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Technical comment

Comment on "Models predict planned phosphorus load reduction will make Lake Erie more toxic"

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Abstract - **Hellweger *et al.* (Reports, 27 May 2022, pp. 1001) predict that phosphorus limitation will increase concentrations of cyanobacterial toxins in lakes. However, several molecular, physiological and ecological mechanisms assumed in their models are poorly supported or contradicted by other studies. We conclude that their take-home message that phosphorus load reduction will make Lake Erie more toxic is seriously flawed.**

Toxic cyanobacterial blooms cause major water quality problems across the globe. Hence, there is a need for models that can predict cyanotoxin concentrations in surface waters. Hellweger *et al.* (*1*) developed an agent-based model that can provide valuable insights in the molecular and physiological mechanisms affecting the toxicity of cyanobacterial blooms. In essence, the proposed mechanisms in Hellweger *et al.* (*1*) are:

(i) High nitrogen (N) but low phosphorus (P) loads will stimulate the production of the N-rich toxin microcystin (MC).

(ii) One of the key functions of MC is protection against oxidative stress.

(iii) Therefore, MC-producing strains will be more resistant to natural H_2O_2 concentrations than non-MC-producing strains, especially under high N but low P conditions.

(iv) Thus, reducing P loads without diminishing N loads will select for MC-producing strains, that will make Lake Erie "more toxic".

Hellweger *et al.* suggest that these mechanisms have contributed to the observed resurgence of toxic cyanobacteria after P load reduction in Lake Erie and many other lakes, and they advocate a dual N and P management strategy. While we agree with Hellweger *et al.* that high N concentrations can be an important driver of cyanobacterial growth and cyanotoxin production (*2,3*), several of their model assumptions and predictions are poorly supported or contradicted by existing literature.

First, contrary to the claim in their title, the model of Hellweger *et al.* does not make predictions about toxicity. MC comprises a large class of cyanobacterial toxins, consisting of hundreds of MC congeners that vary widely in toxicity. Their model considers only the total MC concentration, but ignores changes in MC composition and therefore cannot make predictions about the toxicity of blooms. This is not merely a semantic issue, because excess N may shift the MC composition to the more N-rich variant MC-RR (*2*), which is one of the least toxic MC congeners.

Second, contrary to their Figure 2, cyanobacteria produce only low amounts of H_2O_2 by photosynthesis. Cyanobacteria lack the Mehler reaction, which is responsible for most H_2O_2 production during high light stress in photosynthetic eukaryotes. Instead, cyanobacteria use a 'Mehler-like' reaction with flavodiiron proteins to transfer their excess photosynthetic electrons to O_2, which produces water without H_2O_2 formation (*4*).

Third, Hellweger *et al.* assume that the natural H_2O_2 concentrations in Lake Erie (0.1-0.5 µmol/L) may cause oxidative stress and induce MC binding to proteins. However, the study (*5*) cited by Hellweger *et al.* used a much higher H_2O_2 concentration of 10 µmol/L to induce MC binding to proteins. Dziallas & Grossart (*6*) reported significant reduction of the cellular chlorophyll-*a* content at environmentally relevant H_2O_2 concentrations of 0.025-0.1 µmol/L, but this result appears to deviate from other studies. Most controlled laboratory studies show that H_2O_2 only starts to affect the photosynthetic yield and growth of *Microcystis* strains at H_2O_2 concentrations that are one or more orders of magnitude higher (5-60 µmol/L, depending on the conditions; e.g., *7,8*). This is in agreement with lake treatments that require H_2O_2 concentrations of 60-300 µmol/L to effectively suppress cyanobacterial blooms (*8,9*). We therefore question whether the natural H_2O_2 concentrations in Lake Erie are high enough to induce MC-binding to proteins and to shift the competitive balance between toxic and non-toxic *Microcystis* strains.

Fourth, the function of MC in cyanobacterial cells has remained elusive for decades. For example, MC has been implicated in grazing defense, allelopathic interactions, iron scavenging, protection against oxidative stress, carbon-nitrogen metabolism, and cell signalling (*10*). Hellweger *et al.* adhere to the hypothesis (*5*) that MC binding protects proteins such as RuBisCO against oxidative stress, which would provide a selective advantage to MC-producing strains when exposed to H_2O_2. Binding of MC to proteins has indeed been unequivocally demonstrated (5). However, whether MC-producing cells are better protected against H_2O_2 is less clear and contradicted by other experiments (*11*). Recent work from the research group that originally proposed the "protection against oxidative stress hypothesis" indicates that MC binding to RuBisCO probably serves a very different function. Binding of MC appears to play a key role in the assembly and cellular localization of RuBisCO, which enables rapid acclimation of cells to CO_2-limiting conditions (*12*).

Fifth, which factors govern the competition between toxic and non-toxic strains? Laboratory selection experiments have shown that the MC-producing wildtype has a strong selective advantage compared to the MC-deletion mutant under CO_2-limited conditions, but not under CO_2-replete conditions (*13*). This reinforces the recent idea (*12*) that MC binding to RuBisCO probably plays a role in CO_2 fixation. Other selection experiments investigated the role of N and P limitation. The results showed that the MC-producing wildtype won under N limitation, while the non-toxic mutant dominated under P-limited conditions (*14*), which is exactly opposite to the predictions of Hellweger *et al.*

Sixth, the models of Hellweger *et al.* consider only toxic and nontoxic *Microcystis* strains. However, the main aim of nutrient load reduction programs is not to shift the competitive balance between *Microcystis* strains, but to suppress the entire cyanobacterial bloom and shift the lake to a completely different phytoplankton community. Shifts from bloom-forming cyanobacteria to (nontoxic) eukaryotic phytoplankton are often observed in response to declines in nutrient availability. Models ignoring this important ecological mechanism are therefore unlikely to make reliable predictions of how nutrient load reductions will affect cyanotoxin concentrations in surface waters.

Conclusions

P load reductions have succesfully controlled cyanobacterial blooms in a wide variety of lakes (*15*), but in some lakes achieving sufficiently low P concentrations proves challenging. In these cases, bloom control by dual N and P reductions seems promising and further experience with such dual approaches is desirable. However, there are major issues with several molecular and physiological mechanisms assumed in Hellweger *et al.*, and their models omit common ecological responses to nutrient load reduction such as shifts in phytoplankton species composition. Hence, there is insufficient support for their provocative claim that P load reduction will make Lake Erie and other lakes more toxic.

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