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Microcystin Exposure Pathways and Human Health

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ABSTRACT

Microcystins (MCs) are blue-green algal toxins produced by freshwater cyanobacteria. Their environmentally relevant concentrations throughout global surface waters have tampered with human populations' drinking and recreational supplies. MCs have gained immense public health attention due to their potential health effects. Microcystin-LR (MC-LR) is the most toxic variant of the MCs. Investigations on MC-LR toxicity and detection in water signify a growing potential environmental health concern worldwide. The World Health Organization established a provisional drinking water guidance value of 1 µg/L and a provisional recreational exposure guidance value of 10 µg/L for MC-LR. This review surveys human MC exposure pathways and integrates epidemiological studies to support MCs' critical exposure pathways. A discussion on monitoring and mitigation strategies provides a guide for policy development in adopting MCs' regulatory levels to protect public health.

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Introduction

Cyanobacteria, or blue-green algae, are photosynthetic microorganisms of aquatic ecosystems. They are prevalent in freshwater systems where they can amass into algal blooms [1]. These blooms feed off nutrient pollution from agricultural runoff and municipal wastewater [2]. Most algal blooms are innocuous, while others pose a danger to domestic animals, people, and wildlife [3]. Harmful algal blooms (HABs) are increasing in frequency and magnitude worldwide [4]. About 25% to 75% of HABs are toxic, emitting toxins into water bodies. Toxic HABs are known for disrupting water quality aesthetics of drinking water, fisheries, and recreation [5,6]. The microcystins (MCs) are considered the most hazardous blue-green algae toxins in eutrophic waters [7].

MCs are monocyclic compounds produced by cyanobacterial species [8]. Microcystis is MC's chief producer, but several other species can synthesize the metabolite [9]. MCs are waterborne contaminants with environmental and human health implications [10,11]. Two variable amino acids within MCs determine structural variation and toxicity. Microcystin-LR (MC-LR), the most toxic variant, contains leucine (L) at position 2 and arginine (R) at position 4 [12].

Studies have demonstrated MC-LR toxicology in mammalian organs [13,14]. The liver is the primary target organ for MC-LR, which can inhibit phosphatase activity [15]. Hepatocytes use the bile acid transporter and organic anion transporting peptides to absorb toxic MC-LR concentrations [16,17]. Protein phosphatase 1 (PP1) and protein phosphatase 2 (PP2) inactivation occur by MC-LR binding to active sites on the proteins [18]. Subsequently, phosphatase inactivation results in hyperphosphorylated proteins and irregular PP1 and PP2 cellular functions, including cytoskeleton degradation, hemorrhage formation, and hepatocyte disfiguration [18-20].

In the United States, MC-LR is a priority algal toxin [21]. While MC-LR toxicology in humans is less understood, its association with human health is significant. MC-LR is a potential human carcinogen, and the male testis is considered a target organ [22]. MC-LR toxicity can interfere with sperm morphology and motility and affect the reproductive system [23]. MC-LR is abundant in surface waters at environmentally relevant concentrations [24]. Testing methods have been developed to detect MC-LR in cells and water rapidly [25]. The recommended guidance value of MC-LR in drinking water and recreational water is 1 µg/L and 10 µg/L, respectively [26].

There is evidence of HAB toxins, such as MCs, causing animal and human health effects [27]. When HABs release toxins into their surroundings, MC exposure can occur, causing morbidity or mortality. Animal poisonings are due to direct, high-intensity harmful cyanobacteria exposure [28]. Dogs comprise most animal poisonings because they drink contaminated water, lick their fur, and swallow algal scum [29]. Companion animals may experience acute effects, such as bleeding, convulsions, diarrhea, profuse salivation, vomiting, weakness, and sudden death [30,31]. Thus, it seems harmful cyanobacteria are equally a human health threat.

Short-term effects in humans include gastrointestinal symptoms, kidney and liver failure, and skin irritation [32]. The long-term effects of harmful cyanobacteria remain unclear [33]. Therefore, MCs should receive more attention because they can cause serious environmental health risks. In this review, we describe MC exposure pathways and highlight epidemiological studies on human health. We also provide some insights on monitoring

and mitigation strategies to inform policy development to reduce MC exposure.

Exposure Pathways and Human Health

Acute and chronic exposure to MCs is an environmental health hazard. A complete evaluation of MCs' exposure pathways can help human risk assessment and practical strategies prevent toxic occurrences. The most common exposure pathway to MCs is the accidental ingestion of contaminated drinking water. Aerosol inhalation or dermal contact is not uncommon during water recreation activities. To a lesser extent, algae dietary supplement intake, consumption of contaminated food, and hemodialysis are MC exposure pathways.

Contaminated Drinking Water

Contaminated drinking water is the primary exposure pathway of MCs, representing approximately 80% of human exposure [34]. Algal cell disruption may cause elevated MC concentrations in drinking water used for consumption. Generally, humans are chronically exposed to low MC concentrations [35]. In Lucas County, Ohio, a municipal water supply had MC levels above the Ohio Environmental Protection Agency (EPA) drinking water advisory threshold of 1.0 µg/L [36]. MCs are stable in water reservoirs for a week and endure longer in deionized or filtered water [37]. Consequently, implementing water treatment processes for efficient toxin removal is essential to protecting public health.

Sporadic epidemiological studies have indicated relationships between contaminated drinking water and gastrointestinal cancer [38-40]. Ueno et al. identified blue-green algal toxins in China's drinking water sources of endemic areas of primary liver cancer (PLC). Ditches/ponds and rivers contaminated by MCs constituted an environmental risk factor for increased PLC incidence. In a retrospective cohort study, Zhou et al. correlated high colorectal cancer incidence with MC contaminated drinking water. Those who ingested polluted river water containing MCs had an increased risk for colorectal cancer. Fleming et al. linked hepatocellular carcinoma risk to proximity to surface water drinking supplies in Florida. The above epidemiological findings revealed that MC contaminated drinking water exposure increased gastrointestinal cancer risk.

Dermal Contact

Bathing, canoeing, or swimming are water contact activities of dermal contact exposure. Recreationalists have experienced a wide range of symptoms in cyanobacterial bloom waters, such as asthma, dermatitis, and hay fever, to name a few. Reported symptoms occurred in coastal waters of Australia, Japan, Hawaii, and Florida (41-44). Freshwater cyanobacterial blooms have resulted in reported symptoms among people who partook in swimming or water contact sports [45]. Cyanobacterial toxins, including MCs, can persist in fresh and marine environments. Recreationalists should take preventive measures (avoid entering water body, adhere to local or state guidance) if harmful cyanobacteria harbor recreational waters.

Aerosol Inhalation

Aerosol inhalation is likely when individuals engage in recreational or occupational field activities [44,46,47]. MC are waterborne toxins aerosolized through a bubble-bursting mechanism, leading to increased respiratory symptoms upon exposure [48]. Showering and industrial or agricultural practices involving water use with algal cells and toxins can release aerosols, thereby supporting inhalation as one probable human exposure [45].

Recreational exposure to MCs is a health risk in bloom lakes. MC aerosol exposure at low concentrations was examined in a small lake undergoing a cyanobacterial HAB [46]. Participants recounted no symptom increases after the pursuit of water-based recreational activities. Increased self-reported symptoms for the 7 to 10 days after exposure were more consistent with reported symptoms for 5 days before the study than reported symptoms immediately before or after recreational exposure. As such, MC aerosol inhalation may present symptoms a day or a few days after water-based recreational activities.

Toxic Microcystis HABs in two California lakes were sampled to assess recreational exposure to MCs [47]. Bloom lakes had variable MC concentrations where children and adults planned recreational activities. Personal air samples, blood samples, and nasal swabs were tested for MCs. Low concentrations were detected in personal air samples and nasal swabs, while non-detectable concentrations occurred in blood samples MC detection in human samples may indicate stirred up aerosolized cyanotoxins inhaled during water recreation.

Algae Dietary Supplement Intake

Algae dietary supplement intake constitutes another MC exposure pathway. Globally, the consumption of algae dietary supplements (ADS) is merited for putative beneficial health effects. They are known to alleviate stress, enhance mood, increase energy, improve alertness, and reduce weight [49]. ADS sourced from sizable lakes with periodic toxic Microcystis blooms can become contaminated when harvested for retail, increasing health risks for patrons who consume large doses over time [50].

Contaminated Food

Consumption of contaminated food is an alternative route of MC exposure. Aquatic organisms are integral to ecosystem functioning and provide nutritional value to humanity. Duck, fish, shellfish, prawns, and zooplankton can bioaccumulate MCs when they breathe or feed in water [51]. MCs' effects on animals' hepatic problems support human toxicity through oral consumption of toxic animal tissue [52]. Besides aquatic organisms, fruits and vegetables are probable candidates for MC contamination. Lakes and reservoirs source irrigated water for agriculture. Contaminated water tapped from these waters can reduce the overall quality and yield of crops [53]. Therefore, the consumption of contaminated fruits and vegetables may represent a potential risk factor for humans.

Hemodialysis

Perhaps the most infamous exposure pathway for MCs is hemodialysis. Treatment failures are possible at multiple points in the procedure once dialysate is prepared from surface drinking water supplies [54]. The largest human MC poisoning outbreak occurred in Caruaru, Brazil, killing 76 hemodialysis patients [55]. Since 2001, municipal drinking water in Brazil must undergo reverse osmosis before dialysate preparation to protect hemodialysis patients from cyanotoxin exposure [54]. Careful, consistent monitoring and treatment methods of surface drinking water supplies may prevent harmful episodes of MC poisonings in hemodialysis centers.

Monitoring and Mitigation Strategies

Cyanobacterial HABs are an environmental health problem, diminishing water quality in lakes, reservoirs, and rivers [56]. Toxic HABs impair surface drinking water supplies, despite inconsistent toxin treatment processes for algal toxins in the United States. Cyanobacterial toxins are important algal toxins of public

health concern [57]. Algal toxins are in the Contaminant Candidate List 3 (CCL 3) of 116 chemical and microbiological contaminants [58]. Yet, regulatory methods for the mandatory analysis of algal toxins in drinking water are unstandardized.

In recent decades, monitoring and mitigation strategies of cyanobacterial HAB toxins have become increasingly common for protecting drinking water quality and public health. Bioassays for algal toxins, including MCs, provide relevant toxicological information. They are desirable when the objective is to screen for toxin levels or identify potentially toxic species in environmental samples. Insights on advancements in cyanotoxin detections are presented by a discussion on enzyme-linked immunosorbent assay (ELISA) and quantitative real-time polymerase chain reaction (qPCR).

Enzyme-Linked Immunosorbent Assay

ELISA is widely used for the quantitative analysis of algal toxins. Unlike liquid chromatography-mass spectrometry (LC-MS), ELISA can detect covalently bound MC toxin. LC-MS, however, is reliant on congener standards and the amount of non-covalently bound MC in samples. Immunoassays are affordable, quick, and demand less expertise. Additionally, newly developed, and improved ELISA methods have exhibited lower detection limits for rapid screening and algal toxins monitoring. ELISAs possess technical limitations, including cross-reactivity due to various toxigenic substances, false-positive detection at low concentrations, and overestimation of toxin variant levels [59].

Quantitative Real-Time Polymerase Chain Reaction

An emerging molecular technique for detecting and quantifying low concentration, potentially toxic cyanobacteria is qPCR [60]. Its utility to identify cyanotoxin genes in bloom samples has increased over the years. Anticipated qPCR applications include studying the dynamics of fluctuations in toxin production by different strains in response to environmental conditions and the surveillance of toxic cyanobacterial bloom occurrences [61]. Pioneer studies in the early 2000s demonstrated the quantitative ability of qPCR to detect MC-producing genotypes in water [62-65]. Since then, many studies have combined MC quantification and qPCR to estimate bloom toxicity. The consistent usage of qPCR for cyanotoxin measurement may enhance MC human exposure assessment.

HAB Mitigation Approaches

HAB mitigation approaches serve to reduce HAB incidents. Numerous mitigation strategies have been established in response to human exposures, including physical, chemical, and biological controls. These control methods differ in their mode of action and are described below.

Physical controls use physical means to prevent the proliferation and spatial distribution of blooms and remove cells or toxins from the water column [66]. Closer observations of sediment contact to eliminate MCs from drinking water could prove useful for toxic bloom management. Sediment texture and redox conditions are critical factors in MC elimination during sediment passage [67]. Grützmacher et. al determined that fine-grained aquifer materials and aerobic conditions exhibited the highest rates of adsorption and degradation of MCs, respectively. Though sediment texture may be a reasonable MC control, local processes, mixing processes, as well as pH and oxidation, can wield notable effects on MC concentrations in sediment spatial distribution and adsorption [68].

Chemical controls include compounds that inhibit or disrupt HAB cellular growth [66]. Copper sulfate, a standard commercial algaecide, destroys cyanobacterial cell membranes through interactions between copper ions and lipids. The algaecide, however, can kill other algal species, which reduces HABs [69]. Hydrogen peroxide prevents photosynthesis in cyanobacteria and produces benign final products, such as water and oxygen [70,71]. Water treated with varying concentrations of hydrogen peroxide has been used for cyanobacterial bloom mitigation [72,73]. Sinha et al. demonstrated that 2.5 mg/L hydrogen peroxide treatments were sufficient to reduce observed MC concentrations, with effects lasting up to 5 weeks. One year later, Wang et. al found that treatments with hydrogen peroxide concentrations ranging from 96 μM to 165 μM for 2 hours were successful in mitigating Microcystis blooms.

Biological controls, such as organisms and processes, eliminate HABs [66] Bacterial species, including Acinetobacter, cause lysis of Microcystis aeruginosa through metabolite release, while the bacterial cells themselves reduce MC concentrations [74]. The algicidal compound B3, isolated from Streptomyces species L74 destroys cyanobacterial antioxidant systems, triggering an increase in malondialdehyde production within the cells [75]. Cyanobacterial infection by cyanophages decreased host populations significantly and may contribute to increased resistance in cyanobacterial species over time [76,77]. These biological mitigation techniques appear successful, though uncertainties linger in their long-term effectiveness.

Conclusions

MCs are environmental hepatotoxins hazardous to human health. MC exposure can result in various health effects, ranging from acute to moderately fatal. Evidence suggests that the multitude of MC exposure pathways increases human risk. Ingestion of contaminated drinking water represents the highest percentage of human exposures. Currently, regulations on MC concentrations in drinking and recreational waters vary globally, indicating MC exposure can differ by region. Monitoring HABs using ELISA and qPCR methods may improve cyanotoxin exposure detection and guide policy development to mandate tolerance levels for MCs in surface water supplies. Mitigation approaches can reduce HAB prevalence despite negative ecological impacts and a gradual decline in other control measures' effectiveness. Further investigations on human MC exposure are necessary to identify the most critical exposure pathway for preventing toxic encounters.

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