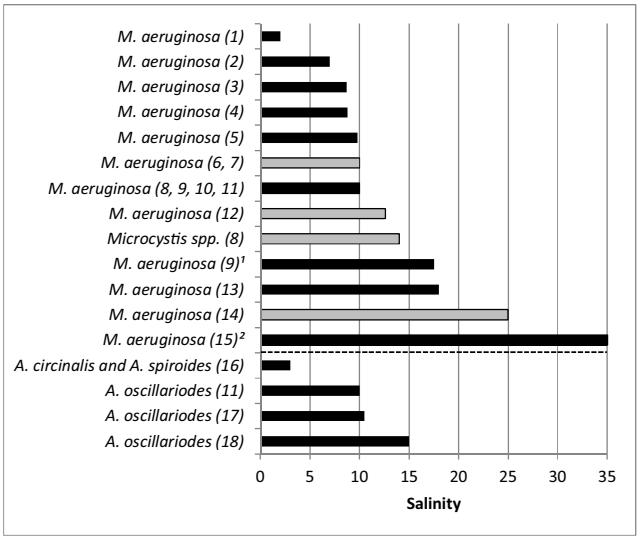

Fig. 2. Salt tolerance of *Microcystis* spp. and *Anabaena* spp. Black bars are reported salt tolerance and grey bars indicate salinity where growth ceased. Data are from the following references: 1. Sellner et al. (1988), 2. Otsuka et al. (1999), 3. Martín-Luna et al. (2015), 4. Albay et al. (2005), 5. Orr et al. (2004), 6. Atkins et al. (2001), 7. Orr et al., 2000, 8. Verspagen et al., 2006, 9. Tonk et al. (2007), 10. Lewitus et al. (2008), 11. Tolar (2012), 12. Black et al. (2011), 13. Lehman et al. (2005), 14. Robson and Hamilton (2003), 15. Miller et al. (2010), 16. John and Kemp (2006), 17. Zhao and He (1999), and 18. Coutinho and Seeliger (1984). [1]Survived nine days. [2]Survived two days.

Variability in reported salt tolerances could be related to unreported environmental variables, intraspecific tolerances between strains, or acclimation to salt exposure. *M. aeruginosa* cultures displayed immediate and substantial die-off when pulsed with salt treatments of 2 g/L, but survived in salinities up to 10 with gradual salt additions (Tolar, 2012). Thus, in coastal areas under the influence of substantial freshwater inputs *M. aeruginosa* can potentially survive, and may even grow (Black et al., 2011). Estuaries generally range in salinity from 0.5 and 17 (Martín-Luna et al., 2015) which is within reported salt tolerance ranges for *M. aeruginosa*. Thus, even with salinity increases in estuaries and nearshore coastal areas that are predicted to accompany climate change (Paerl, 2009; Paerl and Paul, 2012), salinities should not be a major inhibitor of *Microcystis* growth.

Studies have shown *Anabaena* spp. and *Anabaenopsis* spp. can grow and persist in saline environments, with similar variations in reported growth and survival as *Microcystis* spp. (Moisander et al., 2002; John and Kemp, 2006; Tolar, 2012). In the Swan River estuary *Anabaena circinalis* and *Anabaena spiroides* grew in waters with salinity less than 3 (John and Kemp, 2006). Whereas in an experimental setting, *A. oscillariodes* exhibited a threshold salt tolerance at a salinity of 10 to both pulse and gradual treatments (Tolar, 2012). Both *Anabaena aphanizomenoides* and *Anabaenopsis* spp. isolated from the Neuse River Estuary, North Carolina, maintained growth rates in saline waters up to 20 and 15 respectively (Moisander et al., 2002).

While CyanoHABs, such as *Microcystis* spp. and *Anabaena* spp., are not necessarily correlated with high levels of MCs, these species often indicates MC presence (Sivonen and Jones, 1999; Ouellette and Wilhelm, 2003; Sabart et al., 2010). Saline conditions can stimulate lysing or cell leakage, inducing massive toxin excretion (Tonk et al., 2007). Once MC is released extracellularly, toxin concentrations generally reduce over time; however, certain MC variants can persist in the water column for up to several months, even after a bloom has collapsed (Lahti et al., 1997; Zastepa et al., 2014).

There is also evidence MC production can continue in saline waters, and increased extracellular MCs are often observed in higher salinity waters. Most studies have shown that salinities up to 10 do not affect MC production or MC cell quota (Tonk et al., 2007; Black et al., 2011; Martín-Luna et al., 2015). This correlates with the general salinity tolerance of 10 reported for *Microcystis spp.*, *Anabaena* spp., and *Anabaenopsis* spp. Tonk et al. (2007) found MC production continued in salt concentrations up to 17.5, but in salinities greater than 10, MC production was inversely correlated with increasing salt concentrations. In samples cultured from the Swan River Estuary in Western Australia, elevated extracellular MCs were measured in salinities of 21.2 (Orr et al., 2004). Ross et al. (2006) found an 80% increase in toxin release when *M. aeruginosa* cells were transferred to water with a salinity of 32. Extracellular MC also persisted in high salinities (up to 35.6) in an experimental setting, with 80% of the initial extracellular toxin remaining after 20 days (Black et al., 2011). Similarly, MC-LR was detectable for 21 days in seawater collected from Monterey Bay, California (Miller et al., 2010). These results suggest saline conditions can stimulate release of MCs and may increase extracellular toxin concentrations relative to freshwater environments.

3. CyanoHABs in worldwide Estuarine and Marine environments

Estuaries provide transition zones between freshwater and marine ecosystems and are important ecological and economic resources. They typically have high biologic productivity due to high nutrient enrichment from surrounding watersheds. Since estuaries are composed of a dynamic mix of fresh and saltwater,

they can support highly diverse communities of marine and freshwater species including wide-ranging types of phytoplankton. While brackish and estuarine systems have supported CyanoHABs for thousands of years (Bianchi et al., 2000), cyanobacteria species introduced from freshwater environments are increasingly found in coastal waters where they can compete with other phytoplankton species (Fig. 3, Lehman et al., 2005).

Climatic factors such as heavy rainfall and floods often play an important role in transporting invasive, freshwater-derived cyanobacteria to estuaries and coastal waters (Robson and Hamilton, 2003). Once cyanobacteria enter estuaries, cells may survive for long periods in the sediments due to their ability to form resting cells (Livingstone and Jaworski, 1980; Wood et al., 2009). Vegetative cells of many cyanobacteria species can form undifferentiated resting cells or can differentiate into akinetes, which are thick-walled resting cells (Paerl, 1988). These resting cells remain dormant, yet viable, during unfavorable growth periods (Lampert, 1995). Cells reemerge when conditions are favorable, to reinitiate growth within the water column (Preston et al., 1980; Takamura et al., 1984).

3.1. Geographic distribution

3.1.1. Europe

MC-producing CyanoHABs have been reported in European coastal waters from the Baltic Sea and Netherlands to Portugal and Spain. The Baltic Sea constitutes the largest brackish water system on earth and has a wide range in salinities (Brutemark et al., 2015), so it is not surprising that a majority of the European literature on CyanoHABs in saline waters is associated with that system (Lopes and Vasconcelos, 2011). Evidence shows that nitrogen-fixing cyanobacteria have occurred in the Baltic Sea for at least 7000 years and are considered a natural feature (Bianchi et al., 2000). In the 1980s CyanoHABs in the Baltic Sea began to be reported regularly due to a combination of increased nutrients and decreased salinity (Suikkanen et al., 2007,2013; Herlemann et al., 2011). Cyanobacteria blooms characterized by *Nodularia spumigena*, *Aphanizomenon* spp., and *Anabaena* spp. (*Dolichospermum* spp.) (Brutemark et al., 2015) now occur every summer and can cover areas spanning over 125,000 km^2 (Öberg, 2016).

Nodularia was thought to be the sole toxin producer in pelagic waters of the northern Baltic region, until MCs were identified in brackish waters near Fehmarn Island (Luckas et al., 2005) and high levels of MC-LR were detected in several open water sampling sites within the Gulf of Finland (Karlsson et al., 2005). Since first detected, MC producing blooms have become a persistent phenomenon throughout the Gulf of Finland (Fewer et al., 2009). Laboratory studies show *Anabaena flos-aquae* is responsible for MC production (Halinen et al., 2007; Kankaanpää et al., 2007), but it remains unknown if toxic *A. flos-aquae* populations were introduced from freshwater tributaries or if they developed *in situ* in response to increased nutrient loads and altered environmental parameters.

Microcystis spp. have been observed in coastal areas of the Baltic Sea (Nikulina, 2003; Mazur et al., 2003; Rybika, 2005; Tanner et al., 2005; Paldavičienė et al., 2009; Mazur-Marzec et al., 2010). Beginning in the early 2000s, hyper-blooms containing *Microcystis* spp. began forming regularly in the highly eutrophied Curonian

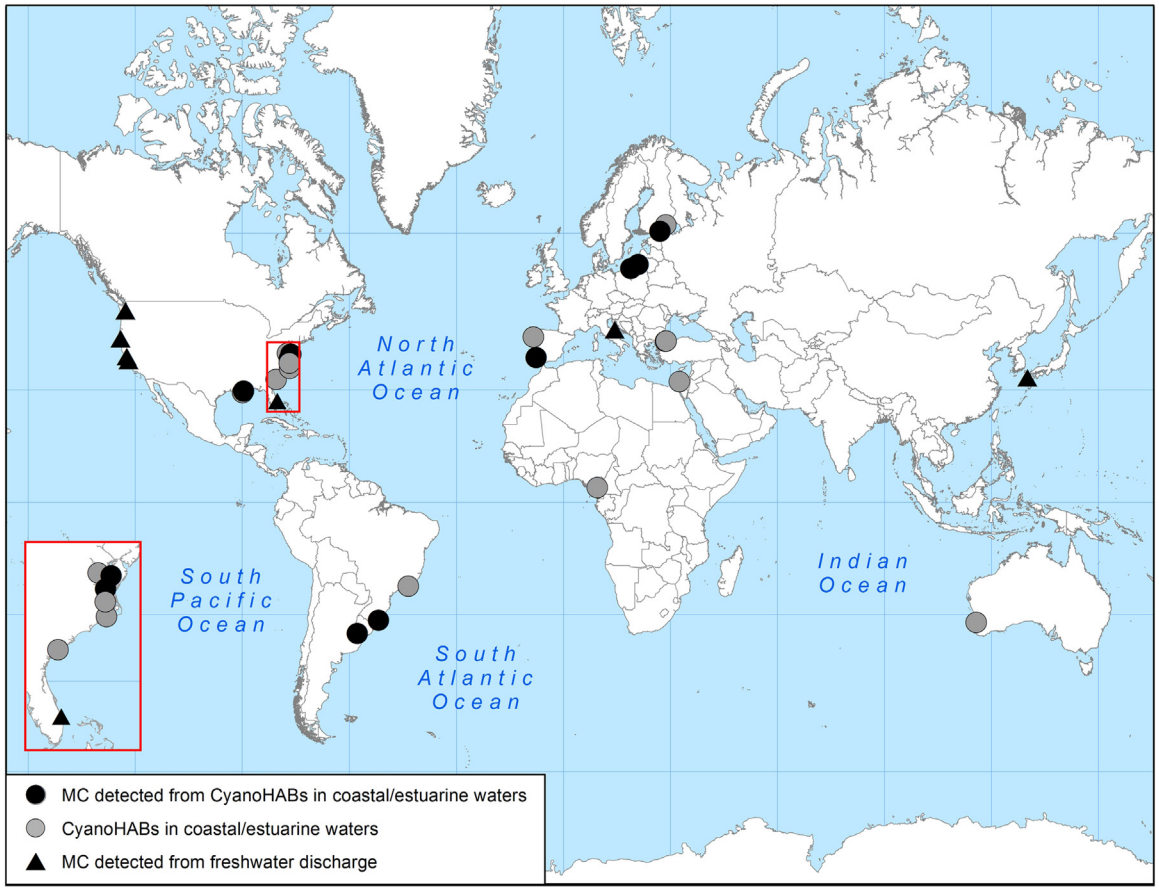

Fig. 3. Location of CyanoHABs and MCs in the world's coastal waters. For references and details, see the text.

Lagoon in the Southeast Baltic Sea (located between Lithuania and Russia). Like *Anabaena* spp., *Microcystis* spp. are most frequently observed in low salinity areas of the Baltic Sea (Paldavičienė et al., 2009; Brutemark et al., 2015), but the exact placement of blooms depends largely on wind speed and direction (Belykh et al., 2013). High MC concentrations, produced by *M. aeruginosa*, were first detected in water samples in the Lithuanian part of the Curonian Lagoon in 2006–2007 (Paldavičienė et al., 2009). Shortly after this documentation, *Microcystis* spp. containing genes for MC synthesis were found in the Polish waters of the Vistula Lagoon (Mazur-Marzec et al., 2010) and Russian waters of the Curonian Lagoon (Belykh et al., 2013). In 2014 MCs were detected in *Aphanizomenon flos-aquae* scum in Russian waters of the Curonian Lagoon, but these were determined to be residual toxins from *M. aeruginosa* (Paldavičienė et al., 2015; Šulčius et al., 2015).

Frequent CyanoHABs and related water quality problems have also been reported in several Portuguese estuaries. For example, *Microcystis* spp. blooms develop regularly in the Guadiana Estuary, located between Portugal and Spain (Rocha et al., 2002; Sobrino et al., 2004). Beginning in the 1980s these naturally-occurring blooms increased in frequency and intensity (Vasconcelos et al., 1996). MC is often associated with the blooms, although salinity appears to have an inhibitory role on MC production (Sobrino et al., 2004). Further north in Portugal, *M. aeruginosa* forms in upstream reservoirs and is then transported downstream to the Minho River Estuary (Vasconcelos and Cerqueira, 2001). MCs have been detected in freshwater upstream of the estuary, but MC presence has not been confirmed within the estuary (Vasconcelos et al., 1996).

3.1.2. Turkey

Two major *Microcystis* spp. blooms were reported in the late 1990s in the heavily polluted Golden Horn Estuary of Turkey (Taş et al., 2006). Unlike other estuarine locations where blooms typically develop in summer, the Golden Horn Estuary blooms often form in winter following heavy rainfalls that decrease surface salinity and cause high nutrient loading (Taş et al., 2006). In Küçükçekmece Lagoon, in Istanbul, Turkey, a massive bloom of toxic *M. aeruginosa* was first detected in 2000 after a heavy bloom coincided with extensive fish mortalities (Albay et al., 2005).

3.1.3. Mid-Atlantic region United States

The east coast of North America has numerous tidal freshwater habitats and estuaries, including the nation's two largest estuaries (Chesapeake Bay and the Albemarle-Pamlico Estuarine System). Reports show increasing seasonal trends in both abundance and biomass of CyanoHABs within Chesapeake Bay and its tributaries (Kemp et al., 2005; Marshall et al., 2005). In the Sassafras River, the maximum cyanobacteria density has increased 10 fold from 2000 to 2009 (Tango and Butler, 2008) and *M. aeruginosa* is now an annual bloom producer in the Potomac River (Marshall et al., 2009). Blooms often extend downstream into Chesapeake Bay where MCs were first detected in 2000. Since then, MC concentrations often exceed both the World Health Organization (WHO) chronic-drinking water guidance values and the recreational safety guidance for children proposed by the National Health and Medical Research Council of Australia (Tango and Butler, 2008). While cyanobacteria are only a minor component of the phytoplankton community in the James River Estuary, Virginia, a sub-estuary of Chesapeake Bay, a study by Wood et al. (2014) found that MC in both water and biota was ubiquitous.

For years, massive *M. aeruginosa* and *Oscillatoria* spp. blooms occurred annually in upstream oligohaline portion of the Neuse River Estuary, one of the major tributary estuaries to North Carolina's Albemarle-Pamlico estuarine system (Paerl et al., 2004; Paerl and Otten, 2016). In efforts to reduce blooms a dual nutrient reduction strategy was implemented by the state that resulted in large reductions in toxic *Microcystis* blooms within the estuary (Paerl and Otten, 2016). However, CyanoHABs still plague the Albemarle-Pamlico Estuarine Basin due to increased large storm events that enhance nutrient export from the watershed (Paerl et al., 2006a).

Further south, *M. aeruginosa*, *Anabaena* spp., *Anabaenopsis* spp., and *Oscillatoria* spp. commonly form in South Carolina coastal stormwater ponds (Lewitus et al., 2008; Siegel et al., 2011; Greenfield et al., 2014; Reed et al., 2016). Pond water exchanged with tidal creeks allows CyanoHABs to move downstream into estuarine environments (Lewitus et al., 2008; Siegel et al., 2011; Greenfield et al., 2014). One study, found *Microcystis* spp., *Anabaena* spp. and MCs in estuarine samples collected between 2004 and 2005 coincided with toxin presence in the ponds (DeLorenzo and Fulton, 2009).

3.1.4. Southeast region, United States

Nutrient rich freshwater pulsed from the Mississippi River affects turbidity, temperature and salinity in the estuarine receiving waters of the Mississippi Delta/Louisiana Coast subregion, optimizing conditions for CyanoHAB formation. In Breton Sound Estuary, Louisiana, MC producing genera *Microcystis* and *Anabaena* spp. dominate the phytoplankton community for much of the year. First documented in Breton Sound Estuary in 2007, MC generally follows the same trends as CyanoHAB abundance, with highest biomass and MC concentrations measured during low river input and toward the outer estuary (Czubakowski, 2010). High salinities in the outer estuary are thought to cause MC producing genera to break apart and release toxins into surrounding waters (Czubakowski, 2010). CyanoHABs also occur persistently throughout the year in the Barataria-Terrebonne Estuary, Louisiana, where MCs have been detected in surface water and in demersal blue crab tissue (Garcia et al., 2010).

3.1.5. South America

MC-producing CyanoHABs have been observed in coastal lagoons and estuaries of Argentina, Brazil, Columbia and Uruguay (Dörr et al., 2010). Most research on MC-contamination of South American coastal waters has occurred in Brazil. The largest lagoonal system in South America is the Patos Lagoon, Brazil, where cyanobacteria are the most abundant group of phytoplankton (Lemes et al., 2008). Although the first scientific record of *M. aeruginosa* presence dates to 1987, local villagers claim blooms have occurred since at least the beginning of the 20th century (Yunes, 2009). It has been suggested that *M. aeruginosa* cells were first delivered to the estuary from the huge freshwater drainage basin (Matthiensen et al., 1999). Seasonal swells cause wide fluctuations in salinity (Table 1) that allow toxic *M. aeruginosa* blooms to develop in lower saline areas then spread throughout the coastal region (Lemes et al., 2008). CyanoHABs often dominated by *M. aeruginosa* are present year round, with the most intense blooms present from March to May (Yunes et al., 1996; Matthiensen et al., 1999). Colonies of *M. aeruginosa* and MCs have been detected in coastal recreational waters and in nearby shrimp fisheries (Matthiensen et al., 1999; Yunes et al., 1996).

Toxic *M. aeruginosa* also often dominates the phytoplankton community in the severely eutrophied Jacarepaguá Lagoon, in Rio de Janeiro Brazil. Here, cyanobacteria can reach up to 90% of total phytoplankton biomass (Gomes et al., 2009). MCs in the lagoon have been detected in surface waters (Magalhães and Zevedo, 1998), zooplankton (Ferrão-Filho et al., 2002) and fish tissues consumed by humans (Magalhães et al., 2001; Hauser-Davis et al., 2015).

Trophic changes caused by climatic pressures and nutrient enrichment have increased CyanoHAB development in the Río de

Table 1
CyanoHABs identified in estuaries and associated MC concentrations where available.

Location	Estuary	Freshwater Source	Primary Genus	Salinity	MC Concentration in Water (μg/L unless noted)	Reference
Europe						
Estonia	Baltic Sea, Narva Bay	Lake Peipsi, Narva River	*Microcystis* and *Anabaena* spp.	N/A	N/A	Tanner et al. (2005)
Estonia/ Finland	Baltic Sea, Gulf of Finland	N/A	*Anabaena* spp.	4.3–6.7	6.0–50.0 pg/L[a]	Fewer et al. (2009)
Finland	Baltic Sea, Gulf of Finland	N/A	*A. Flos-aquae*	N/A	2.0–4.0 μg/kg dry weight[a]	Karlsson et al. (2005)
				5.0–6.7	0.2	Halinen et al. (2007)
Lithuania	Baltic Sea Curonian Lagoon	N/A	*M. aeruginosa*	0.0–6.0	<0.1–134.0 μg dm^{-3}	Paldavičienė et al. (2009)
Russia		N/A	*Microcystis* spp.	N/A	N/A	Belykh et al. (2013)
Poland	Baltic Sea Gulf of Gdańsk	N/A	*M. aeruginosa*	N/A	2.3 μg/g[a]	Mazur et al. (2003)
Finland	Baltic Sea River Neva Estuary	River Neva	*M. aeruginosa, Anabaena* and *Aphanizomenon* spp.	0.3–1.7	N/A	Nikulina (2003)
Border of Spain/ Portugal	Guadiana River Estuary	Guadiana River	*Microcystis, Anabaena, and*Oscillatoria spp.	0.0–6.0	1.0	Sobrino et al. (2004); Rocha et al. (2002)
Portugal	Minho River estuary	Minho River	*Microcystis* spp.	N/A	N/A	Vasconcelos and Cerqueira (2001)
Turkey						
Turkey	Golden Horn Estuary	Alibey and Kağithane Streams and Rainfall	*M. aeruginosa*	<2.0	N/A	Taş et al. (2006)
Istanbul, Turkey	Kucukcekmece Lagoon	Underground springs, three rivers (Eskinoz, Nakkas and Sazli) and ephemeral streams.	*M. aeruginosa*	5.9–8.8	0.06−24.2	Albay et al. (2005)
United States						
North Carolina	Albemarle-Pamlico Sound System/Chowan River Estuaries	Chowan River	*Anabaena planctonia*	N/A	N/A	ARHS (2015)
		Neuse River	*M. aeruginosa*, and *Oscillatoria* spp.	N/A	N/A	Paerl (2008)
South Carolina	South Carolina Estuaries	Coastal detention ponds	*M. aeruginosa, Anabaena, Anabaenopsis,* and*Oscillatoria* spp.	N/A	N/A	Lewitus et al. (2008),Siegel et al. (2011), Greenfield, et al. (2014), Reed et al. (2016)
Virginia	James River Estuary (subestuary to Chesapeake Bay)	James River	*Microcystis* spp.	<0.15	0.92	Wood et al. (2014)
Maryland	Chesapeake Bay	Bush, Sassafras, Potomac, and Transquaking Rivers	*M. aeruginosa*	<0.5–5.0	Max. 658.0	Tango and Butler (2008)
Maryland	Potomac River Estuary	Potomac River	*M. aeruginosa and Microcystis* spp.	1.0–2.0	N/A	Sellner et al. (1988)
Louisiana	Breton Sound Estuary	Mississippi River	*Microcystis* and *Anabaena* spp.	<2.0	2.9	Czubakowski (2010)
Louisiana	Barataria-Terrebonne Estuarine System	Mississippi River	*Microcystis* and *Anabaena* spp.	0.08–0.66	1.4	Garcia et al. (2010)
South America						
Rio Grande Do Sul, Brazil	Patos Lagoon	Multiple rivers from the northern drainage basin	*M. aeruginosa*	3.7–14.8	0.16–244.8	Matthiensen et al. (1999); Lemes et al. (2008)
Rio de Janeiro, Brazil	Jacarepaguá Lagoon	Comorim and Cacambe Rivers, Pavuna Stream	*M. aeruginosa*	0.0–13.0	1.5–979.0[2]	Magalhães et al. (2001); Gomes et al. (2009)
Between Argentina and Uruguay	Río de la Plata Estuary	La Plata River	*M. aeruginosa*	N/A	0.3–1.4	Sathicq et al. (2014)
Australia						
Australia	Swan River Estuary	Swan River	*M. aeruginosa*	7.0–10.0 post rainfall	N/A	Robson and Hamilton (2003)
Africa						
Egypt	Baradiwil Lagoon	N/A	*Oscillatoria* spp.	38.2–62.4	N/A	El-Kassas et al. (2016)
Cameroon	Douala Estuary	Wouri and Dibamba Rivers	*Microcystis* spp.	1.8–20.4	N/A	Fonge et al. (2013)
Cameroon	Gulf of Guinea	Wouri, Limbe and Dibamba Rivers, Mudeka/Tiko creeks,	*Microcystis* spp., *Aphanacapsa* spp., and *Phormidium* spp.	Max: 12.0–20.0	N/A	Oben et al. (2006)

[a] Seston samples.

la Plata estuary located between Argentina and Uruguay (Andrinolo et al., 2007). Toxic *M. aeruginosa* blooms were first observed on the Uruguayan coast of the Río de la Plata in 1999 (De Leon and Yunes, 2001) and in the Argentinean coast of the Río de la Plata River in 2003 (Andrinolo et al., 2007). Since first detected, *M. aeruginosa* blooms have occurred annually (Nagy, 2006). While there are anecdotal reports of people suffering gastrointestinal disorders after coming in contact with blooms, epidemiological records confirming these reports are lacking (Andrinolo et al., 2007). Nevertheless, MC concentrations are high enough to warrant concerns about drinking water in the area (Giannuzzi et al., 2012). Substantial fish mortality events have also been reported, but confirmation of CyanoHABs as causative agents is lacking (Andrinolo et al., 2007).

3.1.6. Australia

In the Swan River Estuary, Australia, low densities of cyanobacterial cells are common. Due to the relatively high salinity in the Swan River Estuary, Australia, it is believed large cyanobacteria blooms primarily occur after major rainfall events transport cells from adjoining wetlands and freshwater (Robson and Hamilton, 2003). This occurred in summer 2000 after record rainfall events caused dilution of estuary surface waters and transported *M. aeruginosa* from the Swan River into the lower estuary, seeding development of a large bloom (Robson and Hamilton, 2003).

3.1.7. Africa

Although cyanobacteria have been documented in 21 of the 54 African countries, most of the continent lags behind other areas of the world in CyanoHAB research (Ndlela et al., 2016). Yet, Africa is particularly vulnerable to CyanoHABs due to eutrophication of many waterbodies (Ndlela et al., 2016). Much of the available African CyanoHAB research is from South Africa and Egypt, where *Microcystis* and *Anabaena* have been noted to occur regularly in inland waters (Oberholster et al., 2009; Ndlela et al., 2016), including waterbodies that drain into coastal areas (e.g., Matthews et al., 2010). One recent study found small amounts of cyanobacteria, including *Oscillatoria* spp., in the hypersaline Baradiwil Lagoon, Egypt (El-Kassas et al., 2016). Although minimal research is extant for CyanoHABs in Central Africa *Microcystis* spp., *Aphanocapsa* spp., and *Phormidium* spp. have been reported along the Cameroon Gulf of Guinea (Oben et al., 2006; Fonge et al., 2013).

3.2. Factors affecting MC-producing CyanoHABs in estuarine waters

3.2.1. Precipitation and runoff

Precipitation and runoff influenced many of the CyanoHAB events discussed above. In saline environments, freshwater flow can enhance vertical stratification by allowing lighter freshwater to layer over denser saltwater, creating conditions that favor buoyant regulating cyanobacteria such as *Microcystis* and *Anabaena* spp. (Paerl, 2014). This phenomenon is well illustrated in the Baltic Sea, where increased freshwater flow combined with reduced saline inflow from the Danish Straits has caused a decreasing salinity trend in some basins (Suikkanen et al., 2007, 2013). Coinciding with this decreased salinity, *Anabaena* spp. biomass increased between 1979 and 2013 (Brutemark et al., 2015). Temporary increases of freshwater flow into estuarine environments, following large storm events, have also caused massive CyanoHABs to form in Australian, North American and Turkish estuaries (Robson and Hamilton, 2003; Paerl et al., 2006b; Taş et al., 2006). Illustrating the importance of precipitation in estuarine CyanoHAB production, toxic *M. aeruginosa* presence is highest in the Patos Lagoon during the rainy season when high freshwater flows drain into the lagoon (Yunes, 2009; Lemes et al., 2008).

3.2.2. Nutrient enrichment

Rising temperatures, shifts in hydrologic patterns and further enhancement of nutrients associated with climate change and expanding human populations are expected to increase CyanoHABs prevalence in estuarine phytoplankton communities (Rabalais, 2002; Rabalais et al., 2009; Nagy, 2006; Paerl and Huisman, 2008; Fulweiler et al., 2012). For example, long residence times and vertical stratification within the Baltic Sea make the waterbody particularly sensitive to eutrophication (HELCOM, 2009) and high nutrients are cited as one of the main reasons for CyanoHAB proliferation throughout the Baltic Sea (e.g. Mazur-Marzec et al., 2010; Paldavičienė et al., 2015; Šulčius et al., 2015). This anthropogenic nutrient enrichment coupled with warmer temperatures from climate change has led to CyanoHAB dominance and persistence throughout the Baltic Sea (Suikkanen et al., 2007). In the Río de la Plata estuary, increased nutrients from urban expansion, agriculture, poor wastewater treatment and industry have been correlated to increasing CyanoHAB events (Giannuzzi et al., 2012; Gómez et al., 2012). Similarly, in the Patos Lagoon, Brazil, eutrophication from agricultural activities and human sewage is the driver of *M. aeruginosa* blooms (Yunes et al., 1996; Matthiensen et al., 1999; Yunes, 2009). Episodic rainfall events and major storms that mobilize nutrients will increase nutrient enrichment of estuarine receiving waters in the future, promoting bloom potential (Paerl et al., 2006b; Paerl and Huisman, 2009). This is exemplified by Atlantic hurricanes that have caused increased nutrient loads and enhanced algal bloom activity in the Pamlico Sound, North Carolina (Paerl et al., 2001, 2005).

3.3. Microcystin presence

Unfortunately, many of the studies discussed above did not report MC concentrations. Even in the relatively well studied Baltic Sea, few studies investigating MC producing CyanoHABs have reported toxin concentrations. To date only one Baltic Sea study has reported MC at levels that may be a threat to human health from recreational exposure (Table 1; Paldavičienė et al., 2009). Worldwide, highest MC concentrations have been measured in Brazilian estuaries and within the Chesapeake Bay, Maryland (Table 1). Although MC presence was reported across a range of salinities, in Brazilian estuaries high levels of MC were detected at relatively high salinities (up to 14.8; Table 1). The only other estuary to report MC concentrations of human health concern was the Kucukcekmece Lagoon, Turkey which is used for recreation and as a fishery (Albay et al., 2005). Here, salinities were also higher than a number of other locations that reported MCs (up to 8.8; Table 1). Higher dissolved toxins in these locations may be a result of salinity stress that causes toxins to be leaked from cyanobacteria cells (Tonk et al., 2007).

A common theme between all estuaries where MC is reported at levels that may be unsafe for human exposure was the presence of severe eutrophication problems (Matthiensen et al., 1999; Magalhães et al., 2001; Albay et al., 2005; Tango and Butler, 2008; Paldavičienė et al., 2009). It is worth noting that *M. aeruginosa* was the main cyanobacteria species present during periods when highest MC concentrations were detected. Although *Anabaena* and possibly *Aphanizomenon* spp. have been shown to produce toxins in estuarine waters, these concentrations tended to be below levels of human health concern (Nikulina, 2003; Halinen et al., 2007; Fewer et al., 2009).

4. Discharge of microcystin-contaminated freshwater into Estuarine and Marine environments

Since MCs are chemically and physically stable (Harada et al., 1996; Welker and Steinberg, 1999) and environmentally persistent

(Tonk et al., 2007), these toxins do not easily degrade during transit from the site of origin (Graham et al., 2012; Fetscher et al., 2015,,2015). Planktonic species have been recorded drifting downstream from lakes and reservoirs (Doi et al., 2008) so it is not surprising that CyanoHABs and MCs can reach waterbodies far from the site of production (Fetscher et al., 2015). Nonetheless, transport of intact MCs from inland waters to downstream estuarine and coastal environments has only recently been recognized (Table 2).

The first published work on MC presence in marine waters, connected to a possible freshwater origin occurred in coastal waters of British Columbia where marine mussels showed MC accumulation (Chen et al., 1993). More recently, Vareli et al. (2013) found evidence showing these toxins were most likely from the marine phytoplankton *Synechococcus* and not of freshwater origin. It was not until MC was detected in waters and biota along the Pacific Coast of the United States (Lehman et al., 2005; Miller et al., 2010; Preece et al., 2015a, 2015b) that concerns emerged regarding pollution of the land-sea interface from freshwater-derived MCs (Fig. 3). Although lakes (Preece et al., 2015a, 2015b), reservoirs (De Pace et al., 2014; Umehara et al., 2015), rivers (Lehman et al., 2005), wadeable streams (Fetscher et al., 2015) and wetlands (John and Kemp, 2006) may all deliver MCs to marine receiving waters, studies on this phenomenon are limited.

4.1. Waterbody type

While rivers are typically the mode of MC conveyance to estuarine and marine waters, they are not always the actual site of toxin production. For the purpose of this review, freshwater waterbodies were divided into coastal lakes, reservoirs and river-dominated estuaries. We define coastal lakes as inland lakes whose outflow travels less than 10 km prior to discharging into coastal waters. Reservoirs are treated separately as the volumes and regimens of discharges are typically regulated. River-dominated estuary literature addressed below focuses on CyanoHABs formed in low velocity river sections, in inland lakes or reservoirs (10 km or greater distance from coastal receiving waters), and in a combination of these locations.

4.1.1. Coastal Lakes

Many lakes throughout the world drain into nearby coastal waters. For example, along the Pacific Coast of the United States, numerous freshwater lakes with annual CyanoHABs drain into the Pacific Ocean during the high rainfall season (late September–December) (Jacoby and Kann, 2007; Trainer and Hardy, 2015). The Pacific Coast is the only location where MCs have been documented traveling from natural coastal lakes (less than 10 km from coastal waters) to marine receiving waters. In Puget

Table 2
Discharge of microcystin-contaminated freshwater into coastal environments.

Marine Location	Distance Water Travels from Freshwater to Marine Location (km)	Primary Genus	MC variant	Maximum Concentration in Freshwater (μg/L)	Maximum Concentration in Marine Waters (μg/L)	Source
Coastal Lakes						
Puget Sound, Washington	Bay Lake, 0.7 Lake Steilacoom, 6.5	*Anabaena* spp., *Microcystis* spp.	MC-LA, MC-LR	Bay Lake, 180.0 Steilacoom Lake, 2,700.0	Bay Lake receiving waters, 0.3 Steilacoom Lake receiving waters, <MDL	Preece et al. (2015a, 2015b)
Reservoirs						
Adriatic Sea, Italy	~67.0	*Planktothrix rubescens*	desmethyl-MC-RR, MC-RR	298.7	0.61	De Pace et al. (2014)
Isahaya Bay, Japan	~10.0	*Microcystis aeruginosa*	MC-LR[a]	2,900.0	0.10	Umehara et al. (2015)
River-Dominated Estuaries						
St. Lucie Estuary, Florida	Lake Okeechobee ~60 km	*Microcystis aeruginosa*	MC-LR, MC-LA, Desmethyl-MC-LR, MC-methylLR, MC-methylLA	10,400.0[b]	740 found within 4 km of seawater, <MDL in seawater	Martin County Final Report (2016)
			MC-LR[a]	163.0–1,188.0[a,b] 95.0	2.1[c]–1 km from seawater N/A	Phlips et al. (2012) Williams et al. (2007)
Klamath River Estuary, California	Copco Reservoir, ~322.0	*Microcystis aeruginosa, Anabaena* spp.	MC-LA, MC-RR,MC-LR, MC-LA[d]	Copco Reservoir, 73,000.0	3.6	Kann et al. (2010); Fetcho (2011); Otten et al. (2015)
San Francisco Estuary, California	~30.0 km (Junction of San Joaquin and Mokelumne Rivers)	*Microcystis aeruginosa*	Desmethyl-MC-LR, MC-LR	San Joaquin River, 0.1	0.1	Lehman et al. (2005)
			N/A	San Joaquin River, 2.1	N/A	Spier et al. (2013)
Monterey Bay, California	Pinto Lake[e], 8.5	*Microcystis* spp.	MC-LA, MC-RR, MC-LR, Desmethyl-MC-LR, MC-LF, MC-YR	2.9 million[e]	Found within 1 km of the ocean	Miller et al. (2010)
	Big Basin Watershed Pajaro River Watershed Salinas River Watershed Camel River Watershed	*Microcystis aeruginosa*	MC-LR, MC-RR, MC-YR, MC-LA	8.2 ng/g[f] 9.0 ng/g[f] 62.7 ng/g[f] 104.3 ng/g[f]	Results presented as a range by watershed, specific marine values not reported	Gibble and Kudela (2014)

[a] Reported as MC-LR equivalents.
[b] MC from the upper St. Lucie Estuary due to an incursion of CyanoHABs from Lake Okeechobee.
[c] Integrated sample.
[d] MC variants detected in freshwater mussels collected from upstream portions of the Klamath River in 2009.
[e] Pinto Lake was initially identified as having high MC production with subsequent transfer to Monterey Bay. However, it cannot be confirmed that this was the MC source that affected marine otter health (Miller et al., 2010; Gibble and Kudela, 2014).
[f] Samples from Solid Phase Adsorption Toxin Tracking (SPATT).

Sound, Washington, MCs originating in two freshwater lakes were first documented in marine mussels in 2012 (Preece et al., 2015a). The following year, MC was detected in the same lakes, corresponding drainage streams, Puget Sound receiving waters and marine mussels (Preece et al., 2015b).

4.1.2. Reservoirs

Reservoirs are often managed so that water is discharged when seasonal rains cause storage capacity to be exceeded. For instance, in 2009 an extended bloom of *Planktothrix rubescens* was present in Lake Occhito, the largest artificial reservoir in Italy. After a series of heavy rainfalls, water was discharged to the River Fortore, which flows into the Adriatic Sea (De Pace et al., 2014). A few small, deteriorated cells of *P. rubescens* were visible in seawater and MC was subsequently detected in marine mussels and fish (Tables 2 and 3; De Pace et al., 2014).

The artificial Isahaya Reservoir, Japan discharges water into Isahaya Bay, during or after precipitation events (Umehara et al., 2015). The reservoir was constructed by enclosing portions of Isahaya Bay, an inner bay of the Ariake Sea on the western coast of Kyushu, Japan. Since completion of the Reservoir in 1997, water quality has steadily deteriorated. CyanoHABs, often dominated by *M. aeruginosa*, now occur annually (Migita et al., 2006; Umehara et al., 2012). Studies have confirmed freshwater-derived MCs are polluting reservoir outflows, seawater and Isahaya Bay sediments (Umehara et al., 2012, 2015). Due to high salinity, no cyanobacterial blooms have occurred in the bay itself (Umehara et al., 2015).

4.1.3. River-dominated Estuarine and Marine areas

In river-dominated estuarine systems, CyanoHABs may be flushed into the system from upstream lakes or reservoirs. If there is sufficient residence time, CyanoHABs can continue to grow and produce MCs within the estuary. This happened recently in the St. Lucie Estuary, Florida which is connected via a series of canals to the St. Lucie and Caloosahatchee Rivers and ultimately to Lake Okeechobee. Lake Okeechobee, Florida, is a natural lake, but expansion to increase storage volume has changed runoff and drainage patterns and the lake is now operated like a reservoir. Exceptionally strong tropical storms in 2005 and 2013 forced reservoir operators to increase outflow from the lake and toxic *M. aeruginosa* blooms were flushed downstream into the St. Lucie Estuary (Ross et al., 2006; Phlips et al., 2012; Lapointe et al., 2015). Heavy rain storms in 2016 again led to reservoir releases and caused an incursion of toxic *M. aeruginosa* bloom into the St. Lucie Estuary. Once toxic cells reached the estuary, *M. aeruginosa* continued to grow due to slow water movement and extended residence times (USACE, 2016).

Toxin-producing CyanoHABs in the Klamath River, Oregon were first identified in 2005. Since then blooms have occurred annually, often in exceedance of 10^5 cells/ml (Jacoby and Kann, 2007). Large blooms generally form upstream in Copco and Iron Gate Reservoirs, then travel downstream throughout the river, continue to grow in river margins and eventually reach the lower estuary (Fetcho, 2008; Otten et al., 2015). Otten et al., 2015, found large quantities of intact *M. aeruginosa* cells can travel over 300 km from the site of production to Klamath estuary receiving waters. Interestingly, co-occurring *Aphanizomenon* cells were progressively lost over 50–100 km, possibly due to head pressure from hydroelectric turbines that may have caused *Aphanizomenon's* relatively weak gas vesicles to collapse (Kromkamp et al., 1986; Otten et al., 2015). Even during the long distance transport, *M. aeruginosa* assemblages remained highly toxic and MCs were detected in estuary waters (Fetcho, 2011; Otten et al., 2015) and in freshwater mussels collected from several sites throughout the lower estuary (Kann et al., 2010).

In 2009, twenty-one federally threatened southern sea otters died from MC poisoning near the mouth of the Pujari River in southern California. MC was detected in the Pujari River and in two smaller rivers that empty into Monterey Bay. At the time of the poisonings, very high MC concentrations were reported in upstream Lake Pinto (Table 2). However, a follow-up study determined freshwater inputs from small and large rivers within the four major watersheds draining into Monterey Bay were probable sources of the marine MCs (Gibble and Kudela, 2014).

Microcystis spp. was first detected in California's San Francisco Estuary in 1999 and blooms have since recurred annually (Lehman et al., 2005, 2008, 2010; Spier et al., 2013). It is thought that CyanoHABs typically form in slow moving, lacustrine areas of the Sacramento-San Joaquin Delta and then spread seaward into the San Francisco Estuary (Lehman et al., 2005). MCs have been found to cause adverse impacts to estuarine fish production in the region from direct toxicity and through exposure to MCs from the food web (Lehman et al., 2010). Wild mussels collected from four locations in San Francisco Bay also tested positive for MCs during

Table 3
Microcystin Concentrations in Seafood that Humans may Consume.

Location	Seafood	MC in muscle μg/kg	MC in other Organs/ Tissues, μg/kg	Source
Shellfish				
Adriatic Sea, Italy	Mussels (*Mytilus galloprovincialis*)	1.7–256.0	N/A	De Pace et al. (2014)
San Francisco Bay, California	Mussels	Max. 22.0	N/A	SFEI (2015)
	Mussels (*Mytilus trossulus*, *Mytilus galloprovincialis*)	Max. 416.23	N/A	Gibble et al. (2016)
	Oysters (*Crassotrea* spp.)	N/A		
Puget Sound, Washington	Mussels (*Mytilus trossulus*)	2.0–15.5	N/A	Preece et al. (2015a, 2015b)
Barataria-Terrebonne Estuarine Systems, Louisiana	Blue crab (*Callinectes spaidus*)	ND-105.0	Hepatopancreas: ND-820.0 Viscera: ND-65.0	Garcia et al. (2010)
James River Estuary, Virginia	Blue crab (*Callinectes spaidus*)	Avg. 20.0	Viscera: ~38.0	Wood et al. (2014)
Finfish				
Adriatic Sea, Italy	Carp (*Cyprinus carpio*), bogue (*Boops boops*), mackerel (*Scomber japonicas colias*)	0.42–3.0	N/A	De Pace et al. (2014)
Jacarepaguá Lagoon, Brazil	Tilapia (*Tilapia rendalli*)	Max 337.3	Liver: 0–31,100 Viscera: 0–67,800	Magalhães et al. (2001)
James River Estuary, Virginia	Blue catfish (*Ictalurus furcatus*)	26.0–93.0	N/A	Wood et al. (2014)
San Francisco Estuary, California	Striped bass (*Morone saxatilis*)	1.0–3.4	Liver: 340–1890	Lehman et al. (2010)

every month of the year, indicating that MCs in this region are persistent and not just a seasonal problem (Gibble et al., 2016). It remains unknown if MC accumulation is from toxins produced in the estuary, from upstream areas in the Delta or from both sources. Recent work shows 2011–2014 MC peaks in water from San Francisco Bay appear to be related to river hydrology suggesting freshwater origins (SFEI, 2015).

4.2. Factors that affect MCs in receiving waters

4.2.1. Weather events

A common observation among these waterbodies is the impact seasonal weather events and major storms have on MCs movement from freshwater to coastal ecosystems. In lakes and river-dominated estuaries seasonal discharge patterns appear to greatly influence toxin transport with MC peaks often occurring in receiving waters during periods of high flows (Gibble and Kudela, 2014; Preece et al., 2015a, 2015b; SFEI, 2015; Gibble et al., 2016). Seasonal weather patterns and large storm events also affect operational strategies of reservoirs. Operators often release large discharges during and after high rainfall events, regardless of water quality within the reservoirs (De Pace et al., 2014; Lapointe et al., 2015; Umehara et al., 2015). Climatic changes including hydrologic perturbations from intense storm events and prolonged droughts followed by increased rainfall events will lead to increased freshwater inputs that transport nutrients and dilute coastal receiving waters. These factors are expected to promote CyanoHABs and increase MC occurrence in coastal environments (Paerl and Huisman, 2009; Funari et al., 2012; Paerl and Otten, 2013). This hypothesis is supported by a recent study in the San Francisco Bay region that showed prolonged drought led to estuarine expansion of *Microcystis* and ensuing rain events caused ephemeral discharge to disperse MCs into the coastal environment (Gibble et al., 2016).

4.2.2. Distance

Although data remain limited, several studies shows MC can travel great distances. For instance, toxic *Microcystis* was found to travel over 265 km from Milford Lake Kansas to Kansas City via the Kansas River (Graham et al., 2012). Many examples described above also demonstrate transport of toxic cells, but the Klamath River case highlights the great distance *Microcystis* can travel to estuarine receiving waters (Fetcho, 2011; Otten et al., 2015). This capacity to travel long distances combined with ability of cells to pass intact through hydroelectric turbines illustrates the persistence of MC-producing CyanoHABs (Otten et al., 2015). This suggests numerous lakes and reservoirs, not just those in the immediate coastal vicinity, are potential sources for MC contamination in coastal waters.

4.2.3. Microcystin Production

In the studies above, *M. aeruginosa* is the primary species to produce MCs in freshwaters that discharge into coastal environments. This is not surprising given *Microcystis* spp. is the most common CyanoHAB in freshwater ecosystems. However, there is one notable exception, the case of Lake Occhito and the Adriatic Sea. Here, *P. rubescens* were persistent and produced MCs levels that caused serious management problems (De Pace et al., 2014). Although *M. aeruginosa* appears to be responsible for much of the MC presence in coastal waters, the Adriatic Sea example presents good evidence for the need to monitor all MC producing CyanoHABs.

5. Human health and microcystins in Marine and Estuarine environments

Expansion of CyanoHABs and spread of freshwater derived MCs into estuarine and coastal ecosystems presents many environmental and human health issues. In waterbodies with non-potable water, MC exposure may occur during recreational activities or from consuming contaminated seafood (Dörr et al., 2010; Backer et al., 2008; Miller et al., 2010; Ferrão-Filho and Kozlowsky-Suzuki, 2011). While there are few reported cases directly linking human health effects from foodborne MCs, a growing body of evidence shows MCs can accumulate and persist in aquatic food-webs (Smith and Haney, 2006; Lehman et al., 2010; Poste and Ozersky, 2013), including seafood that humans consume (e.g. Poste et al., 2011). The case of California sea otters dying from consuming MC-contaminated bivalves supports the hypothesis that higher trophic levels, including mammalian carnivores, can be exposed to toxic levels of MC transferred through the food web (Miller et al., 2010). In addition, two cases in China where MC was detected in human blood serum illustrate how chronic exposure to MCs through consumption of contaminated fish, shrimp and snails may affect human health (Chen et al., 2009; Li et al., 2011). Results from one of these studies suggest chronic MC exposure may be associated with childhood liver damage in the Three Gorges Reservoir Region, China (Li et al., 2011).

Based on potential health risks from MCs in seafood, human health guidelines have been developed for MCs in food (WHO, 2003; Ibelings and Chorus, 2007; Mulvenna et al., 2012). The WHO established a tolerable daily intake (TDI) for daily lifetime exposure of 0.04 μg/kg/day for MC-LR (WHO, 2003). Based on this TDI, a seasonal daily exposure TDI for MCs in seafood was developed for adults (300 μg/kg/day) and children (40 μg/kg/day) (Ibelings and Chorus, 2007). To define acceptable daily limits of MCs in seafood, a scientific advisory group in Australia used the No Observed Adverse Effect Level (NOAEL) of 40 μg/kg/day (Mulvenna et al., 2012). Health guideline values for MC defined in this study for Australian and New Zealand adults was 39 μg/kg for fish and prawns and 83 μg/kg for mussels/molluscs. For children 16 and under the acceptable daily limit was calculated as 24 μg/kg for fish, 32 μg/kg for prawns and 51 μg/kg for mussels/molluscs (Mulvenna et al., 2012).

Worldwide, large numbers of people in coastal regions rely on collecting and eating foods from nearshore environments (Hauser-Davis et al., 2015). Both wild and aquaculture seafood from lagoons, estuaries and nearshore marine coastal environments may be at high risk of MC-contamination when CyanoHABs are present. The few published studies available support this notion, with MC concentrations often above suggested health guidelines in estuarine and marine seafood when CyanoHABs are, or have been present (Table 3). Both shellfish and finfish have been shown to accumulate MCs in amounts considered as high risk for human consumption (e.g. Poste et al., 2011; De Pace et al., 2014). Because shellfish and finfish are often prepared differently prior to consumption, they are discussed separately below.

5.1. Shellfish

Shellfish consumption may present the greatest threat for MC trophic transfer to humans because the entire organism, apart from the shell, is usually consumed. Further, evidence shows shellfish depurate the toxin slowly (Miller et al., 2010) and recent research suggests some shellfish may never completely depurate MCs (Paldavičienė et al., 2015). Thus MCs may be present in shellfish even when toxins are not detectable in the water column.

MC accumulation in freshwater mussels has been well documented (e.g. Watanabe et al., 1997; Yokoyama and Park, 2002; Chen and Xie, 2005; Paldavičienė et al., 2015). A growing number of studies have also confirmed MC accumulation in saltwater mussels (Table 3). Besides the California sea otter case that links MC-contamination in marine shellfish with MCs from freshwater sources (Miller et al., 2010), high levels of MC (max

256 μg/kg) were also found in marine mussels (*Mytilus galloprovincialis*) from the Adriatic Sea exposed to MCs from freshwater sources (De Pace et al., 2014). This latter case resulted in widespread shutdown of mussel commerce in areas of the Adriatic Sea where MC was detected (De Pace et al., 2014). Shortly after the Adriatic study was published, Puget Sound Washington mussels (*Mytilus trossulus*) exposed to freshwater discharges from lakes with CyanoHABs were found to contain MCs (Table 3). These concentrations exceeded consumption criteria values calculated with the WHO TDI and local seafood consumption rates for certain Puget Sound tribal members (Preece et al., 2015a, 2015b). A similar situation occurred in San Francisco Bay where MCs, likely originating in the Sacramento-San Joaquin Delta, were detected in 82% of sampled mussels in 2012 and 100% of mussels in 2014 (SFEI, 2015). MC concentrations in mussels (max: 22 MC μg/kg) were close to regulatory closure guidelines (24 μg/kg) recommended by the WHO (SFEI, 2015). A subsequent study found some San Francisco Estuary mussels contained very high MCs (max: 416 μg/kg), and Tomales Bay (adjacent to San Francisco Bay) aquaculture oysters purchased from a local commercial vendor had low, but detectable levels of MCs (Gibble et al., 2016).

In bivalves, crabs and other shellfish, MC concentrations are generally highest in the hepatopancreas and other viscera, but the toxin can also accumulate in the more frequently consumed muscle (Chen and Xie, 2005; Garcia et al., 2010). Two studies have confirmed MC accumulation by crabs in coastal environments (Garcia et al., 2010; Wood et al., 2014). In the Barataria-Terrebonne Estuarine Systems, Louisiana and the James River Estuary, Virginia, blue crab (*Callinectes spaidus*) muscle, viscera, and hepatopancreas exhibited levels of MCs that exceeded the WHO-TDI guidelines for human consumption (Garcia et al., 2010; Wood et al., 2014).

5.2. FinFish (fish)

Numerous studies have documented MC presence in tissues of freshwater fish (e.g. Papadimitriou et al., 2009; Poste et al., 2011; Hardy et al., 2015), but few studies are available on MC accumulation in estuarine or marine finfish consumed by humans. In fish, like other vertebrates, MCs primarily accumulate in the liver (Carmichael, 1992). Unlike shellfish where humans often consume the MC target organ, livers, and other fish organs are generally removed prior to consumption. Nonetheless, fish muscle can accumulate high levels of MCs, thereby creating a route of MC exposure for humans (Magalhães et al., 2001; Poste et al., 2011).

The first reports of MCs in fish from coastal areas was in tilapia (*Tilapia rendalli*) harvested from the Jacarepaguá Lagoon, Brazil (Magalhães et al., 2001). In this study, MCs measured in fish muscle were above the recommended limit for human consumption; maximum MC measured in fish muscle (337.3 μg/kg) was approximately 42 times higher than WHO recommended consumption guidelines (Magalhães et al., 2001). Subsequent studies continued to detect high levels of MCs in fish muscle tissues (Hauser-Davis et al., 2015), eventually leading to a fishing ban in Jacarepaguá lagoon (Gomes et al., 2009).

Although the Jacarepaguá Lagoon is the only known estuary where finfish fishing has been closed due to MC-contamination, MCs have been detected in fish muscle in other estuarine systems. For example, MCs were detected in gizzard shad (*Dorosoma cepedianum*), threadfin shad (*D. petenense*), blue catfish (*Ictalurus furcatus*) and Atlantic menhaden (*Brevoortia tyrannus*) from the James River Estuary (Wood et al., 2014). In this study blue catfish was the only finfish species potentially consumed by humans (Table 3). However, the other fish species serve as prey for high trophic level fish thereby facilitating transfer of MCs to fish consumed by humans (Wood et al., 2014). Evidence for trophic transfer in an estuarine system has been provided by a study in the San Francisco Estuary which found highest MC levels in striped bass (*Morone saxatilis*) muscle (max 3.42 μg/kg) compared to other prey species (Lehman et al., 2010). More recently, low levels of MC (0.42–2.98 μg/kg) were detected in muscle tissues from carp (*Cyprius carpio*), bouge (*Boops boops*) and mackerel (*Scommber japonicas colias*) harvested from the Adriatic Sea (De Pace et al., 2014). Because seafood is not routinely screened for MCs, and research is geographically spotty, the full extent of MC accumulation by fish from coastal regions is likely underappreciated.

6. Conclusions

MCs have been detected in coastal environments across the world, spanning a large gradient in latitude and ecoregions and reports of CyanoHABs in many of these areas have increased since the early 2000s. Yet, the true geographic occurrence of MCs in coastal waters remains uncertain at this time, primarily due to a lack of field evidence. Growing awareness of cyanotoxins and consequent research may explain increased reports of MC contamination in the past 15 years. Recent findings of toxins in coastal environments may also be due to expanding human populations and associated nutrient loads that drive source CyanoHABs, coupled with more favorable environmental conditions related to climate alterations. In addition, new toxin-forming strains may have been introduced into coastal waters. Whether this is a case of increased sampling finding a phenomenon that was already present or early signs of a growing problem, climate change and continued anthropogenic modifications are certain to escalate MC presence in coastal environments in the foreseeable future (Paerl and Huisman, 2009; Paerl and Paul, 2012; Michalak et al., 2013).

Risks for human exposures to MCs, including from foodborne contamination, will likely increase as CyanoHABs expand their range in estuaries and as MC from inland waterbodies more frequently impact coastal waters. Exposure risks will also be driven by increased human demand for, and reliance on, seafood. Fortunately there are examples where restoration and better management have improved water quality and decreased CyanoHAB occurrences (e.g., Neuse River Estuary, North Carolina and the Golden Horn Estuary, Turkey; Paerl and Otten, 2016; Taş et al., 2009). However, such efforts are usually initiated when the severity of the problems reaches a crisis stage, which translates into amplified expenses and complexity. Further, management plans typically focus on CyanoHABs as a freshwater concern. Now that evidence demonstrates that CyanoHABs affect waters throughout the freshwater-marine continuum, freshwater management decisions must look beyond lacustrine systems. Monitoring seafood species that may be exposed to MCs from inland sources is highly recommended for the protection of human health.

We assert that evidence cited in this review demonstrates the importance of expanding research and monitoring of MC producing CyanoHABs throughout the freshwater-marine continuum. Specifically, there is a need for studies to address how climate change will affect phytoplankton community dynamics in coastal waters. This issue is complex, and impacts will likely differ based on geographical location. Nonetheless, a better understanding of how climate change affects CyanoHABs in coastal waters will help scientists, water managers and human health officials take necessary steps to protect environmental and human health. This objective can be met in part by instituting long term studies to determine how changes occur over time. This review also highlights the ability of CyanoHABs and MCs ability to travel long distances. Additional information on maximum distances MCs can travel will help managers predict the impact of inland CyanoHABs on coastal receiving waters. This will be especially important in the context of climate change, since enhanced freshwater flows are expected to increasingly affect coastal environments.

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