Understanding cyanobacteria and cyanotoxins: implications for human exposure, toxicological risk assessment and management

Emanuela Testai

Mechanism, Biomarkers and Models Unit, Istituto Superiore di Sanità (ISS), Rome, Italy

ABSTRACT

Cyanobacteria, often referred to as blue-green algae, are a diverse group of photosynthetic bacteria that play a crucial role in various ecosystems. However, their proliferation and toxin production pose significant challenges to environmental, animal, and human health. In recent years, the interplay between cyanobacteria, climate change, and the production of cyanotoxins has garnered increased attention. This short note aims to delve into the intricate relationship between cyanobacteria and the production of cyanotoxins, the toxicological risks associated with exposure, and strategies for risk assessment and management.

Introduction

Cyanobacteria are highly adaptable photosynthetic organisms that thrive in a wide range of environmental conditions (Buratti *et al*., 2017). Climate change, characterized by rising temperatures, altered precipitation patterns, and increased nutrient runoff, has been linked to changes in the distribution and abundance of cyanobacterial blooms. Warmer temperatures and nutrient enrichment provide favourable conditions for cyanobacterial growth, leading to more frequent and intense blooms (in magnitude and duration) up to very high-density forming scums in freshwater bodies and marine aquatic ecosystems worldwide (Huisman *et al*., 2018). While cyanobacteria play a crucial role in ecosystem health, such blooms affect colour, odour, and taste of water, which creates aesthetic problems and affects the recreational use of water and its consumption by humans and animals; in addition, certain species have the potential to produce toxins known as cyanotoxins, posing a threat to human and animal health (Chorus and Welker, 2021) (Figure 1). Indeed, cyanobacteria are capable of producing a diverse array of secondary metabolites, including cyanotoxins among which Microcystins (MC), cylindrospermopsins, and anatoxins are the most studied groups, although it is a common belief that they represent only the tip of an iceberg, considering the growing number of bioactive compounds that have been described in the recent years (Codd *et al*., 2020).

It has been reported that the identifications of major cyanotoxins (n=1118) occur in 869 freshwater ecosystems from 6 continents and 66 countries (Svirčev *et al*., 2019), with MCs being most often recorded among cyanotoxins worldwide (63%), followed by cylindrospermopsin (10%), anatoxins (9%), saxitoxins (8%), and nodularins (2%).

The environmental conditions (e.g., nutrient availability, light intensity, temperature, and pH) triggering their production, as well as the exact physiological function of the producing organisms, is not yet fully understood, and it is supposed to be dependent also on the species and strain(s) of cyanobacteria. The production of cyanotoxins is also influenced by the genetic make-up of the cells: a strong variability of the genotype ratio (toxic *vs* nontoxic strains) has been reported to occur, even at a small temporal scale; in addition, an effect of the environmental conditions on the regulation of genes encoding for toxin production is undoubtedly plausible, but not yet clarified (Chorus and Welker, 2021).

Understanding the mechanisms underlying cyanotoxin production is essential for predicting bloom dynamics and assessing associated risks to ecosystems and public health, considering that cyanotoxins can induce adverse effects on humans, animals, and aquatic organisms.

Over the years, some acute intoxication episodes have been reported, especially in countries where water is not properly treated to remove cells and toxins. However, the major health concern is related to repeated exposure to low doses for long periods (Chorus and Welker, 2021).

Corresponding author: Emanuela Testai, Mechanism, Biomarkers and Models Unit, Istituto Superiore di Sanità (ISS), viale Regina Elena 299, Rome, Italy.
E-mail: emanuela.testai@iss.it

Key words: cyanotoxin, toxicity, human exposure, risk assessment, risk management.

Conflict of interest: the author declares no potential conflict of interest.

Funding: none.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Received: 14 May 2024.
Accepted: 6 September 2024

Licensee PAGEPress, Italy
Advances in Oceanography and Limnology, 2024; 15:12665
DOI: 10.4081/aiol.2024.12665

Cyanotoxins can cause systemic effects in domestic and wild animals as well, including mammals, birds, and aquatic species, leading to illness, reproductive failure, and mortality. Poisoning of livestock, wild and domestic animals by cyanotoxins has been reported since the last century: the association was possible due to the rapid onset of toxicological/neurological signs in animals and the presence of blooms or cyanotoxins in ponds and dams used for drinking (Backer and Miller 2016). In most cases, dog poisoning was associated with neurotoxic cyanotoxins produced in rivers by benthic taxa, such as *Phormidium* sp. and *Oscillatoria* sp. Benthic species quite rapidly sediment, forming a biofilm, covering river sediments, stones, and macrophytes on the shoreline, attached as a sticky mass to surfaces, including dog hair during bathing. Poisoning in animals has direct impacts on animal welfare and productivity, and can serve as a sentinel for potential poisoning risk in humans in a One Health approach (Hilborn and Beasley 2015).

Exposure sources, toxicological profiles, and related risk assessment for human health

Human exposure to cyanotoxins can occur through multiple routes (Funari and Testai, 2008).

The most common route of human exposure to cyanotoxins is through the ingestion of contaminated water or food. They can accumulate in aquatic organisms such as fish, shellfish, and crustaceans, which can then be consumed by humans, leading to direct exposure. In addition, the use of untreated contaminated surface water for irrigation and of dried toxic cyanobacteria cells as fertilizer for agricultural crops can be a source of soil contamination (Bouaïcha and Corbel 2016): cyanotoxins in the soil might be transported to other water bodies through leaching, runoff or drainage, or can cause contamination of the vegetation, plants, and crops, potentially affecting health and economy. Indeed, cyanotoxins could be absorbed through roots and be translocated to grains and/or fruits of some plants, sometimes causing phytotoxicity (Chorus and Welker, 2021) (Figure 1). However, information on the amounts of toxins in agricultural foods is still limited, and more quality data should be collected before any conclusions can be drawn on the health risks. Similar considerations apply to other food items, such as dairy products or meat from livestock or wild animals drinking contaminated water or eating contaminated feed (Testai *et al*., 2016; Chorus and Welker, 2021), as well as to food supplements (Vichi *et al*., 2012).

Inhalation may occur during recreational activities such as swimming, boating, or water skiing in contaminated water bodies. Aerosolisation of cyanobacterial cells and toxins can lead to respiratory irritation and inhalation exposure, particularly in areas with high cyanobacterial concentrations and wind-induced wave action (Backer *et al*., 2010; Buratti *et al*., 2017).

Dermal contact may occur during activities that involve direct skin contact with contaminated water, such as swimming or bathing. Dermal absorption of cyanotoxins is generally considered to be lower than ingestion or inhalation (Funari *et al*., 2017).

Parenteral route: the use of improperly treated surface water highly contaminated by MCs for hemodialysis has resulted in direct injection of cyanotoxins in the bloodstream, leading to liver failure and death in patients in Brazil, while a lesser dose was associated with sub-lethal liver injury (Azevedo *et al*., 2002; Hilborn *et al*., 2013).

Different exposure scenarios necessitate tailored risk assessment approaches as well as robust monitoring and treatment measures to ensure water and food safety. In bathing waters, individuals may be concurrently exposed to cyanotoxins through ingestion, inhalation, or dermal contact during recreational activities such as swimming, boating, or fishing. Understanding the relative contributions of these exposure routes is critical for prioritizing risk management strategies and protecting public health. For detecting the presence of cyanotoxins in water and in bacterial cells, official methods are available, although the certified standards availability is limited to a few variants; unfortunately, the occurrence of cyanotoxins in complex matrices, such as food items or human tissues/fluids poses challenges for accurately assessing human exposure and associated risks (Testai *et al*., 2016).

Despite significant research efforts, our understanding of the toxicological profiles of cyanotoxins remains limited. Even for well-studied cyanotoxins, such as microcystins, gaps persist in our knowledge of their long-term health effects, mode of action, and kinetics in humans, which if different depending on the route of exposure (Buratti *et al*., 2017).

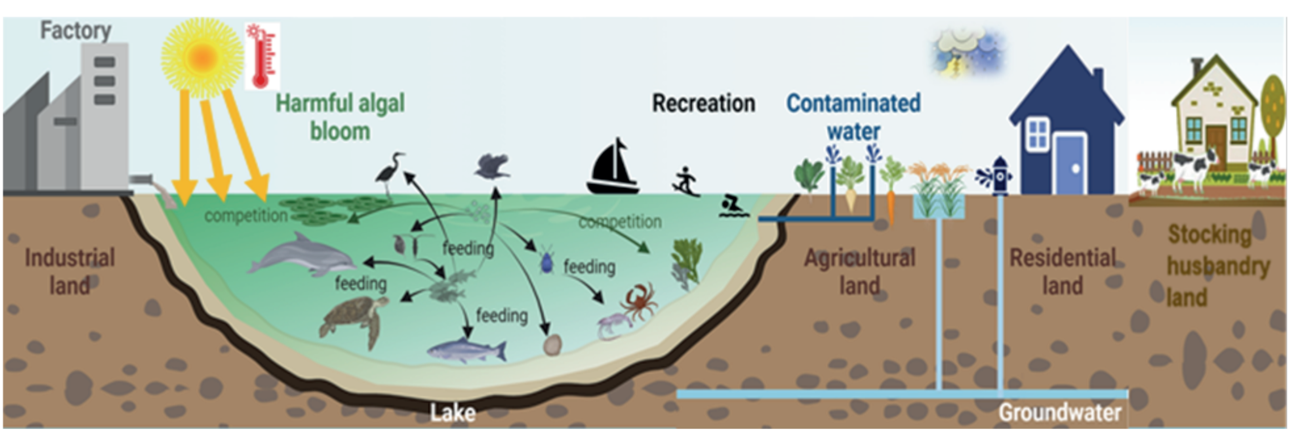

Figure 1. Schematic representation of climate and anthropogenic factors affecting cyanobacterial blooms and potential sources for human exposure.

Human acute effects potentially ascribed to the presence of cyanotoxins in the exposure media (drinking- or recreational water, food), such as gastrointestinal illness or skin irritation, may well be due to other unknown cyanobacterial metabolites or closely linked to pathogens or other substances associated with the bloom (Funari and Testai, 2008). The presence of confounding factors hampered the possibility to consider the epidemiological studies aimed to evidence the long-term exposure robust enough. Therefore, epidemiological studies are only of limited value mainly because of i) the uncertain retrospective exposure estimates, ii) the presence of other contaminants in surface water as confounding factors, iii) limited demographic information, not allowing to establish any cause-effect and/or dose-response relationships (Chorus and Welker, 2021). As a consequence, we have to rely on toxicity studies carried out with animal models and hopefully with animal-free New Approach Methodologies (NAMs) in the future. The great majority of papers on cyanotoxins toxicity dealt with MC, most specifically MC-LR (Testai *et al*., 2016). Only a few variants have been tested, some exclusively by using intraperitoneal injection, with a single dose tested, or using uncharacterised extracts (likely due to the scant availability of pure toxins). These kinds of papers are not useful for risk assessment, since the intraperitoneal injection is not a physiologically relevant route of exposure, with a kinetic behaviour markedly different from the most common ones, and the absence of a dose response prevents the identification of a threshold for adversity (World Health Organization, WHO, 2020).

Chapters 2 and 5 in the recently published WHO Book 'Toxic Cyanobacteria in Water' (TCiW) 2nd edition provide comprehensive guidance on cyanotoxin toxicological profiles and derivation of Health-Based Guidance Values (HBGV) to inform risk assessment and management strategies (Chorus and Welker, 2021). The book also contains the recently derived Guidance Values (GV) for some cyanotoxins in drinking and bathing water (Table 1) to assist policymakers, health authorities, and water quality managers in protecting public health. Besides the lifetime exposure GV, WHO also derived GV for short-term exposure, which refers to about two weeks, giving the risk managers an adequate time frame to implement measures, allowing them to achieve concentrations lower than lifetime GV. These GV are based on the latest scientific evidence and aim to ensure safe drinking or bathing water quality standards worldwide. Implementing these values into monitoring programs and regulatory frameworks is essential for mitigating the risks associated with cyanotoxin exposure.

However, it should be noted that in most cases they are still provisional, being affected by a high degree of uncertainty. For example, in the case of MCs, the GV has been derived for MC-LR, the only MC congener for which data on effects following repeated exposure are available and pragmatically considered valid for all other variants, expressing the sum as MC-LR-equivalents. Although only applicable to risk management measures, this approach has quite a relevant limitation (Codd *et al*., 2020): MC-LR has been considered the most toxic variant based on data on intraperitoneal acute toxicity data on some of them: for repeated exposure, the situation could be different, and the extrapolation from one congener to the others can be hampered by the possibility of different target organs based on transporter expression, different detoxication kinetics and different physico-chemical properties (e.g., hydrophilicity) (Santori *et al*., 2020).

Monitoring programs and alert levels framework

Effective management of cyanotoxin exposure requires a multi-faceted approach that addresses both the prevention and mitigation of cyanobacterial blooms, as well as the monitoring and treatment of contaminated water sources. Among the possible strategies, implementing measures to reduce nutrient inputs (e.g., nitrogen and phosphorus) into water bodies in the long run can help mitigate the proliferation of cyanobacterial blooms. However, for the early detection of blooms and timely issuance of public health advisories, a water quality monitoring plan, foreseeing regular monitoring of water quality parameters, including cyanobacterial cell counts and toxin concentrations, is essential. The Alert Levels Framework (ALF) developed by the WHO and other international agencies and outlined in the TCiW book (Chorus and Welker, 2021) provides guidance on assessing exposure risk and planning short-term responses to mitigate potential health impacts. It represents a systematic approach for assessing the risk posed by cyanobacterial blooms and guiding appropriate management responses. The ALF outlines four alert levels based on cyanobacterial cell counts and cyanotoxin concentrations in water bodies. These alert levels range from low risk (Alert Level 1) to high risk (Alert Level 4), with corresponding recommendations for risk communication, public health advisories, and implementation of control measures.

The ALF operates on the principle of risk-based decision-making, where the level of risk associated with cyanobacterial blooms determines the appropriate response actions. Key principles of ALF include: i) early detection: timely detection of cyanobacterial blooms is essential for implementing proactive management strategies and minimizing potential health impacts;

Table 1. Guidance values for selected cyanotoxins and exposure scenarios (Chorus and Welker, 2021).

Toxin	Exposure media and duration	GV (µg/L)
Microcystins -LR	Drinking water, lifetime	1
Microcystins -LR	Drinking water, short term	12
Microcystins -LR	Recreational water	24
Cylindrospermopsin	Drinking water, lifetime	0.7
Cylindrospermopsin	Drinking water, short term	3
Cylindrospermopsin	Recreational water	6
Saxitoxin	Drinking water, acute	3
Saxitoxin	Recreational water	30

ii) risk assessment: assessing the risk posed by cyanobacterial blooms involves evaluating cyanobacterial cell counts, cyanotoxin concentrations, exposure pathways, and potential health effects on humans and aquatic organisms; iii) risk communication: effective communication to stakeholders, including government agencies, water utilities, health authorities, environmental organizations and the public, is crucial for raising awareness of potential health risk associated to cyanobacterial blooms and cyanotoxin contamination and providing guidance on protective actions. Public education campaigns, community outreach initiatives, and dissemination of information through various media channels can empower individuals to make informed decisions about water-related activities and consumption practices; iv) adaptive management: ALF emphasizes the need for adaptive management approaches, where response actions are continuously reassessed and adjusted based on evolving bloom dynamics and risk assessments.

Depending on the alert level, response actions may include: i) enhanced monitoring, increasing frequency and intensity of monitoring efforts to track bloom development and cyanotoxin concentrations; ii) public health advisories, issuing advisories and warnings to inform the public about potential health risks associated with recreational activities, drinking water consumption, and fishing; iii) water treatment, implementing appropriate treatment technologies, such as activated carbon filtration or ozonation, to remove cyanotoxins from drinking water supplies; iv) nutrient management, implementing measures to reduce nutrient inputs into water bodies, such as agricultural runoff control and wastewater treatment upgrades, to prevent cyanobacterial proliferation.

A similar approach has been applied so far by the Italian Guidelines for managing cyanotoxins presence in bathing water (Funari *et al*., 2017).

Conclusions

Implementing robust monitoring programs, conducting rigorous risk assessments, and communicating effectively with stakeholders are key strategies for addressing these challenges and safeguarding water resources for future generations.

References

Azevedo SMFO, Carmichael WW, Jochimsen EM, et al, 2002. Human intoxication by microcystins during renal dialysis treatment in Caruaru-Brazil. Toxicology. 181-182:441-6.

Backer LC, McNeel SV, Barber T, et al, 2010. Recreational exposure to microcystins during algal blooms in two California lakes. Toxicon. 55:909-21.

Backer LC, Miller M, 2016. Sentinel animals in a one health approach to harmful cyanobacterial and algal blooms. Vet Sci. 3:8.

Bouaïcha N, Corbel S, 2016. Cyanobacterial toxins emerging contaminants in soils: a review of sources, fate and impacts on ecosystems, plants and animal and human health. In: Soil Contamination-Current Consequences and Further Solutions. InTechOpen, London, UK.

Buratti FM, Manganelli M, Vichi S, et al, 2017. Cyanotoxins: producing organisms, occurrences, toxicity, mechanism of action and human health toxicological risk evaluations. Arch Toxicol. 91:1049-130.

Codd GA, Testai E, Funari E, Svirčev Z, 2020. Cyanobacteria, cyanotoxins, and human health. In: Water treatment for purification from cyanobacteria and cyanotoxins. John Wiley and Sons Ltd., Hoboken, USA.

Funari E, Manganelli M, Buratti FM, Testai E, 2017. Cyanobacteria blooms in water: Italian guidelines to assess and manage the risk associated to bathing and recreational activities. Science of the Total Environment. 598:867-80.

Funari E, Testai E, 2008. Human health risk assessment related to cyanotoxins exposure. Crit Rev Toxicol. 38:97-125.

Hilborn ED, Beasley VR, 2015. One health and cyanobacteria in freshwater systems: animal illnesses and deaths are sentinel events for human health risks Toxins. 20:1374-95.

Hilborn ED, Soares RM, Servaites JC, et al, 2013. Sublethal microcystin exposure and biochemical outcomes among hemodialysis patients. PLoS ONE. 8:e69518.

Huisman J, Codd GA, Paerl HW, et al, 2018. Cyanobacterial blooms. Nat. Rev. Microbiol. 16:471-83.

Santori N, Buratti FM, Scardala S, et al, 2020. In vitro detoxication of microcystins in human samples: variability among variants with different hydrophilicity and structure. Toxicol Lett. 322:131-9.

Svirčev Z, Lalič D, Savič GB, et al, 2019. Geographical and historical overview of cyanotoxin distribution and cyanobacterial poisonings. Arch Toxicol. 93:2429-81.

Testai E, Buratti FM, Funari E, et al, 2016. Review and analysis of occurrence, exposure and toxicity of cyanobacteria toxins in food. Available from: https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2016.EN-998

Vichi S, Buratti FM, Testai E, 2016. Microcystins: toxicological profile. p 219-238 In: Marine and freshwater toxins. Springer Nature, Berlin, Germany.

World Health Organization (WHO), 2020. Cyanobacterial toxins: microcystins - Background document for development of WHO Guidelines for drinking-water quality and Guidelines for safe recreational water environments. Available from: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/microcystins-background-201223.pdf?sfvrsn=6d60aa6d_3

World Health Organization (WHO), 2021. Toxic cyanobacteria in water: a guide to their public health consequences, monitoring and management. Available from: https://www.who.int/publications/m/item/toxic-cyanobacteria-in-water—-second-edition