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Original Article

Can cyanotoxins penetrate human skin during water recreation to cause negative health effects?

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ABSTRACT

Cyanobacteria blooms and associated cyanotoxins pose significant public health risks during water recreation. Oral ingestion is the only recognized route of toxin exposure in water recreation guidelines. This review examines human skin as a barrier for the prevention of cyanotoxin absorption and investigates the likelihood of negative health effects through dermal exposure. Epidemiological studies of health effects from recreational exposure to algal blooms and toxins are summarized to highlight the importance of better understanding the toxicological effect of dermal exposure. The ability of a specific cyanotoxin to penetrate human skin is inferred by its physiochemical properties according to transdermal drug studies. The review identifies a disparity between the human health effects described in algal bloom exposure case studies and the toxicological skin exposure data. Skin penetration by algal toxins is likely and deserves further investigation.

1. Introduction

As part of the U.S. Environmental Protection Agency (EPA)'s efforts to better protect Americans' health during water recreation, the EPA issued new recommendations for water quality criteria and swimming advisory values for cyanotoxins in May 2019. These recommendations are based on peer-reviewed and published science, and are supposed to be protective of all age groups. However, the oral exposure route is the only route considered. The EPA acknowledged that dermal exposure occurs during swimming but commented that significant dermal absorption of cyanotoxins is not expected due to the large size and charged nature of these molecules (Butler et al., 2012). The goal of this review is to examine the state of knowledge on cyanotoxins in recreational water and their potential to cause negative health effects through dermal exposure. The ecology of cyanobacteria blooms and potential mitigation strategies have been presented in previous reviews (Buratti et al., 2017; Butler et al., 2012; de la Cruz et al., 2013; Paerl and Paul, 2012), and will not be replicated here. The main focus is to examine the effectiveness of human skin as a barrier in the prevention of cyanotoxin penetration and the likelihood of negative health effects through dermal exposure during water recreation. Analyses of molecular size, charge and structure of diverse cyanotoxins are presented to estimate the penetration potential. Future research directions are suggested for achieving a quantitative risk assessment of dermal exposure to cyanotoxins during recreational water activities.

2. Cyanobacteria and cyanotoxins in recreational water

Cyanobacteria, also called blue-green algae, are found in bodies of water all over the world. When the water is rich with nutrients and the environmental conditions are favorable, the cyanobacteria can flourish into harmful algal blooms (HAB). These blooms have increased in both frequency and severity worldwide as a result of climate change, population growth, and rapid urbanization (Paerl and Huisman, 2009; Paerl and Paul, 2012). Cyanobacteria produce a suite of biotoxins, including microcystins (MC), nodularin, anatoxin, saxitoxin, and cylindrospermopsin (Codd et al., 2005; Ho et al., 2012; Lopez et al., 2008 Loftin et al., 2016). The concentration of toxins is highest during warmer months, which coincides with the busiest times for recreational water activities.

Current recreational water guidelines for cyanotoxins differ for each state in the U.S. (Fig 1) and only include two best known toxins: MC and cylindrospermopsin. Most states do not have guidelines for individual toxins and warn swimmers only if there is a visible algal bloom, or increase in specific density of algal cells. However, the link between toxin concentration in water and visible algal blooms is not always straight forward. These U.S. state advisories also differ from the World Health Organization's (WHO) recreational water guideline, which is

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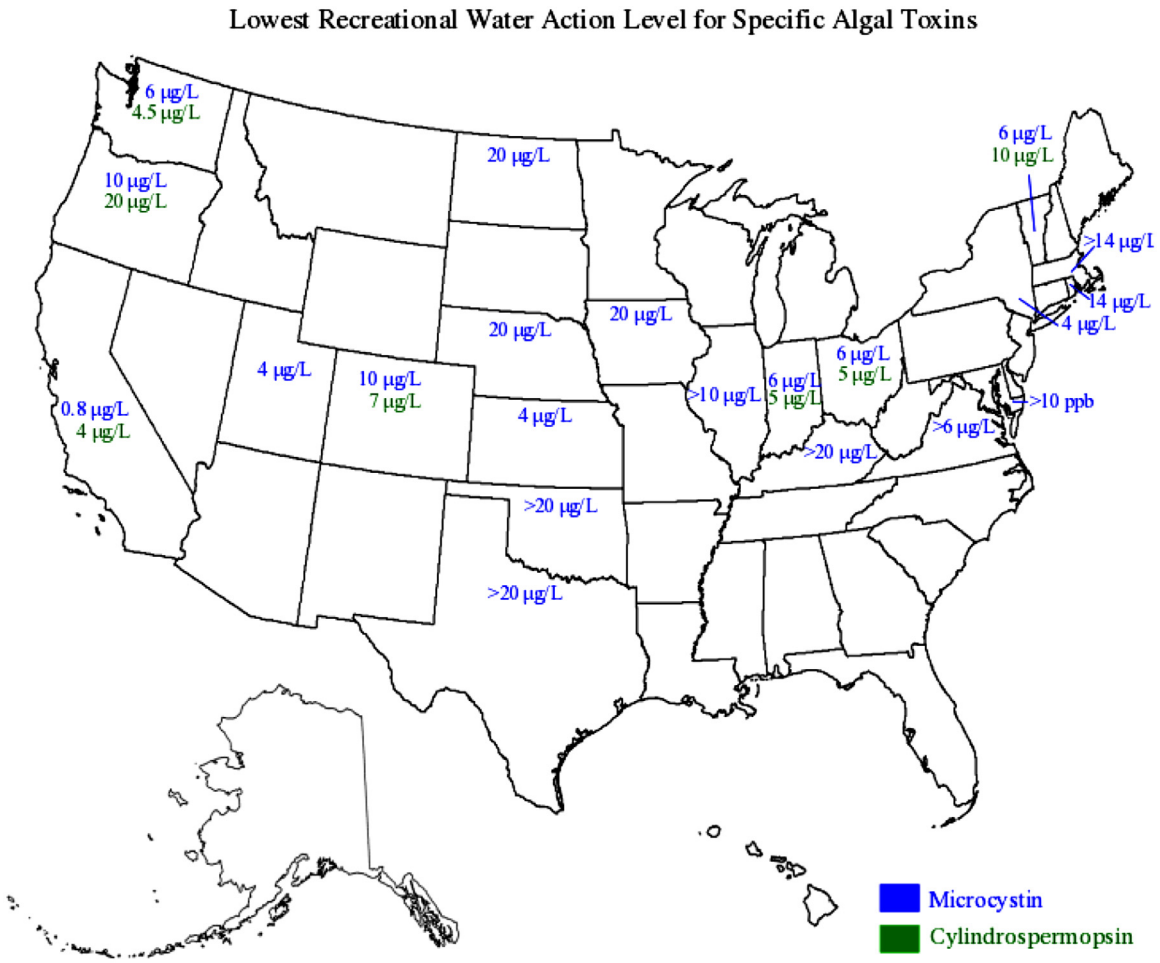

Fig. 1. Lowest Recreational Water Action Level for specific cyanotoxins by individual State in the U.S. based on EPA guidelines.

solely based on the relative probability of acute effects to MC concentration. So far, no regulatory advisory considers the risk through skin penetration.

3. Dermal exposure toxicology studies

Since the skin is the barrier against the outside environment, it is commonly assumed that human skin blocks toxins from entering blood circulation. However, neither dermal exposure nor the effectiveness of skin cells and mucous membranes in preventing cyanotoxin penetration has been well studied. To the best of our knowledge, only one study was published on the exposure of human keratinocytes to MC. The study demonstrated that toxicity was dependent on both exposure time and concentration in a dose-dependent manner and concluded that the observed effects could cause considerable health effects in humans (Kozdęba et al., 2014). Other studies attempted to use crude cyanobacterial extracts to assess dermal exposure effects on humans. Skin patch experiments on volunteers indicated that 5% − 15% of individuals had a significant skin reaction (Pilotto et al., 2004; Stewart et al., 2006a). Skin reactions were also observed using animal models exposed to high concentrations of cylindrospermopsin (Stewart et al., 2006b), yet, a quantitative dose-response relationship was missing.

Overall, the limited dermal exposure studies conclude that cyanotoxins cause mild to moderate skin irritation, and in some individuals allergic reactions are seen, but these data do not consider additional cytotoxic, carcinogenic and penetrative effects. No study has examined the high exposure levels encountered during water recreation when a large skin surface area, including mucous membranes, is submersed for extended periods of time.

4. Epidemiological studies

Outbreaks associated with cyanobacterial blooms are the main source of human health effects data (Trevino-Garrison et al., 2015). There have been several extensive reviews published which have detailed severe symptoms arising after exposure to algal toxins during water recreation. The outbreaks have included data from both adults and children, although children account for most of the cases and usually suffer more severe health effects (Funari and Testai, 2008; Stewart et al., 2006c; Testai et al., 2016). Table 1 summarizes health effects described in documented case studies. Fig. 2 represents the age distribution of the patients described in the case studies from Table 1. These symptoms, which are well beyond skin surface irritation, are in dramatic contrast with the dermal exposure studies described above (section 3.0). These disparities in the observations could be related to other biological mechanisms of algal blooms that are not yet understood, or the compound effects of a mixture of toxins and exposure routes, which are not investigated in toxicology studies. Nevertheless, these observations warrant investigations to explain the epidemiology data in order to create appropriate safety guidelines.

Incidental ingestion of algal toxin contaminated water has been cited has the cause of disease in some of the case studies. However, dermal penetration appears to contribute to negative health effects upon a closer examination of the case reports because the severity of the symptoms is not easily explained by incidental ingestion of water alone. Our analyses showed that based on the no-observed-adverse-

Table 1
Summary of human health effects described in case studies of exposure to recreational waters during cyanobacteria blooms with and without toxin identification.

Toxin	Human health effects from recreational exposure
saxitoxin	Fever, eye irritation, abdominal pains, and skin rash (Rapala et al., 2005)
anatoxin-a	Seizure, heart failure, and death (Stewart et al., 2006c; Testai et al., 2016; Weirich and Miller, 2014)
microcystin (MC)	Joint pain, rash, gastrointestinal illness, pneumonia, fever, liver damage, sore throat, cough, headache, nausea vomiting, and respiratory distress (Giannuzzi et al., 2011; Weirich and Miller, 2014)
cylindrospermopsin	No data specific to cylindrospermopsin
nodularint	No data specific to nodularin.
oxin(s) not identified	Headache, sore throat, vomiting and nausea, stomach pain, dry cough, diarrhea, blistering around the mouth, pneumonia, rashes, eye, nose, mouth or throat irritation, allergic reactions, malaise, respiratory failure, seizure and death (Trevino-Garrison et al., 2015; Wood, 2016)

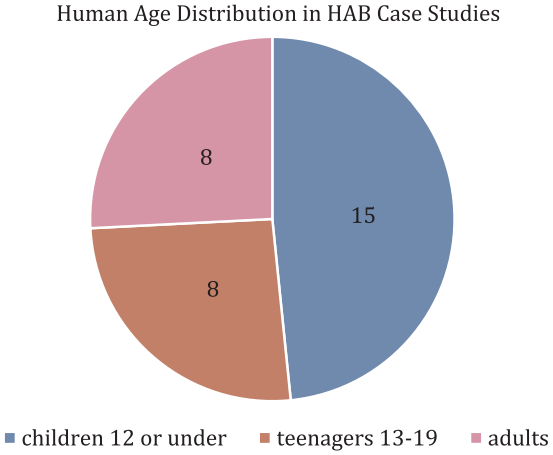

Fig. 2. Age distribution of illness cases from outbreak reports shown in Table 1. (Billings, 1981; Giannuzzi et al., 2011; Heise, 1949; Rapala et al., 2005; Trevino-Garrison et al., 2015; Turner et al., 1990; Weirich and Miller, 2014).

effect-level (NOAEL) of several algal toxins, it would require ingestion of quite a lot of water to elicit the symptoms described.

For example, in the Giannuzzi et al. report, a 19-year old male became severely ill after riding his jet ski and incidentally ingesting contaminated water. The water contained 48.6 ug/L MC (Giannuzzi et al., 2011)and the NOAEL for MC is 40 ug/kg body weight (bw) (Weirich and Miller, 2014). This suggests that the patient would have to incidentally ingest many liters of water to expect to see such severe symptoms as reported.

In Testai et al.'s paper, the report of the teenager that died in Wisconsin stated that he was swimming with four other teenage boys whom all became ill, even though he was the only one that reported incidental ingestion (Testai et al., 2016). According to the paper, his death was most likely explained by anatoxin-a poisoning although the progression did not match that described in toxicology studies (Stewart et al., 2006c). Anatoxin-a kills very fast through oral exposure. In oral toxicity studies, animals die within minutes because anatoxin-a is readily absorbed from the gastrointestinal tract (Stewart et al., 2006c). However, it takes longer for toxins to be absorbed into the bloodstream from the skin, which matches the toxicity progression of the boy who passed away 48 h after exposure. Humans with non-lethal anatoxin-a poisoning from ingestion of contaminated water mainly suffer from gastrointestinal symptoms. The four boys who survived the swimming incident had diverse symptoms including gastrointestinal illness, respiratory distress, fever, and mouth blisters (Testai et al., 2016), suggesting incidental oral ingestion may not have been the only exposure path.

The algal toxin concentrations were not measured in the water in Testai et al.'s paper so we cannot calculate the possible dose of anatoxin-a due to ingestion. However, according to the Health Effects Support Document for the Cyanobacterial Toxin Anatoxin-a, EPA stated that anatoxin-a levels of up to 1,750ug/L have been detected in Wisconsin (U.S. EPA, 2015). If we assume that the five teenagers swam in the maximal toxin levels that have ever been detected, incidental ingestion may have been enough to cause illness. However, it does not explain the severity of the symptoms since the reported LD_{50} from oral exposure to anatoxin-a is ~13.3 mg/kg bw and the NOAEL is 0.5 mg/kg bw per day according to the EPA (U.S. EPA, 2015). Other published literature has reported that the LD_{50} for anatoxin-a in mice with intraperitoneal injection (i.p) is 260–315 μg/kg bw (Stevens and Krieger, 1991; Valentine et al., 1991) whereas the LD_{50} of oral administration is >5000 μg/kg bw (Stevens and Krieger, 1991). If we assume an LD_{50} of 5000 μg/kg bw, and we assume the teenager weighed 40 kg, he would have had to consume 114 liters of water with a toxin level of 1,750ug/L to reach the LD_{50} concentration. If we use the LD_{50} from i.p. injection of 300 ug/kg bw, he would still have had to drink nearly 7 liters of water to consume the LD_{50} concentration of anatoxin-a. We believe that while incidental ingestion does play an important role, dermal penetration of algal toxins compounds with oral ingestion to cause negative health effects.

5. Absorption through the skin

While human skin undoubtedly provides a barrier against chemicals, toxins and microorganisms, it can be permeated. Transdermal drugs are the best example of chemicals that permeate skin to deliver an effective dose to the human body. The skin is made up of three layers: the stratum corneum (SC), the epidermis and the dermis. In order for a molecule to gain entry to the bloodstream, it would need to pass through all three layers. The intact SC layer is made up of mostly dead cells packed in a lipid matrix and is considered the rate-determining layer for most chemicals (Lane, 2013). Therefore, some lipophilic substances can pass with relative ease (Nielsen et al., 2016) while hydrophilic molecules can penetrate through sweat ducts and hair follicles (Bos and Meinardi, 2000). Biphasic substances (soluble in water and lipids) have the greatest propensity for skin penetration (N'Da, 2014). It is believed that once an exogenous substance has passed through the SC, further passage into the epidermis, dermis and capillaries is likely (Idson, 1975).

The skin permeability of a chemical is closely related to the partition coefficient (P) between octanol and water (reported as Log P) of a given compound.

This is defined by the following equation: $Kow = \frac{[solute]_{octanol}}{[solute]_{water}}$ where the partition coefficient is expressed in logarithmic form which is indicated by log K_{ou} or Log P (Moldoveanu and David, 2015).

Log P coefficients can be predicted using computational algorithms such as XlogP3-AA. Low log P values indicate that the compound is more hydrophilic, while high log P values indicate high lipophilicity. Transdermal drug research has demonstrated that an optimal log P value for skin absorption is between −1.0 and 4.0 (Chandrashekar and Shobha Rani, 2008).

The molecular weight of a given compound can also help predict skin permeation. Smaller molecules, less than 500 Daltons (Da), can penetrate the skin more easily than larger molecules (Bos and Meinardi, 2000; N'Da, 2014). However, compounds with molecular weights of 800 Da can penetrate broken skin and compounds up to

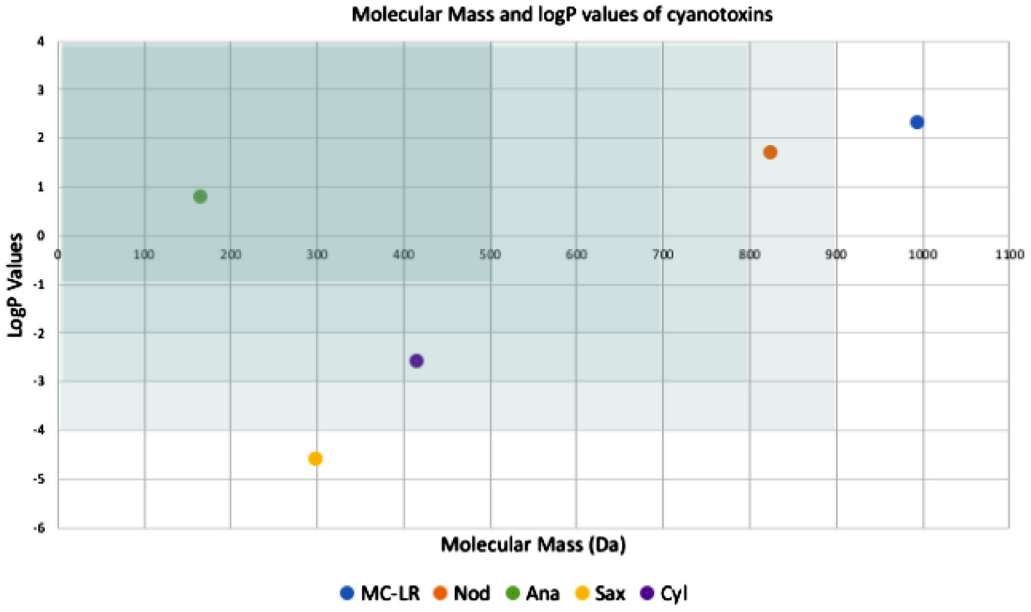

Fig. 3. The plot of five cyanotoxins (MC-LR, nodularin, anatoxin-a, saxitoxin and cylindrospermopsin) according to their logP values and molecular mass for prediction of skin permeation. The likelihood for skin permeation decreases from darker shaded region (top left) to lighter shaded region (bottom right). Graph is based on data acquired from published literature (Bos and Meinardi, 2000; Chandrashekar and Shobha Rani, 2008).

1200 Da have been shown to penetrate mucous membranes (Bos and Meinardi, 2000). Based on transdermal drug absorption research, cyanotoxins' molecular properties can be used to predict skin absorption (Fig 3). As shown in Fig 3, all five toxins discussed in this review have the capability to be absorbed through the skin. Anatoxin-a has an ideal log P value and small molecular weight indicating that passive diffusion through intact skin is likely. MC and nodularin have larger molecular weights, which would make intact skin permeation more difficult, but they have ideal log P values. Saxitoxin and cylindrospermopsin are smaller molecules but their predicted log P values are outside the range for optimal skin absorption.

It is also important to note that predicted skin permeation assumes the drug is applied to intact, healthy skin. Recreational water represents a unique exposure scenario because most of the body is submersed in the water for extended periods of time. This gives the toxins more skin surface contact, including mucous membranes, for long durations, which could lead to increased absorption and toxic effects. Skin penetration by toxins is supported by indirect evidence of irritation and skin reaction after skin exposure because in order for a compound to elicit an immune response, it has to penetrate the SC. Based on the above evidence, skin penetration by algal toxins is likely during water recreation.

6. Skin characteristics affecting permeation

An intact SC layer is one of the most protective characteristics of human skin (Idson, 1975). Damaged skin is more easily penetrated than intact, healthy skin (Nielsen et al., 2007). Many people exposed to recreational water have suboptimal skin integrity due to cuts, irritation, psoriasis, eczema, and even dry skin. Nielsen et al. discovered that slightly damaged skin significantly increased the rate of chemical absorption, even with chemicals that normally have a low penetration rate on intact skin (Nielsen et al., 2016).

Skin hydration status influences transdermal absorption. As the skin is soaked in water, exposed to high humidity, and/or well moisturized, the cells in the SC begin to swell, enabling molecules to permeate more easily (N'Da, 2014). In fact, ethanol/water co-solvent has been used to increase the transdermal delivery of certain pharmaceuticals (Li and Chan, 1999).

Penetration varies with each body site. The biological factors influencing this variation are number of hair follicles, thickness of the SC, distance between capillaries and sebum composition (Nielsen et al., 2016). A study by Feldman and Maibach (1967) assessed the absorption of hydrocortisone for different anatomic locations on human skin and showed that there was a large difference between body sites. Scrotal skin had the largest measured absorption which was a 42-fold increase as compared to forearm skin. Plantar skin was the most resistant to hydrocortisone absorption as compared to the forearm. Back, scalp, axilla, forehead and jaw angle skin all showed increasing rates of absorption, respectively, as compared to the forearm (Feldmann and Maibach, 1967). In addition, mucous membranes, which often come in contact with the water during recreational activities, have increased permeability as compared to skin. It has been estimated that oral cavity mucous membrane absorption is between 4 and 4000 times greater than the skin, and in general is considered an intermediate between the permeability of the epidermis and that of intestinal mucosa. (Galey et al., 1976). The permeability coefficient for amphetamine (135 Da and logP =1.8) in buccal mucosa is 1.5×10^{-5} cm/s as compared to human skin which is 3.9×10^{-9} cm/s (Harris and Robinson, 1992), which is a 3846 fold increase in permeability rate in the buccal mucosa as compared to skin.

Exposure to mucous membranes involves not only incidental splash to the face and eyes, but the constant contact between genital mucosal epithelia and the water. While the rectal mucosa (1 mm) is thicker than the buccal mucosa (500–800μm), the vaginal mucosa (200–300μm) and pulmonary mucosa (0.1–0.2μm) are much thinner (Goyal et al., 2018). Although thickness is not the only characteristic that predicts absorption, it plays a significant role (Goyal et al., 2018). When fully submersed in contaminated water, toxins have access to all body sites, increasing the possibility of skin absorption.

Age is an important characteristic when assessing skin penetration as toxins more readily penetrate the skin of younger individuals (Nielsen et al., 2016). Aging skin has a lower moisture content (Potts et al., 1984) which lessens transdermal absorption of molecules (N'Da, 2014). Children and young adults may be more likely to stay in the water longer, fully submerse their entire bodies and are especially sensitive to algal toxins because of their lower body weight, behavior in the water, and the toxic effects on development (Weirich and Miller, 2014). This could explain the greater number of algal toxin outbreaks in young people in the epidemiological studies.

Chemical penetration enhancers (CPEs) are commonly used in the pharmaceutical industry to help drugs penetrate the skin. Some components of sunblock, such as octyl salicylate are used as CPEs. People often apply sunblock during recreational water activities and this may

facilitate penetration of toxins present in the water.

7. Looking forward

Current recreational water algal toxin exposure guidelines are based on ingestion/intravenous exposure of animals. While this is helpful regarding those particular routes of exposure, the literature does not adequately assess the effects of dermal exposure, including mucous membrane and eye exposure. Based on the discrepancies between dermal exposure studies and epidemiological evidence of severe toxicity, we have to wonder if prolonged submersion in contaminated water and subsequent large skin surface area contact with a wide variety and often unknown mixture of cyanobacterial cells and toxins is at least partially responsible for the disparity.

A better understanding of skin penetration of single toxins, mixtures of toxins and cell components is necessary. The recent development and commercialization of human 3D tissue models presents new opportunities to expand cyanotoxin toxicity research. These human tissue models are more physiologically and metabolically relevant to humans than animal models. Their high reproducibility allows comparison of different toxins and other chemicals using the same testing protocols. Another advantage to using 3D cell models is the unique opportunity to analyze skin penetration of the toxin, which cannot be easily assessed using traditional cell culture, animal models, or humans.

The protective function of skin is not limited to the physical barrier; the skin microbiome may also play a role in the defense against toxins. Numerous microbiome studies have determined that our resident flora metabolize various chemicals (Koppel et al., 2017)(Noh et al., 2017) (Clarke et al., 2019) and that the skin microbiome changes rapidly during water recreation (Nielsen and Jiang, 2019). Investigating the role of the skin microbiome on xenobiotic metabolism is also useful to quantify the risk of dermal exposure to cyanotoxins.

In summary, there is a disparity between the human health effects described in cyanobacterial bloom exposure case studies and the toxicological skin exposure data. The symptoms described in the case studies are more severe and include systemic effects such as fatigue, organ damage, paralysis, and even death. It is difficult to discern whether or not skin exposure to algal toxins is completely responsible for these symptoms as incidental ingestion and inhalation of aerosols also contribute. However, it is imperative that we acknowledge the need for research designed to address the current knowledge gaps in order to prevent future outbreaks. We need to investigate the skin penetration capabilities of algal toxins and assess if toxin mixtures may synergistically compound toxicity and subsequent health effects. This data will help provide information for water quality management authorities to accurately and rapidly evaluate human health risks from harmful algal blooms.

Declaration of Competing Interest

Authors declare no competing interests

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