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Biomagnification or biodilution of microcystins in aquatic foodwebs? Meta-analyses of laboratory and field studies

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ABSTRACT

Cyanobacteria, conspicuous photoprokaryotes in aquatic ecosystems, may produce secondary metabolites such as the hepatotoxins, microcystins (MC). While MC have been quantified in numerous aquatic consumers across a variety of ecosystems, there is still debate whether biomagnification or biodilution of MC generally occurs in aquatic foodwebs. Given the threat that MC pose to aquatic foodwebs, livestock, and humans, we synthesized data from 42 studies on the concentration of MC in consumers, such as zooplankton, decapods, molluscs, fishes, turtles and birds, to determine the dominant process. To compare results across studies, we calculated the biomagnification factor (BMF) as the ratio between the MC concentration measured in consumers and their diet. Biomagnification is indicated when BMF mean and associated 95% confidence intervals (CI) >1. Biodilution is shown if a BMF mean and 95% CI <1. As expected, increasing concentrations of MC in diets resulted in increasing concentrations of MC in consumers. Nevertheless, biodilution of MC was evident for most primary consumers. This finding was robust across four datasets that focused on different aspects of data independence and variance, and may be explained by low hydrophobicity of MC, diet preferences, or detoxification. Zooplankton and zooplanktivorous fish, however, showed some potential for biomagnification (i.e. mean BMF > 1). Plausible, but largely unexplored, possibilities for the relatively higher MC accumulation by these consumers are low detoxification efficiency by zooplankton, MC trophic transfer via the microbial foodweb, contamination of zooplankton net samples with large cyanobacterial colonies and filaments, or the release of both free and bound MC in zooplankton during digestion by fish. Factors related to study design may have influenced the magnitude of MC biodilution. For example, consumers fed diets consisting of highly toxic cyanobacterial lab cultures and large, potentially inedible net phytoplankton showed greater biodilution when compared to seston. Given their hepatotoxic nature, MC concentrations were relatively higher in liver and hepatopancreas tissues than other tissues. Whole organisms exhibited, however, relatively greater MC (i.e. higher BMF) than specific tissues, and this finding could be attributed to the contribution of zooplankton to whole organism MC analyses (89% of BMF estimates > 1). Finally, BMF was positively related to study length showing that longer exposure to toxic food resulted in higher MC accumulation in consumers, which could have important implications in eutrophic or tropical systems where toxic blooms may persist year-round.

1. Introduction

Cyanobacteria are bloom-forming photoprokaryotes commonly observed in nutrient-rich aquatic ecosystems. Many, but not all, cyanobacterial genera are able to produce toxic secondary metabolites, known as cyanotoxins (Carmichael, 1992). The most widely-studied metabolites are a class of hepatotoxins, called microcystins (MC) with more than 80 described variants (Hoeger et al., 2005). *Microcystis* is one of the most conspicuous MC-producing cyanobacterial genera in freshwaters implicated in the intoxication of wild and domestic animals (Stewart et al., 2008) and humans (Jochimsen et al., 1998; Carmichael et al., 2001). Recent evidence of MC intoxication and trophic transfer from *Microcystis* to top marine predators (sea otters) via marine invertebrates shows, however, broader impacts connecting freshwater and marine systems (Miller et al., 2010). Harmful effects are expected to be even more overwhelming due to potential climate change-associated expansion of cyanobacterial blooms (Paerl and Huisman, 2008).

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Besides being able to produce toxins, cyanobacteria may be poor food for consumers due to their low digestibility (Kamjunke et al., 2002), inadequate morphology (Wilson et al., 2006) and/or biochemical composition (von Elert et al., 2003). Nevertheless, cyanobacteria in general and MC-producing genera in particular, are ingested by aquatic consumers (Lirås et al., 1998; Mohamed et al., 2003; Panosso et al., 2003; Dionisio Pires et al., 2004; Ou et al., 2005). Thus, MC may enter aquatic consumers by direct ingestion of toxin-containing phytoplankton cells or indirectly via foodweb-mediated intake of toxin-containing food. In *Daphnia*, damage of the midgut epithelium with the formation of intercellular spaces following ingestion of *Microcystis* cells containing MC or other metabolites was closely associated with a fast uptake of MC in the blood suggesting that this is the pathway by which the toxin enters and gains access to the entire body (Rohrlack et al., 2005). Consumer uptake of MC directly from the dissolved pool and bioconcentration are also possible and significant at times (e.g. Miller et al., 2010). However, as endotoxins, the concentration of dissolved MC in the environment is usually low except during bloom senescence and lysis. Nevertheless, soon after being released into the environment MC may undergo microbial degradation and photolysis or absorb to natural sediments (Zurawell et al., 2005). In addition, these molecules are large and of relatively low hydrophobicity, especially MC-LR (Ward and Codd, 1999) at pH ranges commonly observed during cyanobacterial blooms (De Maagd et al., 1999). Thus, bioconcentration of MC direct from water into biota is expected to be limited turning consumption of toxin-containing particulate matter a more relevant route (De Maagd et al., 1999).

Provided that concentrations of MC in diets are sub-lethal, the extent of accumulation in consumers will depend on a variety of factors intrinsic to the food and consumer, such as the MC profile and concentration in the diet, ingestion and assimilation rates, and consumer detoxification capabilities and physiological state (e.g. Yokoyama and Park, 2002; Adamovský et al., 2007; Deblois et al., 2011). Environmental conditions, such as temperature, availability of alternative food, and length of exposure (e.g. Yokoyama and Park, 2003; Soares et al., 2004; Deblois et al., 2011) may also modulate MC concentrations and effects. Despite the fact that MC have been broadly measured in a variety of aquatic consumers across systems (e.g. Eriksson et al., 1989; Watanabe et al., 1992; Zurawell et al., 1999; Babcock-Jackson, 2000; Vasconcelos et al., 2001; Krienitz et al., 2003; Mohamed et al., 2003; Xie et al., 2004; Ibelings et al., 2005; Nasri et al., 2008) and that MC could pose a potential health risk for human consumers (Ibelings and Chorus, 2007), there is still debate whether MC biomagnification or biodilution is the prevailing process in aquatic foodwebs (Ibelings et al., 2005; Xie et al., 2005; Chen et al., 2009; Zhang et al., 2009).

Meta-analysis represents a powerful tool for synthesizing the findings of related, independent studies, especially when contrasting reports exist (Osenberg et al., 1999). Using meta-analysis, we present the first quantitative synthesis confirming MC biodilution as the dominant process in aquatic foodwebs and show that the magnitude of biodilution varies across consumers and can be influenced by study design.

2. Materials and methods

To determine whether biomagnification or biodilution of MC is the dominant process in aquatic foodwebs, we synthesized data from the available literature documenting MC concentrations in aquatic consumers. Studies included in our analysis were obtained using indexed databases (e.g. ISI Web of Science, ScienceDirect, Medline, Google Scholar, etc.), non-indexed databases (e.g. Ph.D. thesis, M.Sc. dissertations and non-indexed articles), and the reference lists of collected papers.

To compare results collected in 42 studies (see Appendix B, Table 1), we calculated the biomagnification factor (BMF), which is the ratio between the MC concentration measured in aquatic consumers and their diet (sensu Gray, 2002). Only studies that provided simultaneous MC measurements on consumers and their diet expressed on a mass per unit basis, or from which such data could be directly calculated, were included in the analyses. Original concentrations were used to calculate BMF, but in some cases biomass conversions from wet weight to dry weight were applied (factor of 5 or 10 for fish muscle and other tissues and consumers, respectively, according to Xie et al., 2005; Ibelings and Havens, 2008). Studies employing dissolved toxins or aqueous cyanobacterial extracts were not included in the analysis. The diet of carnivorous fish was determined according to available information within the papers or data available in Xie et al. (2005) and in Copp et al. (2009), and the MC concentration in their food (i.e. other fish and/or invertebrates other than zooplankton) was estimated as the average concentration of all available tissues. For experimental studies dealing with MC accumulation and depuration periods, only accumulation data (i.e. exposure to toxic diet) were included. Some studies (Williams et al., 1997; Gkelis et al., 2006; Mohamed and Hussein, 2006; Nasri et al., 2008) provided toxin measurements for the same tissue using multiple analytical methods (i.e. ELISA, protein phosphatase assays, Limieux oxidation gas chromatography–mass spectrometry analysis). In those cases, we used the averaged BMF for analyses. Data in figures were extracted with xyExtract Graph Digitizer v4.1 (2008).

BMF was calculated for each of the following groups of aquatic consumers: zooplankton (jellyfish and other zooplankton), decapods, bivalves, gastropods, phytoplanktivorous, zooplanktivorous, omnivorous and carnivorous fishes, turtles, and birds. We also used additional information provided in each study to separate the data into the following categories: study type (field or lab), phytoplankton diet type (seston, net, or lab culture), and tissue type (liver including hepatopancreas, non-liver, or whole organism). Seston refers to non-concentrated samples of lake water filtered through glass-fibre filters. In some cases, sestonic MC concentrations expressed in biomass were obtained by dividing the volumetric concentration of intracellular MC (i.e. $\mu g\,L^{-1}$) by the concentration of suspended solids (i.e. $g\,L^{-1}$). As these systems were dominated by cyanobacterial blooms, we expect low contribution of inorganic matter to the total suspended matter. Otherwise, high inorganic contribution could affect BMF estimates by leading to low estimates of particulate MC and artificially elevated BMF estimates. Net phytoplankton refers to phytoplankton samples concentrated through phytoplankton nets and also incorporates samples taken from accumulated scums of cyanobacteria.

BMF means and associated 95% confidence intervals (CI) were estimated for all groups to determine whether biomagnification or biodilution occurred. Biomagnification was shown when BMF mean and 95% CI were >1. Biodilution was indicated when a BMF mean and 95% CI were <1.

Given data independence constraints, we used four datasets that focused on different aspects of the complete dataset which included 42 studies comprising 790 observations. The overall dataset included all available data regardless if the data were independent or dependent (e.g. when multiple BMFs were calculated from different tissues of the same consumer). Clearly, multiple BMFs calculated for the same individual consumer are not independent (e.g. the concentration of MC in liver and non-liver tissues was strongly correlated, Fig. 1). Thus, we created other datasets in which all independent data were included with either averaged BMF (AVE BMF) or maximum BMF (MAX BMF) dependent data. Both datasets comprised 492 observations. The fourth dataset comprised only independent data with 334 observations from 28

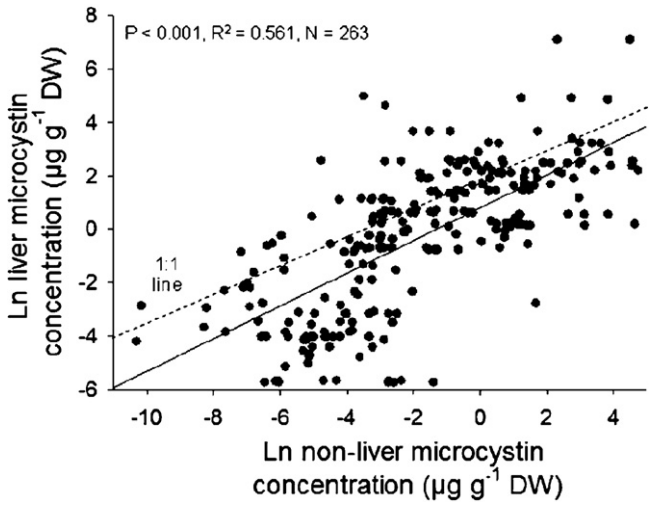

Fig. 1. Relationship between natural log transformed microcystin concentrations in liver and non-liver tissues from aquatic consumers.

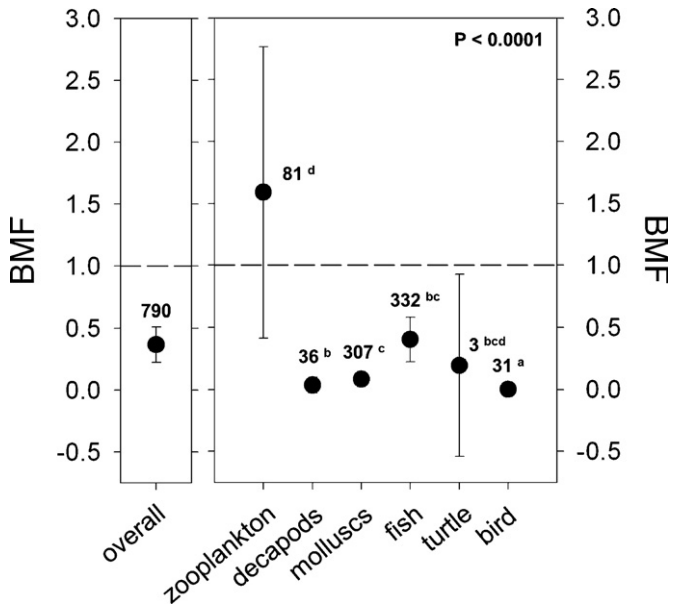

Fig. 2. BMF means and 95% confidence intervals for the complete dataset of all aquatic consumers, and main groups of aquatic consumers (zooplankton, decapods, molluscs, fish, turtles and birds). Sample sizes appear above means, and letters indicate significant differences detected by Tukey's test.

studies. Few studies provided error estimates for MC concentrations in consumers and diets. Thus, we were not able to conduct weighted meta-analyses.

Entire datasets were used for comparisons between study types, whereas reduced datasets (i.e. excluding datapoints of jellyfish, zooplanktivorous and carnivorous fishes that do not directly consume phytoplankton) were used to compare BMF among phytoplankton diet types. Carnivorous fishes that was either directly exposed to toxic cyanobacteria as single food or observed to have ingested cyanobacterial bloom material (Babcock-Jackson, 2000; Cazenave et al., 2005) were considered as omnivorous. Comparisons among tissue types were done using only the complete and independent datasets.

Natural log transformations of BMF (analogous to the response ratio, Hedges et al., 1999) and of the concentrations of MC in food and in consumer tissues were carried out to normalize the data prior to statistical analyses. Analysis of variance (ANOVA) was used to test for differences in BMF means among categories, followed by Tukey's HSD (honestly significant difference) test whenever a significant difference was observed using ANOVA. The relationship between the concentration of MC in liver and non-liver tissues from the same organism, between the concentration of MC in consumers and their diets, and between BMF and the length of experimental exposure to toxic food were evaluated using linear regression. Datasets using BMF differ from datasets using consumer MC concentrations because the latter considered each individual toxin concentration of a tissue sample measured with more than one analytical method, whereas the former considered an averaged BMF of those dependent samples.

3. Results

In general, biodilution of MC was common and consistent when comparing results across the four datasets (BMF and 95% CI <1, Table 1 and Fig. 2). When evaluating consumer group-specific effects, all showed clear biodilution except for zooplankton (Table 1 and Fig. 2). Biodilution varied among the main consumer groups ($p < 0.0001$, Table 1 and Fig. 2). Birds were generally the most effective diluters of MC whereas zooplankton showed potential for MC biomagnification. Although there were some minor statistical differences (Table 1), the BMF trends were consistent across all four datasets.

Within zooplankton, predatory jellyfish incorporated more MC ($p = 0.042$) than other filter- or raptorial feeding zooplankton (Table 1 and Fig. 3). With the exception of independent data, biodilution strength also varied within fish guilds ($p < 0.0001$) with zooplanktivorous fish retaining more MC relative to their diet (Table 1 and Fig. 3), although there was significant variation in these observations. Omnivorous fishes tended to show the greatest biodilution followed by phytoplanktivorous and carnivorous fishes (Table 1). This trend in biodilution magnitude remained the same even when we included carnivorous fishes that directly consumed toxic cyanobacteria (entered as omnivorous) into carnivorous data and removed these data from omnivorous (Table 1). With the complete dataset, mean BMF also differed ($p < 0.01$) within molluscs with gastropods showing greater MC biodilution than bivalves (Table 1 and Fig. 3).

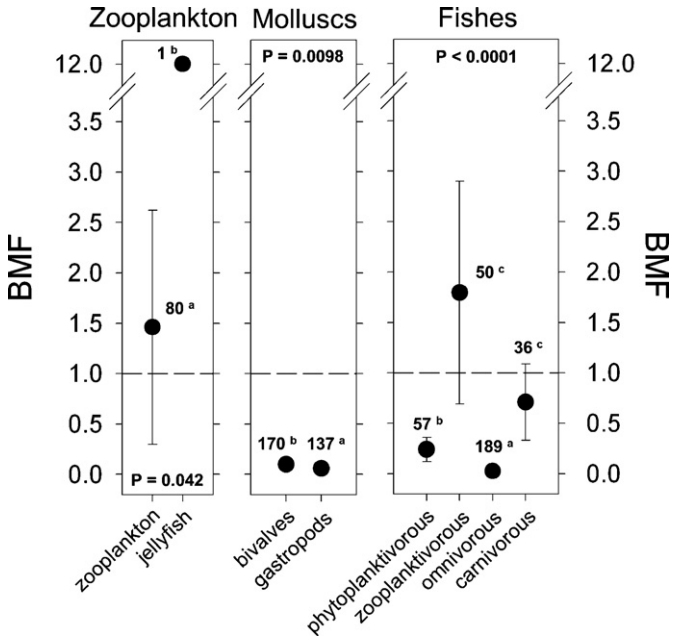

Fig. 3. BMF means and 95% confidence intervals for the complete dataset of consumers within zooplankton, molluscs and fishes. Sample sizes appear above means, and letters indicate significant differences detected by Tukey's test.

Table 1
Results of the meta-analysis comparing BMF means of different groups of aquatic consumers with the different datasets. AVE BMF: independent BMF data combined with averaged BMF of dependent data; MAX BMF: independent BMF data combined with maximum BMF of dependent data; *n*: number of cases; 95% CI: 95% confidence intervals. Different letters indicate significant differences among means with the Tukey's test.

Group/comparisons	Complete dataset					Independent dataset					AVE BMF dataset					MAX BMF dataset				
	n	Mean	Lower 95% CI	Upper 95% CI	*p*-Value	*n*	Mean	Lower 95% CI	Upper 95% CI	*p*-Value	*n*	Mean	Lower 95% CI	Upper 95% CI	*p*-Value	*n*	Mean	Lower 95% CI	Upper 95% CI	*p*-Value
Overall	790	0.3671	0.2229	0.5112		334	0.5662	0.2431	0.8893		492	0.4725	0.2497	0.6952		492	0.5435	0.3141	0.7728	
Zooplankton	81	1.5909d	0.4164	2.7654	0.0000	81	1.5909c	0.4164	2.7654	0.0000	81	1.5909c	0.4164	2.7654	0.0000	81	1.5909c	0.4164	2.7654	0.0000
Decapods	36	0.0353b	−0.0260	0.0966		16	0.0788a	−0.0651	0.2228		26	0.0487a	−0.0373	0.1346		26	0.0487a	−0.0372	0.1347	
Molluscs	307	0.0822c	0.0522	0.1123		196	0.1180ab	0.0720	0.1640		224	0.1057b	0.0652	0.1462		224	0.1091b	0.0684	0.1497	
Fish	332	0.4037bc	0.2232	0.5842		40	0.8967b	−0.3456	2.1389		150	0.5230b	0.1768	0.8693		150	0.7451b	0.3563	1.1338	
Turtle	3	0.1925abc	−0.5406	0.9256							1	0.1925abc				1	1.0650abc			
Bird	31	0.0001a	0.0000	0.0003		1	0.0016abc	0.0016	0.0016		10	0.0003a	−0.0001	0.0006		10	0.0004a	−0.0001	0.0008	
Zooplankton	80	1.4607a	0.3004	2.6209	0.0420	80	1.4607a	0.3004	2.6209	0.0420	80	1.4607a	0.3004	2.6209	0.0420	80	1.4607a	0.3004	2.6209	0.0420
Jellyfish	1	12.0109b				1	12.0109b				1	12.0109b				1	12.0109b			
Bivalves	170	0.0993b	0.0480	0.1506	0.0098	95	0.1736	0.0840	0.2632	0.9243	108	0.1534	0.0740	0.2327	0.9665	108	0.1553	0.0760	0.2345	0.7272
Gastropods	137	0.0610a	0.0386	0.0834		101	0.0656	0.0375	0.0937		116	0.0613	0.0365	0.0861		116	0.0660	0.0399	0.0922	
Phytoplanktivorous	57	0.2405b	0.1195	0.3615	0.0000	1	0.0100			0.6496	19	0.1863ab	0.0490	0.3237	0.0000	19	0.4446ab	0.1369	0.7523	0.0000
Zooplanktivorous	50	1.7972c	0.6929	2.9015		24	1.3438	−0.7634	3.4511		37	1.6502bc	0.2899	3.0104		37	2.2733b	0.8047	3.7419	
Omnivorous	189	0.0260a	0.0127	0.0394		8	0.0618	0.0257	0.0978		75	0.0276a	0.0132	0.0420		75	0.0592a	0.0267	0.0917	
Carnivorous	36	0.7094c	0.3321	1.0868		7	0.4443	−0.2095	1.0980		19	0.6206c	0.1468	1.0945		19	0.7766b	0.1102	1.4431	
Phytoplanktivorous	57	0.2405b	0.1195	0.3615	0.0000															
Zooplanktivorous	50	1.7972c	0.6929	2.9015																
Omnivorous[a]	171	0.0276a	0.0129	0.0423																
Carnivorous[a]	54	0.4766bc	0.2131	0.7401																

[a]Removing carnivorous fish that fed on toxic cyanobacteria from omnivorous and including the same data into carnivorous.

Table 2
Results of the meta-analysis comparing BMF means of study, algae or tissue type with the different datasets. See Table 1 for further explanation.

Comparisons	Complete dataset					Independent dataset					AVE BMF dataset					MAX BMF dataset				
	n	Mean	Lower 95% CI	Upper 95% CI	*p*-Value	*n*	Mean	Lower 95% CI	Upper 95% CI	*p*-Value	*n*	Mean	Lower 95% CI	Upper 95% CI	*p*-Value	*n*	Mean	Lower 95% CI	Upper 95% CI	*p*-Value
Study type																				
Field	606	0.3771	0.1956	0.5585	0.2718	279	0.6647[b]	0.2787	1.0508	0.0000	385	0.5286	0.2465	0.8107	0.0891	385	0.5502	0.2667	0.8337	0.2014
Lab	184	0.3342	0.1713	0.4971		55	0.0665[a]	0.0287	0.1043		107	0.2705	0.1315	0.4095		107	0.5193	0.2448	0.7937	
Algae type																				
Culture	97	0.0196[a]	0.0126	0.0267	0.0000	51	0.0253[a]	0.0147	0.0358	0.0000	73	0.0217[a]	0.0138	0.0295	0.0002	73	0.0256[a]	0.0166	0.0345	0.0007
Net	450	0.1444[a]	0.0879	0.2009		119	0.3955[b]	0.1972	0.5938		221	0.2347[a]	0.1253	0.3440		221	0.2709[ab]	0.1589	0.3828	
Seston	156	0.6134[b]	0.0278	1.1990		132	0.7075[c]	0.0153	1.3997		141	0.6678[b]	0.0198	1.3158		141	0.6722[b]	0.0243	1.3201	
Tissue type																				
Whole	184	0.7750[c]	0.2526	1.2975	0.0000	184	0.7750[c]	0.2526	1.2975	0.0000										
Non-liver	328	0.1212[a]	0.0701	0.1722		15	0.1851[a]	−0.1043	0.4746											
Liver	262	0.4108[b]	0.1881	0.6335		131	0.3338[b]	−0.0428	0.7104											

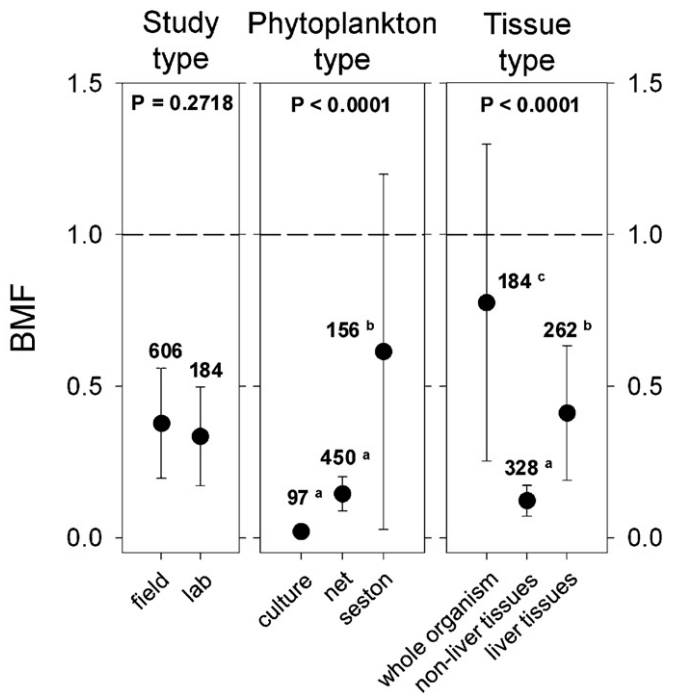

Fig. 4. BMF means and 95% confidence intervals for the complete dataset of different categories related to study type, phytoplankton or tissue type. Sample sizes appear above means, and letters indicate significant differences detected by Tukey's test.

Biodilution of MC was also evident for the other categories examined, with the exception of seston as food and measurements in whole organisms (Table 2 and Fig. 4). Nevertheless, mean BMF for all categories was <1 (Fig. 4). Factors related to study design were shown to influence the magnitude of biodilution. In general, diets consisting of cyanobacterial cultures and net phytoplankton resulted in greater biodilution when compared to seston (Table 2 and Fig. 4). Also, whole organisms exhibited greater BMF than specific tissues (Table 2 and Fig. 4) and, as expected, MC concentrations were greater in liver than in non-liver tissues (Table 2 and Figs. 1 and 4). Field and lab studies yielded, however, similar mean BMF (Table 2 and Fig. 4) except when we analysed only independent data. In that case, field data yielded significantly higher BMF ($p < 0.0001$).

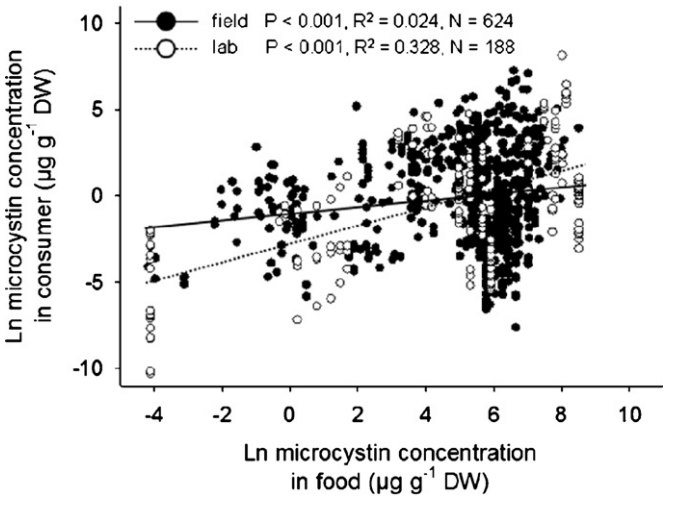

Fig. 5. Relationship between natural log transformed microcystins concentrations in diets and consumers sorted by study type.

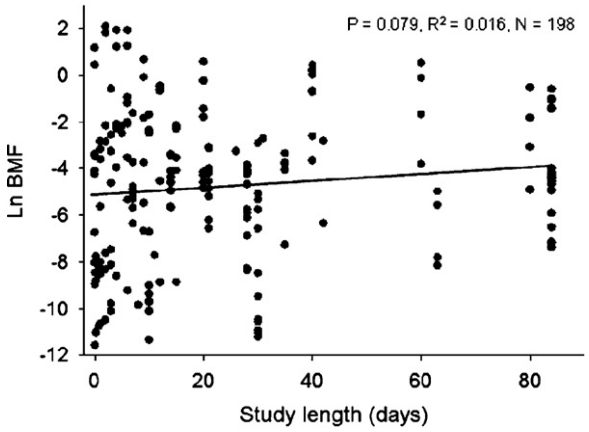

Fig. 6. Relationship between study length and natural log transformed BMF for the complete dataset. The results of the regression analysis using the other datasets were as follows. Independent data: $p = 0.021$, $R^2 = 0.087$, $n = 61$; AVE BMF: $p = 0.085$, $R^2 = 0.026$, $n = 117$; and MAX BMF: $p = 0.018$, $R^2 = 0.048$, $n = 117$.

We also examined the relationship between the MC concentrations in the diet and in consumers, as well as between BMF and the length of exposure to diets containing MC, and found that higher MC concentrations in diets resulted in higher MC concentrations in consumers (Fig. 5) and that BMF was marginally related to exposure length ($p = 0.079$, Fig. 6).

4. Discussion

Our study is the first quantitative synthesis to indicate that MC biodilution is the dominant process in aquatic foodwebs and confirms a qualitative assessment based on the accumulation of cyanobacterial toxins by several groups of aquatic consumers (Ibelings and Havens, 2008). We have further shown that the magnitude of biodilution varies across consumers, with zooplankton and zooplanktivorous fishes showing some potential for biomagnification. Study design and sampling technique may also influence the magnitude and our perception of biodilution.

Despite the large apparent literature of potential studies to include in our analyses ($n = 76$ studies), only 42 studies were included as they provided toxin concentrations on a per biomass basis to facilitate comparisons between consumers and diets. However, as the water content varies among aquatic biota it is recommended that studies express toxin concentrations per unit dry mass (Wilson et al., 2008). Thus, normalizing toxin concentrations on a per dry mass basis will not only allow direct comparisons across studies with different cyanobacterial biomass, but also among trophic levels (Tillmanns et al., 2007; Wilson et al., 2008).

As expected, fish (21 studies) and molluscs (17 studies) were the most studied consumers and were represented by many species that humans consume (Ibelings and Chorus, 2007). Surprisingly, only 7 studies provided MC concentrations per biomass of zooplankton and their cyanobacterial diets despite a vast literature describing interactions between cyanobacteria and zooplankton (reviewed by Wilson et al., 2006). While most of the available literature presented field-collected MC-burdens in different groups and trophic levels of zooplankton, only a single study (Thostrup and Christoffersen, 1999) collected these data for the cladoceran, *Daphnia magna*, under laboratory conditions. No experimental studies dealing with rotifers and copepods were found despite the importance of these grazers in freshwater systems. Few studies dealt with decapods (5 studies), birds (3 studies) and turtles (1 study) despite the potential risks associated with human consumption of these consumers (Ibelings and Chorus, 2007; Chen et al., 2009).

Our findings were based on BMF estimates, but MC biodilution has also been detected in experimental studies documenting toxin retention in aquatic consumers following exposure to toxic diets. For instance, the snail, *Lymnea stagnalis*, may retain up to 61% of ingested MC-LR (Lance et al., 2006), but far lower retention of MC has also been reported. For example, only 1.3% of ingested MC accumulated in the gastropod, *Potamopyrgus antipodarum*, after 5 weeks of exposure to *Planktothrix agardhii* (Lance et al., 2008) and zebra mussels retained only 0.55% of MC-LR after ingestion of toxic *Microcystis* over a period of 2 weeks (Dionisio Pires et al., 2004).

Low hydrophobicity of MC-LR (Ward and Codd, 1999), the most-studied MC variant, renders this molecule more prone to excretion in comparison with other variants and could partly explain this general pattern of biodilution in aquatic foodwebs. Differences in the degree of hydrophobicity among MC variants (Ward and Codd, 1999) could, however, result in differential toxicokinetics and bioaccumulation patterns across species and systems (Vesterkvist and Meriluoto, 2003). In fact, the proportion of the different variants (i.e. the toxin profile) may differ between consumers and their food. For instance, MC-RR may selectively accumulate in bivalves and fish (Yokoyama and Park, 2002; Xie et al., 2004), while MC-LR may be undetectable in omnivorous fish exposed to cyanobacterial blooms (Xie et al., 2007).

Detoxification of MC by aquatic consumers may additionally explain biodilution in aquatic foodwebs. Detoxification is a physiological mechanism consisting of activation and conjugation phases by which a toxic or foreign compound is chemically transformed. This biotransformation usually leads to decreased toxicity of the parental compound and its elimination from the organism. Enzymatic formation of MC-LR-glutathione (GSH) conjugates via glutathione *S*-transferase (GST) was detected in several aquatic organisms and appears to be the first step in the detoxification of cyanobacterial toxins (Pflugmacher et al., 1998). In addition, Wang et al. (2006) detected significant mRNA expression of soluble GST in the phytoplanktivorous fish, *Oreochromis niloticus*, after intraperitonial injection of MC-LR. Nevertheless, consumers differ in their detoxification efficiencies (e.g. Adamovský et al., 2007) with responses ranging from induction to inhibition of in vivo GST activity after exposure to cyanotoxins (Kozlowsky-Suzuki et al., 2009).

Despite the general pattern of biodilution, some aquatic consumers had mean BMF >1. Zooplanktivorous fishes had the highest mean BMF among fish, and, within zooplankton, carnivorous jellyfish accumulated more MC than primary zooplankton consumers. However, only a single measurement in jellyfish was available in the literature (Lehman et al., 2008) and the difference between zooplankton trophic levels was marginally significant. Nonetheless, our findings suggest that MC biomagnification can potentially occur in zooplankton and is probably also related to higher BMF in zooplanktivorous fish. Smith and Haney (2006) suggested that MC are better absorbed through the gastrointestinal tract of fish via a vector such as zooplankton rather than by direct consumption of toxic cyanobacteria (but see Berry et al., 2011) and could reflect utilization of both unbound and bound MC possibly released during digestion by fish. MC bind covalently with protein phosphatases (MacKintosh et al., 1995) and these complexes may comprise more than 99% of total MC (Williams et al., 1997; Nasri et al., 2008, but see Dionisio Pires et al., 2004 for a much lower percentage). However, it is still unclear whether MC-protein phosphatases complexes are digested by typical digestive enzymes (see Kankaanpää et al., 2005; Smith et al., 2010), but predicted MC-peptides resulting from digestion remain half as toxic as the parent MC-LR in in vitro assays (Smith et al., 2010) and could potentially be transferred up the foodweb.

We also found that biodilution magnitude varied across fish trophic guilds and this finding does not corroborate the qualitative assessment by Ibelings and Havens (2008) that observed no relationship between toxin concentration in fish and trophic guild. Here we detected that the biodilution magnitude decreased from omnivorous, phytoplanktivorous, and carnivorous to zooplanktivorous fishes (Fig. 3).

Despite the fact that fishes, such as cyprinids and cichlids (with omnivorous, planktivorous, and herbivorous feeding habits), have longer ilea thus larger digestive surface areas than carnivorous fishes (Fischer and Dietrich, 2000), limited absorption of MC in the omnivorous fish, *Cyprinus carpio*, could be explained by the neutral to slightly basic conditions of the digestive tract since an acidic environment is required for the digestion of cyanobacteria (Carbis et al., 1997). In addition, resistance to cyanobacteria and/or effective MC detoxification have been suggested for consumers that heavily ingest cyanobacteria such as phytoplanktivorous/omnivorous fishes (e.g. Xie et al., 2004; Wang et al., 2006). Carnivores/piscivores, on the other hand, could retain MC not only from their planktivorous prey, but through consumption of large zooplankton and other invertebrates (e.g. Wilson et al., 2008; Copp et al., 2009).

Although statistically powerful, meta-analysis can be compromised by poor data selection (Hedges and Olkin, 1985). For our analyses to be exhaustive and our findings to be most general, we considered all relevant studies for our meta-analyses, despite a number of our effect size measurements originating from the same publication (e.g. Lehman et al., 2008), research group (e.g. Xie et al., 2004, 2005), and/or focal organism (e.g. *C. carpio*, Zhang et al., 2009). Clearly, all data were not independent. To investigate the robustness of our results, we compared results from our general analyses with results generated from analyses using three subsets of our general dataset which included only data that we deemed more independent (i.e. single tissue consumer BMF (independent), average tissue consumer BMF, or maximum tissue consumer BMF). Although there were a few instances where we found contradictions in statistical significance (p-values) across all four datasets (e.g. field vs. lab studies), we found consistent trends in effect sizes across all datasets (Tables 1 and 2). Thus, despite some differences among datasets when comparing BMFs between study types, our findings were generally robust. Field and lab studies resulted in similar biodilution except when only independent data were considered, and in this case lab studies resulted in greater MC biodilution. Accordingly, diets comprising cyanobacterial laboratory cultures only yielded greater dilution than algal bloom material collected with a phytoplankton net and seston samples when considering the independent data. Otherwise, lab cultures and net samples resulted in similar biodilution when compared to seston.

Low BMF or strong MC biodilution could result if cultures or bloom material were very toxic or too large to be ingested, thus being avoided or little consumed by grazers. Nevertheless, we found that higher MC concentrations in diets resulted in higher MC concentrations in consumers (Fig. 5), suggesting consumption of toxic food. Increasing ingestion rates on toxic food may lead to increasing consumer toxin burden (e.g. Kozlowsky-Suzuki et al., 2003; Zhao et al., 2006), thus the positive relationship between MC in diets and consumers (Fig. 5) suggest that our assumption was realistic (i.e. toxic food was consumed even in the field where consumers had the possibility to choose alternative prey). The availability of other food sources may influence MC accumulation by consumers (e.g. Soares et al., 2004; Lance et al., 2008) and could explain the lower utilization of toxic food in the field (i.e. the slope of the regression was 0.53 vs. 0.19 for lab and field data, respectively) especially at higher diet MC concentrations.

Seston samples, provided they are integrated through the entire water column (e.g. Ibelings et al., 2005; Wilson et al., 2008) and not collected at the surface especially on calm days at eutrophic

waterbodies, are more representative of the natural feeding environment of many aquatic consumers, and could result in higher BMF estimates in comparison with net samples. For example, BMF estimates up to 43 were found using data from our previous work (Ferrão-Filho et al., 2002). These estimates were based on MC concentrations in zooplankton (0.3–16.4 $\mu g\ g^{-1}$ DW) and in seston (up to 5.8 $\mu g\ g^{-1}$ DW) and led to the conclusion that zooplankton accumulated MC efficiently. If the concentration of MC in net phytoplankton (300–3900 μg MC g^{-1} DW) was used instead, BMF estimates would have been much lower than 1. Thus, as the choice of sampling methods and procedures can influence toxin concentrations (Lehman et al., 2005; Tillmanns et al., 2007; Wilson et al., 2008), studies aiming to contrast toxin concentrations in consumers and food should consider the inclusion of seston toxins estimated as dry biomass within their sampling strategies.

As hepatotoxins, we expected liver tissues to provide the strongest signal towards MC biomagnification. Instead, whole organisms accumulated more MC indicating that comparisons between aquatic consumers (e.g. zooplankton vs. fish) could be valid and not necessarily give a skewed representation of biomagnification as previously suggested (Ibelings and Havens, 2008). Whole organism MC analyses were dominated by molluscs and zooplankton, but the latter contributed to 89% of BMF estimates >1. Higher accumulation efficiency by zooplankton could be attributed to low detoxification capability (e.g. Kozlowsky-Suzuki et al., 2009) or to fast uptake of MC associated with the disruption of epithelial cells of the midgut after digestion of cyanobacterial cells (Rohrlack et al., 2005). However, some contamination of zooplankton net samples with large cyanobacterial colonies or filaments cannot be ruled out despite careful clean-up and isolation procedures (e.g. Ferrão-Filho et al., 2002; Ibelings et al., 2005; Lehman et al., 2008).

Another plausible but yet largely unexplored possibility is toxin transfer to zooplankton via the microbial foodweb. Thus, besides grazing directly on cyanobacterial colonies and filaments (e.g. Koski et al., 2002; Panosso et al., 2003) and accumulating their hepatotoxins (e.g. Kozlowsky-Suzuki et al., 2003; Sopanen et al., 2009), zooplankton may accumulate toxins by preying upon components of the microbial foodweb. As microzooplankton (including dinoflagellates and ciliates) can successfully graze on toxic *Microcystis* (Davis and Gobler, 2011), which in turn are consumed by larger predatory zooplankton (Jürgens and Jeppesen, 2000; Zöllner et al., 2003), it is reasonable to assume that the transfer of toxins by the microbial foodweb could be considerable. In fact, nodularin, a closely-related hepatotoxin to MC, can be transferred to copepods through this pathway with an estimated contribution of up to76% of the total toxin transfer (Sopanen et al., 2009). An even larger contribution of toxin transfer through the microbial foodweb could be expected in systems dominated by toxic pico- and nanoplanktonic cyanobacteria. MC may, however, undergo degradation by bacteria and flagellates (e.g. Lam et al., 1995; Ou et al., 2005), thereby losing their toxicity (Lam et al., 1995). Thus, the role of bacteria and other components of the microbial foodweb as a sink or source of MC remains to be estimated.

We also observed that longer exposure to toxic food resulted in higher BMF. Prolonged exposure to toxic cyanobacteria may, for instance, suppress the content of GSH or inhibit the activity of glutathione reductase in fish (Adamovský et al., 2007, but see Pasková et al., 2008). Reduction of intracellular GSH as MC are transported and incorporated into the cell has also been suggested as one of a series of cascading events that take place during intoxication, which could result in decreased detoxification capability and culminate in cell apoptosis (Amado and Monserrat, 2010).

The amount of metabolites in consumers and the time required for detoxification are a result of the ingestion and detoxification rates, concentration of metabolites in the food, degree and rate of absorption and physiological state of the consumer (McLean and Duncan, 2006). Accordingly, Deblois et al. (2011) related distinct phases of accumulation of MC in tilapia (*O. niloticus*) with different physiological responses of the fish. At low doses, absorption takes place and a large proportion of MC in the diet accumulates in fish liver; at higher doses, accumulation in fish is a net result of accumulation and, active and effective depuration until a certain threshold after which depuration is not as effective and accumulation of MC starts to build up. From this point the relationship becomes linear and higher toxin intake results in higher concentration of MC in fish liver, ultimately leading to death by overdose.

Long-term exposure to toxic food may as well overwhelm depuration processes resulting in linear MC accumulation in fish liver (Deblois et al., 2011). However, accumulation and depuration processes are complex and even decreases in MC concentrations of fish liver may occur despite continuous exposure (e.g. Soares et al., 2004; Xie et al., 2004; Smith and Haney, 2006) reinforcing the need for toxicokinetic studies. Nevertheless, as pre-exposure to toxic cyanobacteria increases consumer resistance and fitness (Hairston et al., 1999; Gustafsson et al., 2005; Sarnelle and Wilson, 2005), continuous or prolonged exposure to toxic food leading to higher accumulation of MC could have greater implications in eutrophic or tropical systems where toxic blooms persist year-round.

5. Conclusions

Using meta-analyses, we show that MC biodilution is the prevailing process in aquatic foodwebs and consistent across groups of aquatic consumers with the exception of zooplankton and zooplanktivorous fish. Nevertheless, biodilution magnitude varied across consumers and is likely dependent on large differences in consumer feeding mode and physiology. Thus, studies on the toxicokinetics of different variants of MC are clearly needed as the dynamics of MC uptake and depuration/detoxification are not only species-specific but dependent on several factors, such as molecule hydrophobicity, environmental variation, behaviour, and availability of alternative food sources. Generally low MC hydrophobicity and poor trophic transfer are additional factors that may support biodilution and hinder biomagnification. Also, the choice of sampling strategy and method (i.e. seston vs. net samples) may affect BMF estimates. Future studies are also needed to determine the relative importance of the microbial foodweb as a MC sink or source to the classical foodweb, as well as the extent to which covalently-bound MC are transferred up the foodweb. Although generally negligible, the potential for bioconcentration of dissolved MC should also be considered, especially at transient periods of bloom senescence and lysis. Our analyses also highlighted some trends such as higher accumulation in secondary consumer fishes and differences among trophic guilds. Suggested next steps might be to apply a higher resolution approach (i.e. analysing the data at the family or genus level), since anatomy and life strategies (e.g. Cazenave et al., 2005) may influence accumulation of toxins. However, a larger number of observations are needed. In addition, comparisons across systems of varying trophic status or from different geographic areas would be of interest as toxin accumulation can be strongly linked to the biomass of toxin producers (e.g. Kotak et al., 1996; Zurawell et al., 1999) and to the frequency and persistency of toxic blooms. Finally, to ensure that similar studies are comparable, the standardization of methods and protocols is required since sampling techniques, sample preparation, extraction and analytical methods (e.g. Williams et al., 1997; Tillmanns et al., 2007) will influence toxin measurements in both cyanobacteria and consumers.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hal.2012.04.002.

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