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Review

Health impacts from cyanobacteria harmful algae blooms: Implications for the North American Great Lakes

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ABSTRACT

Harmful cyanobacterial blooms (cHABs) have significant socioeconomic and ecological costs, which impact drinking water, fisheries, agriculture, tourism, real estate, water quality, food web resilience and habitats, and contribute to anoxia and fish kills. Many of these costs are well described, but in fact are largely unmeasured. Worldwide cHABs can produce toxins (cyanotoxins), which cause acute or chronic health effects in mammals (including humans) and other organisms. There are few attempts to characterize the full health-related effects other than acute incidences, which may go unrecorded. At present these are difficult to access and evaluate and may be ascribed to other causes. Such information is fundamental to measure the full costs of cHABs and inform the need for often-costly management and remediation. This paper synthesizes information on cHABs occurrence, toxicology and health effects, and relates this to past and current conditions in the Great Lakes, a major global resource which supplies 84% of the surface water in North America. This geographic region has seen a significant resurgence of cHABs since the 1980s. In particular we focus on Lake Erie, where increased reporting of cHABs has occurred from the early 1990's. We evaluate available information and case reports of cHAB-related illness and death and show that cHABs occur throughout the basin, with reports of animal illness and death, especially dogs and livestock. Lake Erie has consistently experienced cHABs and cyanotoxins in the last decade with probable cases of human illness, while the other Great Lakes show intermittent cHABs and toxins, but no confirmed reports on illness or toxicity. The dominant toxigenic cyanobacterium is the genus *Microcystis* known to produce microcystins. The presence of other cyanotoxins (anatoxin-a, paralytic shellfish toxins) implicates other toxigenic cyanobacteria such as *Anabaena* (*Dolichospermum*) and *Lyngbya*.

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1. Introduction

The term harmful algal blooms (HABs) was first applied to blooms of marine algae, largely dominated by eukaryotic flagellates and diatoms that produce toxins and/or have other serious negative effects. Currently HABs refer to marine and inland, brackish and freshwater blooms that lead to poisonous seafood, mortality of fish and other animals, economic impacts, losses to aquaculture enterprises, and long-term ecosystem changes. Harmful effects include human illness and mortality from direct consumption of the toxins or indirect exposure to organisms that accumulate the toxins or the toxins themselves. Freshwater harmful algae bloom toxins also affect animals, birds, fish and other eukaryotes causing livestock and fish mortalities. The accumulated cell mass and production of volatile metabolites cause taste and odour in water, fish and shellfish, foul shorelines and industrial and drinking water intakes, and cause beach closures and losses to fisheries, recreational, food and real estate industries (Paerl, 2008; Cheung et al., 2013; Watson et al., 2015). Equally important, but often overlooked, are the detrimental effects that HABs have on ecosystems, suppressing other primary producers and reducing foodweb resilience and biodiversity due to habitat degradation, disease, and impaired community structure. Massive bloom dieback and decomposition can lead to oxygen depletion resulting in fish kills, and associated anoxic sediment release of nutrients, metals and gasses.

In brackish and fresh inland waters, HABs have widespread and often severe socioeconomic and ecological effects, particularly blooms dominated by cyanobacteria (cHABs) which are currently by far the most common causes of harmful blooms and toxins in these waterbodies (Hudnell, 2008). With this increased awareness, research and management activities directed towards the mitigation and control of cHABs have increased—largely focused on their potential to produce toxins and decrease water quality. In most cases the actual risk from toxins is not well characterized, in part because the mechanisms driving bloom toxicity are still unresolved. Few attempts have been made to characterize the full health-related and other socioeconomic effects of freshwater blooms, largely because they are often unrecorded, attributed to other causes, or the records are difficult to access. We feel it is important to fully characterize these harmful effects to provide a balanced assessment of the cost of their management and remediation.

While cHABS occur globally, they have become increasingly important in the Laurentian Great Lakes of North America, which collectively represent approximately 20% of the world's fresh water and 84% of the surface water supply in North America. The Great Lakes Basin is home to some 35 million people, and despite lake-wide restoration efforts in the late 1900s, there have been a significant resurgence in cHABs in some of the most populated areas of these Lakes (Steffen et al., 2014).

In this paper we review and summarize the effects on animal and human health of cHABs and their toxins (cyanotoxins). This includes the general features of cHABs that affect their toxicity and occurrence, their general distribution, health effects and regulatory measures. In particular we report on Lake Erie, where combined human and climate-related impacts have led to an increase in cHABs from the 1990s to the present. We include material from a variety of sources, including the open literature, unpublished reports, case histories and personal communications from agency personnel and the general public, and undertake a systematic and comprehensive evaluation of the data gaps and health-related impacts of cHABs on humans and other organisms in the Great Lakes basin.

2. Cyanotoxins

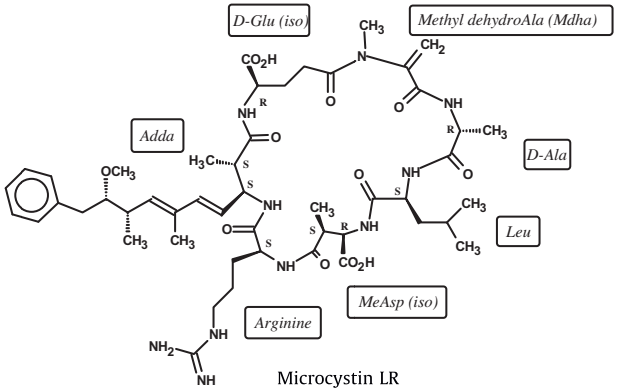
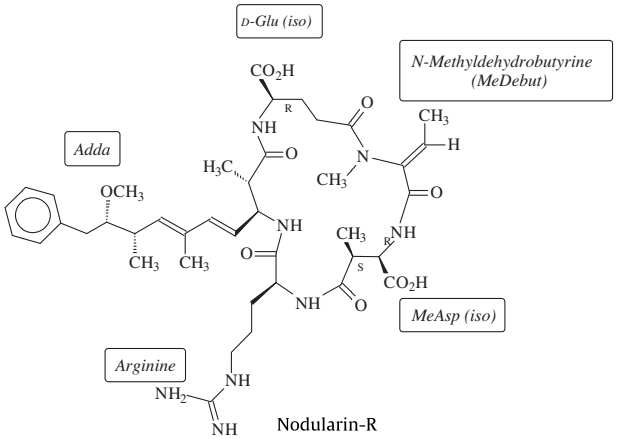
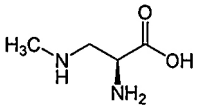
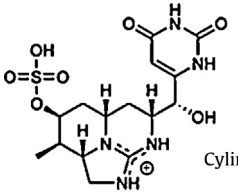
Starting with the chemical identification and mechanism of action, of the neurotoxin anatoxin-a (ATX-a) by the freshwater cyanobacterium *Anabaena* (syn. *Dolichospermum*) *flos-aquae* (Carmichael et al., 1975), a growing body of research has advanced our knowledge of these and other toxic metabolites, now called cyanotoxins. Cyanobacteria range from minute unicellular picoplankton (~1–2 μm) to lobed or clathrate colonies and large macroscopic branched and unbranched filaments that are several millimetres in size. Members of all of these morphotypes can produce a diversity of cyanotoxins. Cyanotoxins are responsible, worldwide, for illness and death of wild and domestic animals (aquatic and terrestrial) and human health issues ranging from contact irritations and gastrointestinal distress to acute, chronic and lethal poisonings.

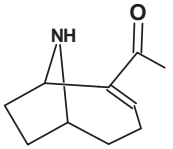
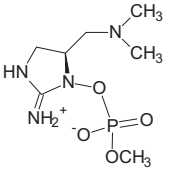
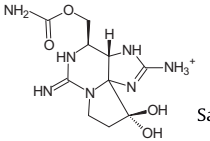
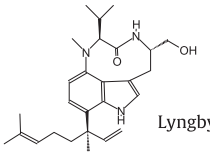
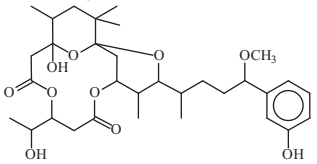
Cyanotoxins are generally classified into three major groups based largely on their primary toxicological effects; hepatotoxic peptides, neurotoxins and contact irritants. Their molecular structure and properties have been reviewed in several papers (Carmichael, 1997; Pearson et al., 2010; Merel et al., 2013; Table 1), and as new toxins and variants are identified, our knowledge of these compounds is expanding. However, our understanding of their health effects is based largely on animal assays (usually mouse, pig or rat), with some indirect data on humans taken from forensic and epidemiological studies (Hudnell, 2008). Only in a few cases have these studies been extended to chronic or teratogenic impacts on populations at risk (Meneely and Elliott, 2013).

2.1. Peptides

Cyanobacteria contain a large number of bioactive peptides (Smith et al., 2008), however most documented human and animal poisoning by cyanobacteria involves acute hepatotoxicosis, caused by a structurally similar group of small molecular weight cyclic hepta- and penta- peptides referred to as microcystins (MCs) and nodularins (NODs), respectively (Carmichael, 1997; Carmichael et al., 1988; Hudnell, 2008; Sarma, 2013a; Table 1). Nodularins are pentapeptides (ca. 9 variants) with a similar mode of action to MCs (Chen et al., 2013; Boopathi and Ki, 2014), however their production is generally limited to saline environments and terrestrial symbiotic associations (Gehringer et al., 2012) and will not be further discussed here. Microcystins are cyclic

Table 1
Summary of major cyanotoxins, known producers, toxicity, structure and occurrence within the Great Lakes Basin.

Toxin	Toxin-producing genera (reported worldwide)	Health effects; LD50 (i.p. mouse)	Structure of the major congener	Great Lakes Basin: cyanotoxin occurrence
Microcystins Microcystins (multiple congeners) Variations at positions 1, 2 in ring; e.g. MC-LR: leucine (L),arginine (R); MC-RR: arginine at both	*Dolichospermum* (*Anabaena*), *Anabaenopsis Aphanocapsa, Arthrospira, Hapalosiphon, Microcystis, Nostoc, Oscillatoria, Planktothrix, Snowella, Synechocystis, Woronichinia*	Hepatotoxins; Tumour Promoters; LD_{50} 25–>1000 μg/kg	>100 different congeners:  Microcystin LR	Widespread throughout Lake Erie, the embayments of Lake Ontario, Lake Huron and Lake Michigan.
Nodularins 5 amino acids Adda-γGlu-Mdhb-βMeAsp-Arg in core ring system.	*Nodularia*	LD_{50} 30–60 μg/kg	7 Known congeners:  Nodularin-R	General limited to saline environments, isolated reports in the inland lakes of the basin.
β N-methylamino-L-alanine (BMAA)	Some to many cyanobacteria	Neurodegenerative LD_{50} ND	1–8 Isomers of similar mass; only 1 congener 	Unknown. Not widely distributed in the free form.
Cylindrospermopsin	*Dolichospermum* (*Anabaena*), *Aphanizomenon, Cylindrospermopsis, Raphidiopsis, Umezakia*	General cytotoxin (liver, kidney, gastrointestine, heart, spleen, thymus, skin) LD_{50} 2.1 mg/kg (24 h) LD_{50} 200 μg/kg (5–6 days)	3 Known congeners:  Cylindrospermopsin	Cylindrospermopsis/ Raphidiopsis is locally present. Isolated unconfirmed reports of the toxin itself in the Great Lakes basin.

Anatoxin-a; homoanatoxin-a	*Dolichospermum* (*Anabaena*), *Aphanizomenon*, *Arthrospira*, *Cylindrospermum*, *Microcystis*, *Oscillatoria*, *Phormidium*, *Planktothrix*, *Raphidiopsis*	Neurotoxins LD_{50} 200–375 μg/kg	8 Reported Congeners:  Anatoxin-a	Lake Erie and embayments of Lake Ontario. Locally common in the inland lakes of the basin.
Anatoxin-a(s)	*Dolichospermum* (*Anabaena*)	Neurotoxin LD_{50} 20–40 μg/kg	1 Known congener  Anatoxin-a(S)	Unknown: Not currently monitored in Great Lakes area.
Paralytic shellfish toxins (saxitoxins)	*Dolichospermum* (*Anabaena*), *Aphanizomenon*, *Cylindrospermopsis*, *Lyngbya*, *Planktothrix*	Neurotoxin LD_{50} 10–30 μg STX/kg	57 Reported congeners  Saxitoxin (STX)	Widely present in the inland lakes of the Great Lakes basin. Present in the St Lawrence river.
Lyngbyatoxin A	*Lyngbya*	Possible gastro-intestinal inflammatory toxin 250 μg/kg (LD_{100})	 Lyngbyatoxin A	Not currently monitored in Great Lakes area.
Aplysiatoxin, debromoaplysiatoxin	*Lyngbya*	Dermal toxins; probable gastro-intestinal inflammatory toxin 107–117 μg/kg	 Debromoaphysiatoxin	Not currently monitored in Great Lakes area.

heptapeptides composed of five common amino acids, plus a pair of variable L-amino acids. Most of the differences in the ~130 variants (congeners) now described occur in these two variable regions, or at methylation sites around the molecule. A prevalent congener on a global scale is MC-LR (leucine/arginine variant), though this congener may not be the most toxic nor most common in the Great Lakes basin (see Section 4.2). Microcystins are produced by a variety of cyanobacteria; especially species belonging to the genus *Microcystis*. In particular, *M. aeruginosa* is widely identified in toxic cHABs in the Great Lakes and surrounding areas, but other *Microcystis* species such as *M. viridis*, *M. botrys* and *M. novacekii* are also reported producers (Murphy et al., 2003). Other MC-producing genera-found in the Great Lakes include *Dolichospermum* (syn. *Anabaena*), *Planktothix*, *Nostoc*, *Aphanocapsa* and *Oscillatoria* (Table 1, Fristachi et al., 2008).

Microcystins act primarily-through the inhibition of protein phosphatases 1 and 2A. Once ingested MCs are transported throughout the body where they enter the cell through the membranes organic anion transporter polypeptides (OATP). The primary target cells for MCs is the liver, where these OATP mediate their uptake into hepatocytes (Fischer et al., 2005), however these toxins can affect other tissues (kidney, reproductive tissue, colon, brain) that contain the appropriate OATPs (1A2, 1B1, 1B2, 1B3) (Chen et al., 2015). Expression of the OATP in the blood brain barrier may explain the neurological symptoms associated with human intoxication by MC in Brazil (Azevedo et al., 2002). Microcystin inhibition of eukaryotic serine/threonine protein phosphatases results in hyperphosphorylation of the key regulatory proteins in the signal transduction process that controls cytoskeleton organization (Meng et al., 2011). That damage is accompanied by oxidative stress to the liver, kidney, brain, and reproductive organs (Chen et al., 2015 and references cited within).

2.2. Neurotoxins

The alkaloid neurotoxin anatoxin-a (ATX-a; Table 1) is a potent post-synaptic depolarizing neuromuscular blocking agent and causes death within minutes to hours depending on the species, the amount of toxin ingested, and the amount of food in the stomach. Clinical signs of ATX-a poisoning follow a progression of muscle fasciculations, decreased movement, abdominal breathing, cyanosis, convulsions and death (Aráoz et al., 2010). No known antidote exists for ATX-a, although respiratory support may allow sufficient time for detoxification to occur followed by recovery of respiratory control. Anatoxin-a was originally isolated from a Canadian isolate of *Dolichospermum* (*Anabaena*) *flos-aquae* (Devlin et al., 1977), but is also reported in *A. planktonica*, *Oscillatoria* spp., *Planktothrix* spp., and *Cylindrospermum* (Aráoz et al., 2010). Homoanatoxin-a, a toxic homologue with a propyl group replacing the acetyl group, was isolated from *Phormidium* (*Oscillatoria*) *formosa*. The dihydroderivatives of anatoxin-a and homoanatoxin-a have also been reported in several *Phormidium* (*Oscillatoria*) species (Mann et al., 2012) and degradation products (ATX-a epoxide, dihydro-ATX-a) have also been reported in natural waters (James et al., 2005).

Species of *Dolichospermum* (*Anabaena*) (*A. flos-aque*, *A. lemmermannii* and *A. spiroides*) also produce another alkaloid toxin, the cholinesterase inhibitor anatoxin-a(s) (ATX-a(s)) (Aráoz et al., 2010). Anatoxin-a(s) is structurally unrelated to ATX-a; and was named due to salivation by intoxicated animals. ATX-a(s) is very toxic (Table 1) but somewhat unstable and inactivated at high temperatures (>40 °C) or alkaline conditions (Matsunaga et al., 1989). While there are no known human cases, toxicosis associated with ATX-a(s) has been observed in dogs, pigs and geese, with survival times of 5–30 min. Clinical signs of toxicosis include hypersalivation, lacrimation, mucoid nasal discharge, tremors, ataxia, diarrhea, recumbency and seizures prior to death (Mahmood and Carmichael, 1986). In addition, opisthotonos (rigid "s" shaped neck) is observed in avian species. The occurrence of ATX-a(S) has been reported in the United States and Canada but less often than the more common that ATX-a (Dörr et al., 2010). This has been attributed to the instability of ATX-a(S) in alkaline media, the lack of commercially available analytical standards, and fact that the common assay using acetylcholinesterase inhibition also responds to many common organophosphate pesticides (Devic et al., 2002).

Species of *Anabaena* (*Dolichospermum*), *Aphanizomenon*, *Cylindrospermopsis*, *Lyngbya* and *Planktothrix* produce the alkaloid family of neurotoxins referred to as paralytic shellfish toxins (PSTs). The PSTs found in cyanobacteria are structurally more diverse than the PSTs found in marine dinoflagellates with more than 58 congeners now reported (Wiese et al., 2010) and several "new" ones in the pipeline (M. Quilliam, NRC Halifax, Canada pers. communication). Australia has widespread occurrence of PSTs and related neurotoxins in blooms of *Dolichospermum* (*Anabaena*) *circinalis* in rivers and water storage reservoirs (Humpage et al., 1994). Saxitoxin analogues have been identified from the freshwater mat-forming cyanobacteria *Lyngbya wollei*, which is found in the southern and south central United States (Carmichael et al., 1997; Onodera et al., 1997; Foss et al., 2012). *L. wollei* is common in western Lake Erie and a few embayments of Lake Ontario (Bridgeman and Penamon, 2010; Boyer and Watson, unpublished); populations of this cyanobacterium are also found in Lake St Claire and the St Lawrence River where they have tested positive for these toxins (Lajeunesse et al., 2012; Vijayavel et al., 2013). *Cylindrospermopsis* from Brazil has been shown to produce PSTs (Lagos et al., 1999).

Most of the human health studies have used the parent compounds, saxitoxin and neosaxitoxin (Carmichael, 1997; Batoréu et al., 2005). These sodium channel blocking agents inhibit transmission of nervous impulses and lead to death in animals by respiratory arrest. The biological activity of many of the PST analogues produced by cyanobacteria is poorly understood in comparison to those historically found in dinoflagellates (Wiese et al., 2010)

The tricyclic guanidine cylindrospermopsin (CYN) is also an alkaloid cyanotoxin, but does not lead to neurotoxicosis but rather hepato and renal toxicosis (de la Cruz et al., 2013). Cylindrospermopsin was first identified from *Cylindrospermopsis raciborskii* and first implicated in a cHAB event in North Queensland (Australia) in 1979, and which led to severe hepatoenteritis in 138 people (Hawkins et al., 1985). Since then CYN and/or its two congeners epi-cylindrospermopsin and deoxycylindrospermopsin have been found in *Dolichospermum* (*Anabaena*), *Umezakia*, *Aphanizomenon* and *Raphidiopsis*. Beginning about 1995, toxic strains of *C. raciborski* were identified in eutrophic Florida lakes (Chapman and Schelske, 1997; Frey, 2004) and this taxon has since been found in ever expanding areas, especially in the Midwest (Holland et al., 2006; de la Cruz et al., 2013). To date CYN has not been found in the Great Lakes.

2.3. Bioactive amino acids

Another bioactive peptide produced by cyanobacteria, different in action from MCs, is ß-methylamino alanine (BMAA, Table 1). Consumption of flour prepared from the cycad seeds containing this metabolite was proposed in the 1960s to lead to amyotrophic lateral sclerosis or Parkinsonism dementia, based on a study of indigenous Chamorro people (Guam). Questions arose about the levels of BMAA in the flour required for these symptoms (Duncan, 1992), which were resolved when it was recognized that BMAA was produced by a cyanobacterial root symbiont (*Nostoc* sp.) living

in association with the cycad plant. Cycad seed were being consumed by flying fox bats, which were in turn consumed by the Chamorro as an important part of their diet (Murch et al., 2004; Cox et al., 2005). BMAA was subsequently detected in the brain tissue of Alzheimer patients in Canada and the United States, but not in the brains of other patients that died of other causes (Pablo et al., 2009). Cycads and their *Nostoc* symbiont were not a likely source of BMAA in these regions; thus other cyanobacteria were hypothesized as the sources. Free or protein-bound BMAA was found in numerous strains of planktonic, benthic and terrestrial cultures of cyanobacteria tested by Cox et al. (2005) and they proposed that widespread human exposure to this toxin may occur. These earlier studies were plagued by questions in methodology (Faassen, 2014), while other research (Jonasson et al., 2010; Bidigare et al., 2009) suggested that the BMAA concentrations in natural cyanobacteria may be much lower than reported. A detailed review of the analytical methodology for BMAA has been provided by Bienfang et al. (2011). Boyer and coworkers (unpublished) have used highly sensitive LC-MS/MS methodology to look for the presence of free BMAA in the Great Lakes phytoplankton. To date, free BMAA has not been detected in over two thousand samples tested. ß-methylamino alanine is, however readily biomagnified in some marine ecosystems and can accumulate in fish and shellfish (Jonasson et al., 2010; Christensen et al., 2012; Réveillon et al., 2015). The presence of bound BMAA and its potential for bioconcentration in species higher on the trophic level thus remains a possibility.

2.4. Endotoxins and contact irritants

Weise et al. (1970) were the first to isolate cytotoxic lipopolysaccharides (LPS) from the cyanobacterium *Anacystis nidulans*. LPS are an integral part of the cell wall of gram-negative bacteria, including cyanobacteria. They can elicit irritant and allergenic responses in human and animal tissues with contact. Cyanobacterial LPS is less potent than LPS from gram-negative bacteria (Stewart et al., 2006b), but may contribute to human health problems associated with occurrences of cHABs. Some researchers and health officials believe that some water-based cases of contact irritation and gastroenteritis are due to cyanobacteria LPS (J. Hyde, NYS-DOH, pers. communication, 2013). Stewart et al. (2006b), however failed to find robust evidence that cyanobacterial LPS have significant allergenic or irritant effects with normal exposure to these compounds. Swimmers itch or dermatitis in many Great Lakes waters can also be caused by a larval form of flatworms from the Schistosomidae family (*aka* cercarial dermatitis). Schistosomatidae are fairly common in many of the Great Lakes basin and indeed, globally (Jarcho and van Burkalow, 1952; Verbrugge et al., 2004), and produce symptoms quite distinct from the contact dermatitis from cyanobacterial LPS.

Species of *Lyngbya*, including *L. majuscula* and *L. wollei*, also produce a large array of bioactive natural products. Most work has focused on the marine species *L. majuscula*, which is widely known to produce the dermatoxic lyngbyatoxins and debromoaplysiatoxins (Taylor et al., 2014). Freshwater *Lyngbya* species, in addition to producing the neurotoxins ATX-a and PSTs, have also been reported to cause skin irritation and dermatitis in scuba divers coming in contact with *Lyngbya* blooms in the freshwater Florida springs (Burns, 2008). It was generally thought that these toxins did not occur in northern waters, in part because most cases of swimmers' itch in the waters surrounding the Great Lakes are attributed to cercarial dermatitis (Michigan DEQ, 2014). However the blisters and associated rash that occurred on the exposed skin after cleaning up "beach wrack" in *Lyngbya*-infested waters of Sodus Bay (Lake Ontario) were very consistent with exposure to *Lyngbya* dermatoxins (Werner et al., 2012; Boyer, unpublished), raising the possibility that dermatoxic strains do exist in northern freshwaters.

3. CHABs: General features, occurrence, health effects and regulatory measures

Worldwide, fresh, brackish and marine cyanobacteria have many of the same health and environmental effects as marine HABs. Animal poisonings from blooms of cyanobacteria in a water supply are part of the published record since 1878 (Francis, 1878). A comprehensive reference for the worldwide occurrence and history of toxic cyanobacteria can be found in a monograph by Codd et al. (2006) and in detailed reviews and books on toxic cyanobacteria (Chorus and Bartram, 1999; Falconer, 2004; Huisman et al., 2005; Hudnell, 2008; Sarma, 2013b).

Cyanobacteria are photosynthetic prokaryotes. Along with eukaryotic algae, they naturally co-exist as balanced planktonic assemblages in a diversity of lentic, lotic and coastal ecosystems. Their long evolutionary history (~3.5 billion years; Allen and Martin, 2007) has enabled them to adapt to numerous geochemical and climatic changes, and more recently, to anthropogenic stressors such as eutrophication, inter-basin exchange, hydrologic engineering, chemical pollution, drawdown and salinization (Paerl and Otten, 2013). Many cyanobacteria exhibit optimal growth rates and bloom potential at relatively high water temperatures; hence global warming plays a key role in their expansion and persistence (Paerl and Paul, 2012; Paul, 2008).

Importantly, cHAB predictability and risk are greatly influenced by factors such as nutrient supplies, hydrology and weather, as reviewed in detail by a number of authors (e.g. Paerl, 2008; Boopathi and Ki, 2014, see also articles in this special journal issue). Importantly, these factors operate over different time scales to influence spatial–temporal bloom dynamics, and the associated risk of human exposure. The timing, levels and chemical composition of nutrient supplies often control overall bloom magnitude, and influence their species composition and duration. Blooms generally occur in the summer and fall months and can be more frequent in times of drought. As the number of algal cells in water increases, the risk of serious issues also increases. The decay of settled bloom material in the benthos leading to anaerobic conditions, and potential for these conditions to release of nutrients from sediments back to the water column, can fuel further bloom growth. This scenario is particularly problematic in long-residence time (i.e. months) systems, where it can exert a strong positive feedback on future events (Paerl, 2008; Paerl and Otten, 2013).

The World Health Organization (WHO) defines problem blooms as populations of algal cells exceeding 100,000 cells/mL (Chorus and Bartram, 1999). This definition is often problematic, given the significant range in cell size and secondary morphology (i.e. formation of filaments or colonies) and toxin content/cell among and within strains, populations, species and genera. There are no standard practices for bloom monitoring and assessment, and due to limited capacity, agencies often carry out sampling on a reactive basis in response to public complaints. Individual jurisdictional and health agencies may have different standards, and differ in the scope of their analyses of specific toxins (Chorus and Bartram, 1999; Chorus, 2005, 2012). Light microscopy methods traditionally used to identify cyanobacteria are also problematic. There are often inconsistencies in species identification and nomenclature, making it difficult to compare different studies. Cyanobacteria are highly variable in morphology and many of the diagnostic features that are traditionally used to identify these taxa are affected by environment and growth stage (Yoshida et al., 2008). With the increasing development of genetics and biochemical diagnostics,

many of the earlier systematics have been extensively revised using a 'polyphasic approach', combining physical, physiological, biochemical and genetic traits (Komárek and Anagnostidis, 1998, 2005; Komárek, 2013, 2012). Nevertheless, it remains a challenge to reconcile existing literature and reports where species are identified using different synonyms or taxonomic keys.

The North American cHAB history is mostly documented from the US, and likely originated as indigenous peoples' knowledge of the potential implication of seasonal changes in the color of inland waters (Carmichael and Stukenberg, 2006). Cyanobacteria harmful algae blooms had been reported in more than 35 US states by 2008 (Fristachi et al., 2008) and recent increases monitoring for algal toxins indicate they are likely present in all 50 states (US-EPA, 2012). The earliest documented investigation in the US into the toxic potential of cyanobacteria was recorded in The Bulletin of the Minnesota Academy of Science (Arthur, 1883), though the first written description of an outbreak was made in 1925 when a farmer lost 127 hogs and four cows after they drank from Big Stone Lake in South Dakota. Examination of the lake water showed the presence of cyanobacteria and the livestock deaths were thus attributed to 'algal poisoning' (The Wilmot Enterprise, September 14, 1926). A few years later, a description of five Minnesota cases of animal 'algal poisoning' was published in the Cornell Veterinarian (Fitch et al., 1934).

There were few reported cases of human or animal illness linked to algal blooms during the 1900s, but these showed a gradual increase in animal poisonings with an annual average of 5–10 reports between the 1930s through to the 1970s, increasing to twelve in the 1980s and nineteen in the 1990s (Carmichael and Stukenberg, 2006). The first serious human poisoning event was described in 1931, when a significant outbreak of intestinal illness in more than 5000 people in Charleston, West Virginia was linked to contaminated drinking water from the Ohio and Potomac Rivers during a massive *Microcystis* bloom. The treatment process used at the time (precipitation, filtration and chlorination), and still in place in many small communities in North America, was ineffective against this bloom (Miller and Tisdale, 1931). In other cases, cHABs were linked to cases of gastrointestinal disorders in 1968 (Schwimmer and Schwimmer, 1968), chills, fever and hypertension in 23 dialysis patients in 1974 (Hindman et al., 1975), and gastrointestinal and skin maladies in 2004 (Walker et al., 2008).

We note that there is a potential inaccuracy in these statistics, as reporting such events in the US has always been voluntary. As some of the symptoms of mild toxin exposure, such as gastrointestinal, ear, eye and dermal irritation, are also symptomatic of flu, food poisoning or other illnesses, many cases may not be directly linked to cHAB exposure and can go unreported. Since 1971, however, in a US-EPA and Centers for Disease Control and Prevention (CDC) cooperative effort, surveillance data from waterborne outbreaks have been more consistently compiled and more conclusively upheld as cyanobacteria-related (Lopez et al., 2008). Beginning in 2007, the CDC supported a Harmful Algal Bloom-related Illness Surveillance System (HABISS) where 11 states contributed reports for 3500 freshwater bloom events between 2007 and 2011 (Backer et al., 2015). Most of these represented routine monitoring information, but MCs were identified in 2629 samples. States reported more than 175 animal mortality events and contributed 57 case reports of human illnesses identified with exposures to cyanobacteria or their toxins. Rashes from unknown organism or toxin accounted for another 90 cases. In the 52 case reports specifically identified as exposure to cyanobacteria, exposure to *Microcystis* was the most common (28 cases or 54%), followed by exposure to *Anabaena* sp. (20 or 38%) and *Aphanizomenon* species (4 or 8%).

A 1996–1998 survey of 45 drinking water supplies in Canada and the US showed detectable levels of MC in 80% of the raw and treated water surveyed, but these exceeded the WHO drinking water guideline of 1.0 μg/L (Table 2) in only 4% of the samples (Carmichael, 2001a). Several comprehensive surveys for cyanotoxins in US water bodies were completed more recently. Between 2000 and 2004, an extensive survey of 81 lakes in New York and the lower Great Lakes showed detectable levels of MCs in nearly 60% of the 2500 samples collected during bloom season, 15% of which exceeded the WHO advisory limit (Boyer, 2008). Perhaps the most extensive survey on the distribution of cyanobacteria toxins in the United States was conducted by the US EPA as part of the National Lakes Assessment in 2007 (US-EPA, 2007). Over 1150 random lakes were sampled during the summer growing season for cyanobacteria and cyanobacteria toxins (CYL, MCs and PST) by ELISA. Microcystins were the most abundant and detected in 32% of the lakes, followed by PSTs (7.7%) and CYL (4%). The occurrence of potentially toxic cyanobacteria species was widely distributed and found in over three quarters of the lakes. For those cases where MCs were analysed, only nine (0.7%) lakes exceeded WHO recreational guidelines (20 μg/L), while 143 (12%) lakes exceeded WHO drinking water guidelines (1.0 μg/L). Lakes were sampled for MCs again in 2011 (US-EPA, 2012) using similar methodology, and MCs were found in 24% of the 692 lakes tested, of which only 1% exceeded 1.0 μg/L.

In Canada, there are few records of human illnesses related to cHABs, although there are numerous anecdotal reports of livestock deaths, most notably from the Prairie region where these blooms are widespread and often severe in many of the small eutrophic lakes and dugouts used for domestic and agricultural consumption (Carmichael and Stukenberg, 2006). The issue of cHABs and toxins

Table 2
Canadian and United States Guidance Values or Standards and other national regulations or recommendations for managing cyanotoxins in drinking water compared to World Health organization (WHO) guidelines.

Country/source document	Cyanotoxins and/or Cyanobacteria addressed	S, (P)GV, (P)MAV, (P)MAC or HAG**	Comments: Specific action in case of derogation.
World Health Organization (WHO)	Microcystin-LR	1.0 μg/L	Guidelines based on cell concentrations rather than on cyanotoxin concentrations.
Canada	Microcystin-LR	MAC: 1.5 μg/L	MAC for MC-LR considered protective against exposure to other MCs. Monitoring frequencies driven by bloom occurrence and a history of bloom formation.
	Anatoxin-a	PMAC: 3.7 μg/L	Regulated only in Quebec.
United States of America	Microcystin-LR	HAG: 0.3 μg/L for 0–6 yr old 1.6 μg/L for school age to adult	HAG is based on a 10-day average.
	Cylindrospermopsin	HAG: 0.7 μg/L for 0–6 yr old 3.0 μg/L for school age to adult	HAG is based on a 10-day average.
Australia	Microcystin-LR (totals)	PGV 1.3 μg/L microcystin LR equivelents	

** Standard (S); provisional guidance value ((P)GV); provisional maximum value or concentration ((P)MAV/(P)MAC)); health alert level (HAV); Health advisory guideline (HAG).

Table 3
Canadian and United States national regulations or recommendations for managing cyanotoxins in waterbodies used for recreation compared to WHO Guidelines.

Country/source document	Management framework; comments	Parameter regulated	Values	Actions taken/consequences of derogations
World Health Organization		Cell counts Microcystin-LR	≤100,000 cells/mL ≤20 μg/L	Guidelines based on cell concentrations rather than on cyanotoxin concentrations
Canada	Bloom risk management programs in some provinces	Cell Counts Microcystin-LR	≤100,000 cells/mL ≤20 μg/L	If either of guideline values is exceeded, a swimming advisory may be issued. Contact with posted waters should be avoided until advisory has been rescinded
United States of America	No national requirements, but action has been taken by many of the individual States. This includes indicators based on visual, chlorophyll-a, Secchi depth, cell counts and toxicity-based measurements (Radicello, 2015). Recreational guideline values based on cell counts currently range from 5,000 to 100,000 cells/mL, and guideline values based on microcystin-LR measurements range between 0.08 μg/L and 20 μg/L. US-EPA is currently reviewing state guidelines			

was formally recognized in 2002, when Health Canada set a finished drinking water guideline of 1.5 μg/L total MC-LR (Table 2), which was recently updated to include a guideline of 20 μg/L for total MCs in Canadian recreational waters. Drinking water falls under Provincial jurisdiction in Canada, and most provinces have adopted the Health Canada drinking water guideline. A number of provinces have also adopted the recreational guideline of 20 μg/L or lower (Giddings et al., 2012).

Health Canada in 2002 conducted a risk assessment review that classified MC-LR as "possibly carcinogenic to humans" placing it in Group IIIB (inadequate data in humans, limited evidence in experimental animals). For compounds in Group IIIB, the lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL) from the most suitable chronic or sub-chronic study is divided by an appropriate uncertainty factor, to derive a tolerable daily intake (TDI). Such an approach was used for MC-LR, which was the only cyanotoxin for which there is sufficient information available to derive a guideline value. A TDI of 0.04 μg/kg body weight per day was derived from a NOAEL of 40 μg/kg body weight per day for liver changes in a 13-week mouse study (Fawell et al., 1994), using an uncertainty factor of 1000 (×10 for intraspecific variation, ×10 for interspecific variation and ×10 for the less-than-lifetime study). A maximum acceptable concentration (MAC) of 0.0015 mg/L (1.5 μg/L) for MC-LR was calculated from the TDI by assuming a 70-kg adult consuming 1.5 L of water per day, as well as allocating 80% of the total daily intake to drinking water (the major route of exposure to these toxins is via drinking water). Although the MAC was derived for MC-LR, it is considered to be protective against exposure to other MCs (total MCs, i.e. free plus cell bound) that may also be present.

Recently, the US-EPA has issued drinking water health advisories for MCs and CYLs (Table 2). When developing these guidelines, the US-EPA considered not only chronic studies in laboratory animals, but also sub-chronic effects on the liver and kidney, reproductive effects and developmental effects. Using the EPA 2005 Guidelines for Carcinogen Risk Assessment, they decided there was inadequate information to assess the carcinogenic potential of MCs (US-EPA, 2015a). In contrast to the WHO guidance values, the US-EPA health advisories (US-EPA, 2015d) are based on a 10-d exposure, and include considerations for susceptible populations, specifically infants and children, whose formula may be prepared with tap water and whose mean drinking water ingestion rate is much higher than for adults. Based on these considerations, the US-EPA issued a 10-day drinking water health advisory for MCs of 0.3 μg/L for infants and children up to 6 years of age, and 1.6 μg/L for adults (US-EPA, 2015b). The 10-day health advisory values for CYLs are 0.7 μg/L for infants and children up to six years of age, and 3 μg/L for school age children older than 6 and adults (US-EPA, 2015c). There are currently no national guideline values for ATX-a or for recreational contact with cyanobacterial toxins in the United States, but actions have been taken by many of the States (Table 3) and more are likely to, in the aftermath of the drinking water event in Toledo Ohio (see section 7.0).

4. CHABs in the North American Great Lakes

With a total surface area of 244,000 km^2, the Great Lakes collectively serve as the largest and one of the most important providers of freshwater ecosystem services in North America. These services include the provision of drinking water to over 24 million US and Canadian consumers, wastewater processing, and support of agriculture, industry, shipping, power, fisheries, recreation and tourism. The drainage basin to these Lakes basin covers over 750,000 km^2 and includes major urban centres, rural and First Nations communities representing more than 10% of the US and 25% of the Canadian populations. The basin is jurisdictionally fragmented into two provinces, eight US states and multiple local and regional jurisdictional bodies. Significantly, nearly 25% of the total Canadian and 7% of the US agricultural production are located in the basin. Numerous smaller lakes in the Great Lakes basin provide recreational opportunities for inhabitants and visitors to this region. Cyanobacterial blooms and cyanotoxins are integral to many water bodies throughout the U.S. and Canada, especially in the summer and fall months. The USGS and USEPA surveys (USGS, 2006; US-EPA, 2007) also showed that the greater numbers of cHAB events occurred in the northern Midwest states, and the following section demonstrates that this situation extends to the Great Lakes area, where these events have shown a recent and significant resurgence.

The severe eutrophication and degradation of the Great Lakes during the last century led to the establishment of one of the world's largest and longest-standing restoration initiatives, which has operated since 1987 under the binational Great Lakes Water Quality Agreement (GLWQA). Early eutrophication resulted in severe and often spatially extensive algal and cyanobacteria blooms, targeted under the GLWQA for remediation in the 1970s. Widespread blooms (planktonic and attached, e.g. *Cladophora*) impaired offshore and nearshore areas in the Great Lakes in the 1960s and 1970s (Ashworth, 1986). Also present were cyanobacteria blooms dominated by filamentous nitrogen-fixing taxa such as *Aphanizomenon flos-aquae* as well as non-fixers including the potentially toxic cyanobacteria *Microcystis* and *Planktothrix* (Allinger and Reavie, 2013; Steffen et al., 2014). These blooms had multiple impacts (defined under the GLWQA as Beneficial Use Impairments): eutrophication or undesirable algae, restrictions on drinking water consumption or taste and odour, beach closures, degradation of aesthetics, costs to agriculture and industry and degradation of phytoplankton and zooplankton populations. Lake-wide restoration and nutrient reduction during the 1980s significantly reduced these issues but over the past decade there has been a significant resurgence of cHABs which are now dominated by more toxic taxa. Thus concern with cyanotoxins

in these lakes has escalated, particularly in Lake Erie. Cyanobacteria harmful algae blooms now occur annually in most of the Great Lakes, especially Lake Erie, Lake Huron (Saginaw and Sturgeon Bays), Lake Michigan (Green Bay) and nearshore areas of Lake Ontario (Bay of Quinte, Sodus Bay and Hamilton Harbour). A number of papers have documented the earlier remediation and recent resurgence of cHABs (e.g. Steffen et al., 2014; Scavia et al., 2014) but until this review, little has been published to on their impacts on animal and human health in the Great Lakes basin.

4.1. Toxic cHABs in the Great Lakes

Nutrient and bloom impairment differ widely among the Great Lakes, reflecting their sizes, morphometry and basin development (Watson and Boyer, 2009; Allinger and Reavie, 2013). There is little quantitative information on cHABs in Lake Superior, the largest, deepest and least developed of the Great Lakes. Severe blooms have not been documented in this lake, although low abundances of cyanobacteria, including *Microcystis*, are present in samples taken during routine monitoring. Lake Michigan is shallower than Lake Superior with a fairly extensive nearshore zone which has a strong influence on the lake ecosystem. Cyanobacteria blooms are reported in some coastal regions in eutrophic embayments of this lake, notably Green Bay and Muskegon Bay (Xie et al., 2011). Lake Huron is the second largest and one of the more oligotrophic of the Great Lakes, yet algal blooms and potentially toxic cHABs occur in some nearshore areas, notably Saginaw Bay (Fahnenstiel et al., 2008) and embayments such as Sturgeon Bay along the south-east Georgian Bay coastline.

The smallest, warmest and shallowest of the Great Lakes, Lake Erie, is also the most densely populated and this waterbody has a high vulnerability to algal blooms, both of cyanobacteria and eukaryotic taxa (notably diatoms). Water levels in Lake Erie typically fluctuate about 36 cm/yr, but there has been a steep decline in levels from a 1997 peak to below average during recent years, with significant fluctuations due to climate and storm events. This, together with the corresponding dynamics in the physical and chemical regime, has been accompanied by some disturbing trends in biota and system integrity. Not only does Lake Erie have the most extensive nearshore area, but as noted above, toxic cHABs in this lake are a particular concern and the focus of several recent studies (Stumpf et al., 2012; Ho and Michalak, 2015). The Lake Ontario Basin has extensive watershed development and urban input. Blooms of cyanobacteria and related impairments (cyanotoxins, taste and odour compounds) have been identified in both the embayments and nearshore areas on both the Canadian (Watson et al., 2008) and US side (Makarewicz et al., 2009; Perri et al., 2015; Boyer et al., 2015) of the lake.

Most focus on the great Lakes connecting channels is related to toxic contaminants and their role in the transport of water and nutrients into the Lakes; however, these systems are in fact also vulnerable to HABs, both planktonic and benthic. *Cladophora* has traditionally been an issue in many of these waterways, but recently, blooms of toxic *Microcystis* and the benthic cyanobacterium *Lyngbya* have been documented in Lake St Claire, and the Detroit and St Lawrence Rivers (Lajeunesse et al., 2012; Davis et al., 2014).

Since the mid to late 1990s, algal blooms in the Great Lakes have been increasingly dominated by cyanobacteria such as *Microcystis aeruginosa*, capable of producing harmful metabolites or toxins which were largely unrecognized or unmeasured in the earlier blooms in these Lakes (Brittain et al., 2000; Watson and Boyer, 2009; Steffen et al., 2014; Ho and Michalak, 2015). Phytoplankton surveys have shown an increasing trend for toxigenic cyanobacteria in the Great Lakes and surrounding areas since 2001 (Barbiero and Tuchman, 2001; Boyer, 2007; Winter et al., 2011). This significant species shift has been attributed by some authors to changes in regional climate and the bioavailability, sources and timing of nutrient inputs (Michalak et al., 2013; Steffen et al., 2014; Scavia et al., 2014). In addition, the widespread invasion of dreissenid mussels has had a profound effect on water clarity, nutrient recycling and food web structure in these Lakes, which may also facilitate dominance by these taxa (Higgins and Vander Zanden, 2010).

One of the earliest surveys for toxins in the Great Lakes was carried out by Murphy et al. (2003), who compared samples collected in the summer of 2001 from Hamilton Harbour (Lake Ontario), and two sites in the East Basin of Lake Erie, Wendt Beach and Presque Isle. Microcystin concentrations varied largely; most were below Health Canada drinking water guidelines but varied between 60 and 400 μg/L in wind-concentrated scum in Hamilton Harbour where the bloom was dominated by *Microcystis botrys*, *M. viridis* and some *M. wesenbergii*. Microcystin congener analysis showed a predominance of MC-RR, with MC-YR and MC-LR also present. Dying birds were seen in the cyanobacterial surface scum in Lake Erie, although MC concentrations were below 1 μg/L and the authors noted that the analytical methods used for MCs (ELISA and HPLC) are unable to measure the covalently-bound form that is assimilated into the food chain, and may have contributed to the total MC burden that the birds were exposed to. Toxic cyanobacterial blooms are observed annually in Hamilton Harbour and also in the Bay of Quinte (Lake Ontario) (Watson et al., 2003, 2008). More rigorous bloom monitoring and risk management program have been established in these eutrophic embayments, including a beach monitoring program by Hamilton Health (see below). Makarewicz et al. (2009) surveyed Lake Ontario embayments, ponds, rivers, creeks, shore side, and nearshore and offshore sites of Lake Ontario in the US for MCs. These authors reported low MC-LR concentrations (0.006–0.007 μg/L) in May which increased slightly through the summer, peaking in September (0.032–0.070) and then declining in October. Considerable variability in toxin concentrations was observed between and within the different waterbodies and between inshore and offshore sites in the lake itself. Perri et al. (2015) documented the occurrence of both ATX-a and MC during a three year study (2010–2012) of Sodus Bay, NY, with MC concentrations ranging from 0 to 60 μg/L and ATX-a levels ranging from non-detect to a maximum of 3.1 μg/L at a local marina.

Harmful and Nuisance Algal Blooms (HNABs) are now included as one of the Great Lakes Ecological Indicators, and assessed in the binational State of the Lakes Ecosystem (SOLEC) Reports and the US State of the Nation's Ecosystem Reports (The State of the Nation's Ecosystem Reports, 2008; Watson and Boyer, 2009, 2014a, 2014b). These assessments, however, face the challenge of integrating infrequent and unbalanced sample design and inconsistencies in the measurements and data collected (e.g. toxins, bloom composition and biomass, fluorescence etc.; Watson and Boyer, 2009, 2014a). The most recent status of these blooms in the Great Lakes was given as: Lake Superior: good, Lakes Michigan, Huron and Ontario: fair and Lake Erie: Fair to Poor (Watson and Boyer, 2014a). Watson and Boyer (2009) concluded that Lake Erie channels and embayments are among the most severely impacted areas of the Great Lakes (Fig. 1). July to October outbreaks of planktonic and benthic taxa show significant interannual, seasonal and spatial variation in origin and impacts. Blooms are more frequent and severe in the inshore areas, due to the higher nutrients, warmer temperature and shallower waters and immense surface blooms (>20 km^2) have been recorded in the West basin of Erie near the Maumee and Sandusky Rivers (Stumpf et al., 2012), which can be wind- and current driven towards the West-Central basins.

The most common cyanotoxin reported across North America is MC, and in the Great Lakes, this is largely produced by certain

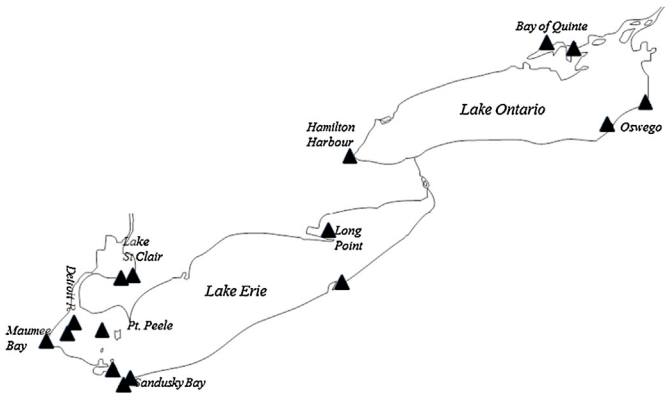


Fig. 1. Geographic distribution of high levels of microcystin (>1.0 μg/L) in the Lower Great Lakes, 1996–2014 (Watson et al., 2008; Watson and Boyer, 2009, 2014a).

species and strains of *Microcystis* (Ho and Michalak, 2015; Rinta-Kanto et al., 2009). Elevated MC levels (i.e. exceeding the WHO guideline of 1.0 μg/L) have been measured at numerous sites in the lower Great Lakes (Fig. 2). Summer field surveys carried out between 2000 and 2004 measured MC levels ranging from detection limits (in 2002) to >20 μg/L (in 2003). Toxicity and bloom distribution varied spatially and were not restricted to the Western basin. In 2001 and 2002, some significant localized MC occurrences occurred in the Central and East basins, and in 2003, highest concentrations were measured in Maumee Bay and Sandusky Harbour in the West, and Long Point Bay in the East basin (Fig. 1). Neurotoxins (ATX-a, saxitoxin, neosaxitoxin) and

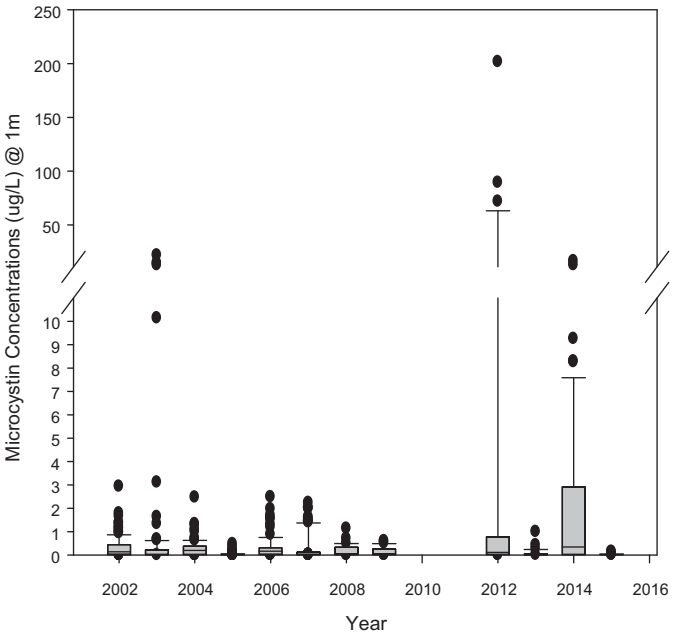


Fig. 2. Microcystin concentration from a sample bottle positioned at 1 m depth in Lake Erie between 2002 and 2015. Samples were obtained during the late summer as part of Environment Canada Microbial Ecology of Lake Erie Ecosystem (MELEE) and Lake Erie Water Quality (LEWQ) cruises and analysed by the protein phosphatase inhibition assay and/or by LCMS (Watson and Boyer, in preparation). Box whisker plots show the medium (bar), 25 and 75% quartiles (box) and the 95% percentiles (whisker). The closed circles are outliers-a consequence of the heterogeneity of blooms in these open waters. For 2003 and 2014 the closed circles near the axis break are on the upper scale. *N* ranges from 30 to 140 for the different years.

CYN occurred at or near detection limits, and were at levels below any guidance value (Watson and Boyer, 2009).

It is worth noting that remote sensing has recently been used to demonstrate the increased cHAB trend in the Great Lakes and to monitor and 'measure' the level of impairment for the purpose of modelling and bloom forecasting (Becker et al., 2009; Stumpf et al., 2012; Obenour et al., 2014; Wynne and Stumpf, 2015). However, while these can provide a measure of surface material and in some cases, resolve this to phycocyanin-rich taxa (i.e. cyanobacteria), they cannot determine the species or toxin production. Molecular methods are being employed (Rinta-Kanto et al., 2005; Ouellette et al., 2006; Hotto et al., 2007; Davis et al., 2014) which allow more targeted information on the identity, distribution and abundance of *Microcystis* and other cHAB taxa, and the detection of genes involved in growth, toxin synthesis and other important cell processes. This has provided important understanding about the origins and activity of these species, indicating, for example, that the same toxigenic strain of *Microcystis aeruginosa* may be present throughout the Great Lakes system (Davis et al., 2014), although other work also shows significant strain diversity among cHAB populations across the Lakes (Wilson et al., 2005; Rinta-Kanto and Wilhelm, 2006; Hotto et al., 2007; Dyble et al., 2008; Rinta-Kanto et al., 2009).

4.2. Health effects of cHABs in the Great Lakes

Based upon the HAB status reports of these Lakes discussed above, it is expected that cyanotoxin poisonings might be more prevalent in Lake Erie and to a lesser extent Michigan, Huron and Ontario. With the widespread concern and potential for intoxication, it is surprising that no formal records or database existed to locate case reports of cyanobacterial illness and death among animals and humans despite the fact that severe cHABs have been occurring in the basin for over a decade. The US Centers for Disease Control and Prevention (CDC) HABISS program addressed this issue on a national scale beginning in 2007. Data collected through CDC provided an expanded picture of the human health impact from HABs and cHABs. Between 2007 and 2011, ten US states (FL, MD, NC, NY, MA, IA, OR, SC, VA, WI) were funded to develop and implement activities to address the public health effects from HABs and collect data on HAB-related human illnesses for input to the CDC HABISS (Backer et al., 2015). During that time period, there were over 450 possible cases of illness associated with HABs. Of those, over 200 were identified as suspect/probable cases of illness associated with HABs, most related to ciguatera fish poisoning. From the original possible cases, over 170 (36%) were associated with a freshwater cHAB exposure. However, as with most cases of cHABs, very few were confirmed with positive findings for cyanobacteria/cyanotoxins and were classified as probable or suspect.

To help correct this lack of reporting, funding has been created for a HABs module within CDCs National Outbreak Reporting System (NORS) which will be tailored to include environmental data and animal poisonings. Since the majority of reported freshwater and marine HAB poisonings involve wild and domestic animals, this format will allow a more accurate reporting of HAB toxicities. Once developed, NORS will also incorporate earlier data collected for HABISS (L. Backer pers. communication). (NORS website: http://www.cdc.gov/nors/) (HAB reports: http://www.cdc.gov/mmwr/pdf/wk/mm6301.pdf)

The HABISS reporting system was discontinued in 2013 when funding ended (Backer et al., 2015). Recently the "One Health Collaborative Framework" was proposed to meet this need (Hillborn and Beasley, 2015). The level of current risk to human health across the Great Lakes was recently evaluated using publically available Federal, state and provincial case reports of

Table 4
Cyanobacteria exposure related human and domestic animal reports for Ohio bathing season 2010-2015, as of 11-November 2015. BL = bloom reported; Tx = toxin reported; P = probable*; S = suspect*; NL = not likely; UI-under investigation; NF = no follow-up; D = died; Courtesy of Laurie M. Billing, Health Assessment Section, Bureau of Environmental Health Ohio Department of Health.

Year	Waterbody	Counties	Human illness		Animal illness & death				Total	
			BL/Tx	P	BL/Tx	S/NL/UI/NF	D	P	Human	Animal
2010	Burr Oak	Athens	BL;Tx	7	Tx		2	2	7	4
	Grand L St. Marys	Auglaize; Mercer	BL;Tx	8	Tx		3	4	8	7
	Lake Erie	Multiple	BL;Tx	2		7			9	
	Lake Mac O'Chee	Logan	BL;Tx	19					19	
	Deer Creek	Madison	BL;Tx	3					3	
	Lake Alma	Vinton	BL;Tx	2					2	
	Lake Hope	Vinton	BL			1			1	
	Lake Loramie	Shelby	BL;Tx					1		1
	Total State-wide			41		8	5	7	49	12
2011	Grand L St Marys	Auglaize; Mercer	BL;Tx	1					1	
	Buckeye Lake	Fairfield; Licking; Perry	BL;Tx	1					1	
	Lake Erie	Out of state	BL;Tx	1					(1)	
	Heron Pond, Three Creeks	Franklin	BL				1			1
	Total State-wide			2			1		6	1
2012	L Erie—Headlands Beach		BL			1			1	0
	Total State-wide					1			1	0
2013	Total State-wide								0	0
2014	East Fork					2 (NL)			2	
	Total State-wide								2	0
2015	Grand L St. Marys	Auglaize; Mercer	BL;Tx	1					2	
	L Erie, Kelley's Isl.					1 (NL)			1	
	L Erie, Reno Beach					1 (NL)			1	
	L Erie, Lakeside					3 (NL); 1(NF)			3	
	L. Erie, East Harbor					1 (NL)			1	
	Ohio River	Louisville, KY				1 (UI)				
	Total State-wide			1		9			10	0
2010–2015	Total State-wide		14 (BL)/11TX	44	2 (TX)	18	6	7	68	13

* **Suspect**: Exposure to water or to seafood with a confirmed algal bloom AND onset of associated signs and symptoms within a reasonable time after exposure AND without identification of another cause of illness. **Probable**: Meets criteria for Suspect Case AND there is laboratory documentation of a HAB toxin(s) in the water. **Confirmed:** Meets criteria for a Probable Case combined with professional judgment based on medical review.

cyanobacterial illness and death among animals and humans for areas adjoining the Great Lakes (Carmichael, 2013). Case definitions for this evaluation were based on those provided by the Ohio Department of Health, and fell under three levels, Suspect, Probable and Confirmed, based on the evidence of exposure to toxins (e.g. in contaminated food or water), concurrent and unique source of illness (i.e. toxic bloom) and symptoms. There is no certified laboratory test for cyanotoxins or their metabolites in human blood, tissues, or urine, hence these reports were not confirmed by biomarker studies. These reports showed that in the Great Lakes Basin, most of the probable/suspect cases of cHAB human and animal poisoning meeting these criteria have, to date, been associated with Lake Erie and its surrounding watershed, with the exception of reports of ATX-a neurotoxicosis among dogs at a small lake in the Lake Ontario watershed and embayments (Hoff et al., 2007), and in Lake Champlain (Mihuc et al., 2005). The cases reported in the Lake Erie Basin vary among years, and show no clear connection with measures of bloom severity in the Lake (Stumpf et al., 2012). These human and animal illness records for the State of Ohio are shown in Table 4.

4.3. Human health effects

As a general statement, acute lethal toxicosis in humans from cyanotoxins, in treated water supplies, should not occur because normal filtration, coagulation and other treatment processes in municipal water supplies is designed to remove toxic cells and released toxins to levels below that necessary to cause acute lethal effects. However, toxic cells and free toxins have been present in finished drinking water supplies in cases of heavy cyanobacteria blooms and where the normal water treatment process is inadequate or not properly operated (Carmichael, 2001a, see Section 7.1). Cyanotoxins have been implicated in human illness (i.e. acute non-lethal or chronic toxicity) from municipal water supplies, especially after the bloom has been treated by copper sulfate to lyse the cells and release more of the toxins into the distribution system (Funari and Testai, 2008). In these and other cases involving accidental ingestion, the symptoms reported include abdominal pain, nausea, vomiting, diarrhoea, sore throat, dry cough, headache, blistering of the mouth, atypical pneumonia and elevated liver enzymes in the serum (Chorus and Bartram, 1999).

The only confirmed route of exposure for acute lethal human toxicity from cyanotoxins is from dialysis water used in a medical facility in Brazil. The confirmed outbreak occurred at a dialysis centre (termed Clinic A) in Caruaru, Brazil located 134 km from the state capital of Pernambuco at Recife. At Clinic A, 116 (89%) of 130 patients experienced visual disturbances, nausea and vomiting following routine haemodialysis treatment between February 13–20, 1996. Subsequently, 100 patients developed acute liver failure and of those 70 died. As of October 1997, 53 of the deaths could be attributed to a common syndrome now called "Caruaru Syndrome". The history of this outbreak and the history and summary of the epidemiology have been published (Jochimsen et al., 1998; Pouria et al., 1998). More detailed information on this outbreak provided evidence for the cyanotoxins present and the cyanobacteria that produced them (Carmichael et al., 2001; Azevedo et al., 2002).

Some more recent acute toxicity case reports have been published where MCs were responsible. These include a report from Argentina (Giannuzzi et al., 2011), and two from China (Chen et al., 2009; Li et al., 2011). In the latter of these two China events, MC was detected in most samples of water and aquatic food from two lakes in the Three Gorges Reservoir Region. Children who drank water from the lake with the highest MC concentrations had a total estimated daily MC intake of 2.03 μg, a value higher than the tolerable daily intake of 0.40 μg proposed by the World Health Organization. Hepatitis B virus (HBV) infection, use of medicines with hepatotoxic side effects, and MC exposure were associated with liver damage. When those participants who were HBV-positive or hepatotoxic medicine users were excluded from the analysis, liver enzyme levels for AST and ALP were significantly greater in children exposed to high MC levels than in those who were exposed to low MC levels or to none. In conclusion, their study results suggest that chronic exposure to MC may be associated with liver damage in children in the Three Gorges Reservoir Region.

Exposure from cyanotoxins can also occur through the food web, as demonstrated by a Great Lakes study from 2006 focused on algal toxin levels in perch collected from in Lake Erie during the summer of 2006 when a toxic bloom of *Microcystis aeruginosa* was present in the western basin (Wilson et al., 2008). Across eleven sites, intracellular, particulate-bound MC increased to levels that exceeded World Health Organization guidelines for drinking water exposure (1 μg/L). In contrast, MC concentrations in yellow perch (*Perca flavescens*) muscle tissue ($n = 68$) declined from June to August, were negatively related to algal toxin levels, and did not exceed a conservative chronic exposure concentration estimated using proposed US EPA guidelines. Microcystin concentrations in perch livers exceeded these guidelines and were on average 125 times higher than muscle toxin concentrations per unit dry weight, varying little throughout the summer. Overall, the study suggested that based on current guidelines, humans are not at risk when consuming the muscle tissue of Lake Erie yellow perch even if collected during a large-scale cyanobacterial bloom. Other more recent studies have shown that MC accumulation in fish is highly variable; both among fish of the same type and between different species of fish (Schmidt et al., 2013). These studies highlight the need for a better understanding of the trophic transfer of cyanobacterial toxins through aquatic food webs in diverse ecosystems, with an emphasis on understanding if these compounds could accumulate sufficiently to affect human health (Schmidt et al., 2014).

The recreational use of lakes and rivers may also be a major route of exposure to cyanotoxins (Stewart et al., 2011; Backer et al., 2010). The consumption of drinking water, use of showers in public and private locations, and from water sports such as waterskiing (dermal and inhalation) is the second most common route of exposure, although no confirmed fatalities are known due to recreational exposure. An additional and minor route of potential exposure is via ingestion of cyanobacteria health food supplements (Codd et al., 1999). Three epidemiological studies on cHABs in recreational waters have been carried out in the United States (Stewart et al., 2006a; Backer et al., 2008, 2010). In the 2008 study of a small lake in Michigan, pertinent to the Great Lakes area, documented low levels of MCs in the water and in aerosol samples along with low levels of *Escherichia coli* (Backer et al., 2008) were found. It should be noted that yearly duration of exposure is shorter in those countries (i.e. U.S. and Canada) where the growth season is shorter (3–6 months) compared to countries with milder climates such as Australia and South Africa (6–12 months). Stewart et al. (2006a) found a positive relationship between cyanobacteria abundance and symptoms such as muscle pain, skin irritation, earaches, nausea, diarrhoea, stomach ache and vomiting, and suggested that cyanobacteria LPS was correlated with the symptoms.

More recently, a prospective study of acute health effects related to cyanobacteria exposure was conducted in Canada (Lévesque et al., 2014). The study focused on three lakes: Lake William, Lake Roxton and Lake Champlain's Missisquoi Bay. Participants kept a daily journal of symptoms and recorded any contact (full or limited) with the water body. Samples were collected to document cyanobacteria and MC concentrations. All of these waterbodies are used for recreational purposes while Missisquoi Bay also supplies water to a drinking water treatment plant which serves some residents in the area. Results of the study found that gastrointestinal (diarrhea, abdominal pain, nausea, vomiting, fever or abdominal cramps) were associated with recreational exposure. Furthermore, participants who received their drinking water supply from the Missiquoi Bay treatment plant where the source was contaminated by cyanobacteria showed a statistical increase in muscle pain, gastrointestinal, and skin irritation.

5. Risk associated from exposure to cHABs

Toxic cyanobacteria are now recognized as the group of organisms primarily responsible for HAB related events in fresh and brackish waters. It is difficult to assign reliable estimates of health risk from cHAB exposure which requires an estimate of the expected frequency of adverse effects caused by exposure to these toxicants. Clearly, this is affected by many factors, including the frequency and severity of blooms and the species and toxin production/cell (Donohue et al., 2008). Estimation of risk also involves establishing relationships between actual exposures and the expected response. While research is slowly providing this information, the term risk should be used in discussion of cyanotoxins only when quantities of toxic cells (and their toxin content) are known. Otherwise, the term 'hazard' should be used to designate a general threat from exposure to cyanotoxins. The most likely routes for human exposure to cyanotoxins is via drinking water, medical dialyses, recreational waters or consumption of cyanobacterial food supplements (Gilroy et al., 2000). Detailed discussion of human risk and exposure to cyanotoxins is provided by Carmichael (2001b), Ressom et al. (1994), Chorus and Bartram (1999), Hitzfeld et al. (2000), Codd et al. (2005), Orr and Schneider (2006), Funari and Testai (2008), Poste et al. (2011), and Chorus (2012).

5.1. Chronic exposure

Non-lethal dose effects are another important factor to be considered in risk assessment. In particular, the hepatotoxins MCs and NDs may act as potent tumour promotors through their inhibition of protein phosphatases (Falconer and Humpage, 1996), and carcinogenicity may become important in factoring into risk calculations, along with data obtained from animal exposures and other toxicological and chemical parameters (Zegura et al., 2011). Epidemiological evidence of tumour promotion and human liver cancers from MC exposure has been provided by the studies of Yu (1989) in China, and Svircev et al. (2009) in Serbia. While there are little data on cancer risk from cyanotoxins from the Great Lakes basin, a preliminary epidemiological study of this risk factor was carried out for drinking water from hypereutrophic Grand Lake St. Marys (GLSM) in Ohio, which has severe cHABs dominated by *Planktothix* and toxic *Microcystis* (Steffen et al., 2014). This study compared data on cancer incidence from the city of Celina (Mercer County) Ohio, with a periodically contaminated surface water supply from GLSM, with two control cities served by ground water, St. Marys, and Wapakoneta (Auglaize County) in Ohio. Results

found inconclusive evidence to support that cyanotoxins from GLSM are associated with excess risk of cancer from drinking water (Soward, 2011). In 2006, the International Agency for Research on Cancer (IARC) reviewed current evidence for carcinogenic potential of MC-LR and found that to date, there is strong evidence of mechanistic carcinogenicity, but inadequate evidence in humans and experimental animals. MC-LR was therefore classified to group 2B, indicating that it is possibly carcinogenic to humans (Grosse et al., 2006).

5.2. Risk associated with plant exposure to cyanotoxins

It is now well established that cyanotoxins have been responsible for intermittent but repeated outbreaks of wild and domestic animal illness and death for over 100 years. The occurrences are worldwide and include Canadian and United States Great Lakes areas. In addition to animal and human poisonings, exposure of plants to cyanotoxins also carries risk-both for plants and for animals and the humans who consume them. A literature review by Babica et al. (2006) indicated that plants are generally not killed by environmentally relevant levels of cyanotoxins but growth is inhibited, which lowers crop yields and increases the risk of human exposure via the consumption of exposed plants. In a recent study by Hereman and Bittencourt-Oliveira (2012) lettuce leaves sprayed with MCs at concentrations of 0.62–12.5 μg/L accumulated approximately 8–177 μg MC/kg, indicating that plants can accumulate MCs to levels that exceed 2 μg/day, the daily intake limit set by the WHO for drinking water.

6. CHAB indicators and evaluation of health risk

Indicators are designed to: (i) educate/influence policy and decision on status and trends; (ii) improve data accessibility; (iii) measure success; (iv) foster 'adaptive management', watershed level ecological health assessment, and support for additional remedial/preventive management; (v) promote stewardship through public outreach (Watson and Boyer, 2014b). Well-designed and carefully selected indicators serve as practical, economical and responsive tools for tracking ecosystem changes. Indicators are specific, well-defined, and measurable variables that reflect some key characteristic that can be tracked through time to signal what is happening within and across ecosystems. For example the US Heinz Center's "State of the Nations Ecosystems" report uses 108 indicators used to gauge the nations health (The State of the Nation's Ecosystems, 2008). Two of these Indicator categories are particularly relevant to the current review, Biological—which included the indicator harmful algal events, and Chemical—which includes the indicator nutrients nitrogen and phosphorus. While a comprehensive list of the cHAB species in the Great Lakes has not been compiled, this list would likely include most of those species listed in Chapman (2010). Ideally, cHABs should be quantified on some basis, i.e. low, medium and high intensity. While there is currently no continent or nation-wide monitoring or reporting programs or accepted definitions of low, medium, and high density for these events in North America, there has been some progress in this respect in the Great Lakes Basin. Levels of HAB impairments were recently defined for the Great Lakes under the International Joint Commission (IJC) Indictor Series (Watson and Boyer, 2014b), while in 2015, NOAA-GLERL launched an online tool which tracks and forecasts cHABs in Lake Erie using remote sensing, monitoring to provide advanced warning for water utilities and public sectors (http://www.glerl.noaa.gov/res/HABs_and_Hypoxia/habsTracker.html).

There are important indicators for cHAB health risk, notably the species, and the toxin(s) and levels produced. In an attempt to reach a semi-quantitative conclusion on cHAB risk for the Great Lakes and transboundary waters, the following discussion relied on data available for nutrient trends, cHAB events, species present and cyanotoxins identified.

In the US, guideline levels for some cyanotoxins in drinking or recreational waters have only recently been set (Tables 2 and 3). Many states rely on guidelines published by the WHO or on risk assessments based on the WHO data to manage these water bodies. However, these guidelines were based on cell concentrations rather than on cyanotoxin concentrations, and not all cyanobacterial blooms produce toxins. Resource managers and public health officials can be left with the choice between protecting public health by closing a water body with a significant algal bloom that may not be producing toxins, or protecting the local tourism economy by keeping a water body with a visible, aesthetically unappealing bloom open for use. In addition to using the WHO guidance, some states have completed their own risk assessments to develop guidelines to support public health decision making, such as advisories or closures related to drinking water supplies and recreational areas. For example, the Office of Environmental Health Hazard Assessment of the California EPA issued guidance on six cyanotoxins in 2012 (Butler et al., 2012). The guidance provides calculated action levels that may be applied by local, regional, state, or tribal entities to reduce or eliminate exposure of people and animals to algal toxins. Oklahoma was the first state in the US to pass legislation limiting exposure to freshwater algae (http://legiscan.com/gaits/view/366438). The new law requires the Oklahoma Tourism and Recreation Department to maintain a public website (www.checkmyoklake.com) that provides information about cHABs to the public, including monitoring data collected by the Oklahoma Department of Environmental Quality, the US Army Corps of Engineers, and municipal authorities. It also requires any agency with authority to manage recreational waters to post signs directing people to the website for information. The legislation also formalizes the responsibility for warning people about cyanobacteria and cHABs and sets the health-related warning thresholds: tourism officials will warn lake users if algae cell counts exceed 100,000 cells/mL and MC concentrations exceed 20 μg/L (Backer, 2012). Since legislation is based on algae cell counts and MC concentrations, either of these measures could be used as an indicator of health risk.

Canada has adopted guidelines for MCs in drinking and more recently, recreational waters; some of the provinces (which are most affected by these events) have developed bloom risk management programmes (Giddings et al., 2012). In the Great Lakes region, Hamilton Health has been applying a cyanotoxin monitoring and risk management program at the two public beach areas in Hamilton Harbour (Lake Ontario), which are annually impaired by algal/cyanobacterial blooms and cyanotoxins during the summer and fall. This program has been added to the health agency's routine beach testing for bacterial contamination. It is based on the use of a of on-site commercially available ELISA-based strip testing kit for MCs which require minimal training and no specialized equipment to use. These kits provide rapid (on site) semi-quantitative screening for the presence of MCs, and is used to make informed decisions on beach postings/closures, further sampling and to monitor for toxins for several weeks after the disappearance of any visible blooms (Watson et al., 2012; Watson et al., unpublished).

The development of such tools and legislation will allow us to better assess the risk for cHABs. Development of the appropriate indicators will make it possible to employ a risk assessment matrix for cHABs. For example, using the WHO action level of 100,000 cells/mL (Table 3), blooms exceeding this level should have their source water closed to recreational use until cell levels fall below this level. In a more formal risk assessment, it is also important to

know if the toxigenic bloom is producing one or more cyanotoxins, and what are the toxin concentrations. It is now established that blooms can have highly variable levels of cyanotoxins, ranging from non-detect to thousands of micrograms per litre. Historically, most states and provinces set up their initial monitoring and management plans to respond to cell counts once a toxigenic species is identified. With recent advent of rapid assays for the toxins themselves, there has been a gradual shift towards direct measurements of cyanobacterial toxins (Chorus, 2012; Radicello, 2015). Cell abundance worked well for initial establishment of occurrence and distribution of cHAB events, but with the increasing number of cHAB events reported, it may be too conservative to post or close waterbodies based solely upon cell counts, and in some cases the economic costs involved from recreational, fishing and increased water treatment may be unwarranted. This places renewed importance on having rapid, sensitive, established analytical, immunological and genetic tests available (Meriluoto and Codd, 2005; Sivonen, 2008; Rasmussen et al., 2007; Fortin et al., 2010). In addition to the example discussed above for Hamilton Harbour, there are numerous other examples of this risk process in the US and Canada (e.g. Holland et al., 2006; Chorus, 2012; Radicello, 2015) which could serve as the basis of a more standardized approach for the Great Lakes as cHAB programs progress.

7. Socioeconomic effects

Economic costs from eutrophication and harmful algal blooms have only recently been estimated. Dodds et al. (2009) compared current total nitrogen (TN) and total phosphorus (TP) concentrations for the US-EPA nutrient ecoregions with estimated reference conditions. In all nutrient ecoregions, current median TN and TP values for rivers and lakes exceeded reference median values. In 12 of 14 ecoregions, over 90% of rivers currently exceed reference median values. They calculated potential annual value losses in recreational water usage, waterfront real estate, spending on recovery of threatened and endangered species, and drinking water. The combined annual costs were approximately $2.2 billion as a result of eutrophication in U.S. freshwaters. The greatest economic losses were attributed to lakefront property values ($0.3–2.8 billion/yr, although this number was poorly constrained) and recreational use ($0.37–1.16 billion/yr). The authors note that their evaluation likely underestimated economic losses incurred from freshwater eutrophication, and identified cases where restoring natural nutrient regimes could have the greatest economic benefit. This research exposed gaps in current records (e.g. accounting for frequency of algal blooms and fish kills) and suggested further research was necessary to refine cost estimates.

Steffensen (2008) provided estimates on economic losses for several case studies from Australian rivers and water storage facilities from the late 1980s through the 1990s. Economic losses considered the costs associated with recreation and tourism such as accommodation, transport and tourism, commercial recreation facilities such as caravan and tourist parks, the amenity value including aesthetics; and long-term costs related to permanent loss of trade. Australian Dollar losses for three cases totalled about $10 million. Total estimated costs for this time period were 180–240 million per year but costs have increased considerably since then and are now more likely in the billions of dollars per year. Similar arguments could be made for all developed countries.

Economic losses from cHAB blooms in the Great Lakes area have not been well documented, apart from anecdotal accounts of estimated losses to tourism (recreation, fishing etc.), increased water treatment costs, decreased property values and losses from environmental degradation. The loss from operation of approximately 100 licensed charter boats (out of 800) due to the extensive cyanobacteria blooms on Lake Erie in 2011 is a typical example of such loss (Rick Unger, pers. communication to Jennifer Boehme, IJC, Hamilton, Ontario). It is reasonable to estimate that individual cHAB events on Lake Erie cause significant economic losses. In particular, a single cHAB-related drinking water episode caused by *Microcystis* bloom in the western basin of Lake Erie cost the City of Toledo several hundred thousand dollars, while the total lost revenue and additional costs to other sectors (industrial, hospitality, tourism) are uncalculated.

7.1. Lake Erie drinking water event of August 2014

The City of Toledos water treatment plant (WTP) draws from the western basin of Lake Erie from a shallow (~5 m) nearshore intake (Figs. 1 and 2). On August 2, 2014, residents receiving water from this treatment plant received a "Do Not Drink" and "Do Not Boil" order from the local water authority, based on two sample test results for MC levels in excess of the WHO drinking water guideline of 1 μg MC-LR/L (Ohio EPA, 2014). Public concern was escalated by news media reports of toxin levels as high as 2.5 ppm, two orders of magnitude higher than the μg/L (ppb) levels of the test results (i.e. micrograms were reported as milligrams). The subsequent drinking water shutdown affected nearly 500,000 users, and elicited a declared a state of emergency for the region (City of Toledo, 2014, 2015). The WTP, Health Department and City of Toledo responded promptly to the situation by increasing the activated carbon levels, and tap water MC levels rapidly dropped to below the analytical detection limit (0.3 μg/L) by late August. This advisory remained in effect for three days until testing showed consistent MC levels in the treated water below the WHO guideline. The socioeconomic impacts resonated more widely, with temporary suspension of restaurants and food facilities, swimming pool and brewery operations, and the establishment of bottled water distribution centers until the advisory was lifted.

During this event toxin levels in excess of guidelines were caused by a *Microcystis* bloom in the west basin of Lake Erie. While the bloom was not exceptionally large in size, strong winds from the north concentrated the surface material near the intake, resulted in significant levels of bloom material entering the treatment system. The capacity of the WTP to deal with this was further taxed by the routine addition of potassium permanganate at the raw water intake to control mussel fouling. This chemical can lyse cells, releasing cell-bound toxins, odorants and other dissolved material which are more difficult to remove with traditional flocculent treatment methods (Peterson et al., 1995).

Toxin-producing cHABs have occurred regularly in Lake Erie over the past 20 years (Brittain et al., 2000; Watson et al., 2008; Steffen et al., 2014, see also Fig. 2). Many of these blooms are caused by *Microcystis*, and significant toxin levels have been reported for more than a decade. Toxin concentrations associated with the western basin *Microcystis* blooms in 2000 exceeded 25 μg MC-LR/L (Brittain et al., 2000) and have since ranged from 1 to 250 μg MC-LR/L in surface water samples (Watson et al., 2008). Microcystin levels exceeding 1000 μg/L have been reported in wind-borne shoreline scums (Jeff Reuter, Ohio Sea Grant program, Ohio State University, pers. communication). During the Toledo event, water samples collected near the WTP intake indicated that the bloom material was not unusually toxic, containing 1–15 μg MC-LR/L and typical for Lake Erie cHABs (0.1–0.3 μg MC/μg chl-a; Watson et al., 2008).

When responding to this HAB event, the Toledo water utility relied on the current "Public water system harmful algal bloom response strategy" provided by Ohio-EPA. This document indicated a "Do Not Drink" response was warranted when finished water exceeded 1 μg/L. However, when WHO released its guidelines s for MC in drinking water, the 1 μg/L was based upon a lifetime TDI

(total daily intake) which by definition is allowed for each and every day and considered safe (Chorus and Bartram, 1999; Ohio EPA, 2014). Given the additional safety factors applied to the guideline value it would be possible to allow for exceedance of 1 μg/L for a few days before issuing a Do Not Drink order. This was pointed out in a newspaper commentary in the Toledo Blade (March 8, 2015) by Joseph Cotruvo, former head of the US EPA drinking water standards division. This issue with the guidelines regarding health and risk from MCs led to a number of confusing and conflicting questions. United States Environmental Protection Agency recent adaptation of a 10-day average for its health advisory value is, in part, due to recognition of this potentially confusing language in the WHO guidelines, and is intended to give water utilities time to implement additional remediation measures before the health advisory values are exceeded. While relatively minor compared to other cHAB related drinking water events (e.g. Lake Taihu; Qin et al., 2015), the 'Toledo incident' received national and international attention by media, managers and public, and served as a powerful illustration of the challenges associated with providing the public with credible and understandable information about complex issues involving human health. The incident has drawn attention to the declining state of Lake Erie water and many other freshwater resources, leading to renewed calls for action at the national level for more robust bloom risk management programmes, water treatment practices and communication to deal with future cHAB events.

8. Summary of CHAB health effects in the Great Lakes area

It is most likely that cHABs have been occurring in the Great Lakes at least since European settlement in North America. Their frequency, intensity and duration have increased beginning post World War II with their greatest increase in the 1970s. Research now allows us to understand the bioactive compounds and toxins that these blooms produce and to begin to document human and animal poisonings, plus economic losses. This documentation shows that cHABs occur in all regions of North America but are most prevalent in the Midwest where agriculture and development have altered the environment most. This includes manmade dugouts, ponds and reservoirs plus natural lakes, ponds and rivers where development has been greatest and environmental planning less. Weather and climate variations also influence cHABs.

All states and provinces in the Great Lakes area are affected by cHABS, with some reports of animal illness and death, primarily dogs and livestock. The Great Lakes, due to their size, water mass and lesser degree of eutrophication, largely restrict cHABs to inshore areas and to the more nutrient rich areas of a lake. Lake Erie is thus the most vulnerable to cHABs and cyanotoxins with probable cases of human illness. All other Great Lakes experience intermittent and periodic cHABs with documented levels of certain cyanotoxins, but no confirmed or probable human illness or toxicity have been reported. The dominant toxigenic cyanobacterium found in the Great Lakes is the colonial genus *Microcystis* which is only known to produce MCs of the known cyanotoxins, but since these have been detected, it can be concluded that other cyanobacteria are present and producing cyanotoxins including anatoxin-a, cylindrospermopsin and paralytic shellfish toxins (PSTs or saxitoxins). These are most likely species of *Anabaena (Dolichospermum)* and *Planktothrix*, but other cyanotoxin producers should not be ruled out. Clearly more research is needed to understand the dynamics of cHABs and health risk in the Great Lakes.

Current records of death and illness among humans, animals and other organisms suggest that relative to other known health risks (e.g. influenza, HIV etc.), cyanotoxins may represent a relatively minor concern. However, our historical context for understanding the full effects of cHABs and their toxins is only ~30 years old and only ~20 years old in the Great Lakes. The low number of confirmed cases of human illness directly resulting from exposure to cHABs or cyanotoxins should not be interpreted to mean that there is negligible risk or impact upon human health. In fact, there are numerous examples in infectious disease and toxicology where confirmed cases of human toxicity have been scant, but the widespread importance of protecting humans from exposures or minimizing the prevalence of the agent in question was well appreciated. One example is norovirus, where the pathogen lacks an *in vitro* cell-culture system for human diagnosis, but is estimated to cause up to 15% of acute gastroenteritis in people of all ages. Norovirus is a focus of vaccine research and prevention guidelines (Hall et al., 2011; Lee and Pang, 2013). With this appreciation and the dedication of resources to the further study of HAB effects in humans, the true risk to human health can be measured, and the population appropriately informed and protected. One need look no further than the IARC Group 2B carcinogens list, which includes MC-LR, to find another example of this need to additional work. Group 2B identifies those compounds that are possibly carcinogenic to humans. Aflatoxins are produced by the fungus *Aspergillus*, that grows on grains and other crops, which means these toxins can readily find their way into human and animal foods. The metabolite M1 is an epoxide metabolite of aflatoxin B1 that has long been considered to be one of the most potent naturally occurring liver carcinogens. M1 is produced by animals that ingest feed contaminated with aflatoxin B1, and can find its way into milk and dairy products, including infant formula. When this was realized, increased efforts and resources to study its carcinogenicity led to the understanding that M1, like its precursor B1, is in fact a group 1 human carcinogen and did not belong on the Group 2B list where it was originally placed.

The parallels between MC-LR and aflatoxin M1 are intriguing with respect to Group 2B placement: synergistic effects when ingested by people infected with Hepatitis B, strong mechanistic understanding of the carcinogenic potential (M1 affects the tumour suppressor p53), yet limited toxicological data in humans or animals at the time of its assessment for group 2 or 1 placement (Anfossi et al., 2011). We note in particular that the increased exposure risks of humans to M1 are what prompted their increased study. The effects of global warming and a rise in the incidences of HABs are likewise leading to increased exposures of people to cyanotoxins, especially in recreational waters. This realization should lead to increased support for toxicological studies of cyanobacterial toxins, and a better assessment of their real risks to human health, not just as carcinogens but also as gastrointestinal irritants and dermatoxins. In their recent paper, Brooks et al. (2016) ask the question "Are Harmful Algal Blooms becoming the greatest inland water quality threat to public health and aquatic ecosystems?". While this question is open to debate, it is clear that the worldwide increase in the occurrence and persistence of cyanobacteria and their toxins makes the issue one of the more significant hazards to our inland water supplies.

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