Environmental Science & Technology

pubs.acs.org/est

Critical Review

Toxic Cyanobacteria: A Growing Threat to Water and Air Quality

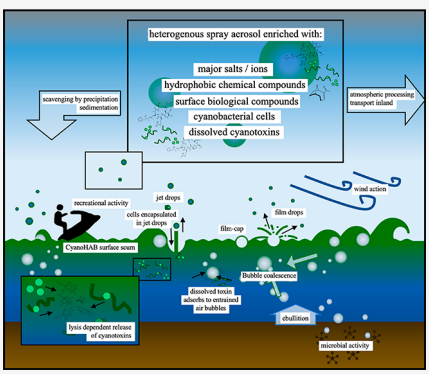
Haley E. Plaas and Hans W. Paerl*

Cite This: https://dx.doi.org/10.1021/acs.est.0c06653

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: The global expansion of harmful cyanobacterial blooms (CyanoHABs) poses an increasing threat to public health. CyanoHABs are characterized by the production of toxic metabolites known as cyanotoxins. Human exposure to cyanotoxins is challenging to forecast, and perhaps the least understood exposure route is via inhalation. While the aerosolization of toxins from marine harmful algal blooms (HABs) has been well documented, the aerosolization of cyanotoxins in freshwater systems remains understudied. In recent years, spray aerosol (SA) produced in the airshed of the Laurentian Great Lakes (United States and Canada) has been characterized, suggesting that freshwater systems may impact atmospheric aerosol loading more than previously understood. Therefore, further investigation regarding the impact of CyanoHABs on human respiratory health is warranted. This review examines current research on the incorporation of cyanobacterial cells and cyanotoxins into SA of aquatic ecosystems which experience HABs. We present an overview of cyanotoxin fate in the environment, biological incorporation into SA, existing data on cyanotoxins in SA, relevant collection methods, and adverse health outcomes associated with cyanotoxin inhalation.



1. INTRODUCTION

The environmental health of aquatic ecosystems is threatened by the global proliferation of harmful cyanobacterial blooms (CyanoHABs).[1,2] CyanoHABs are dominated by toxigenic cyanobacterial genera, e.g., *Cylindrospermopsis, Dolichospermum* (formerly *Anabaena*), *Microcystis*, and *Planktothrix*, characterized by gene sequences encoding the production of toxic metabolites known as cyanotoxins.[3,4] Under eutrophic conditions, some cyanobacterial genera can concentrate as dense surface scums (Figure 1).[5,6] In recent decades, the occurrence of CyanoHABs has increased temporally and spatially due to anthropogenic nutrient overenrichment[7−10] and climatic changes.[11−13] CyanoHAB events negatively impact water quality, degrade ecosystem integrity, and pose a threat to human health.[14−20]

The main health concern stemming from CyanoHABs is the production of cyanotoxins in drinkable, fishable, and recreational water resources. Several cyanobacterial genera produce a suite of toxins across variable environments, including anatoxin (ATX), cylindrospermopsin (CYN), microcystin (MC), nodularin (NOD), and saxitoxin (STX). The types and concentrations are largely determined by interactions between environmental factors that promote toxigenic genotypes and toxin gene expression. The extent of these interactions has not been comprehensively examined,[21−23] and thus, cyanotoxin production and subsequent human exposure remains challenging to forecast.[21,24]

Exposure to cyanotoxins is linked to an array of adverse public health outcomes.[25−27] We refrain from discussing cyanotoxin-related health threats comprehensively; many works exist to elucidate the exposure routes and toxicological effects associated with cyanotoxins.[25−29] Instead, we explore the inhalation-specific health threats associated with CyanoHABs and the physicochemical properties of aquatic ecosystems that may promote the aerosolization of cyanotoxins, primarily MC, which is among the most widespread and frequently detected cyanotoxins.[30] The health concerns associated with cyanotoxin exposure routes such as ingestion are commonly investigated,[19,29,31−34] but the inhalation of cyanotoxins in aerosol and related health impacts remain understudied. This is despite convincing evidence to suggest that cyanobacteria and their metabolites occur in aerosol.[35−43] Several aquatic cyanobacterial species have been detected in the atmosphere,[44−50] including toxigenic genera. Furthermore, aerosol containing biologically derived material is ubiquitously formed in marine airsheds,[51−53] and recent research has presented similar findings in freshwater ecosystems.[54−57]

With CyanoHAB events increasing in frequency, severity, and expanding geographically, cyanotoxin incorporation into respirable aerosol may increase in regions that experience recurrent blooms. Airborne algae have long been suspected to

Received: October 2, 2020
Revised: December 4, 2020
Accepted: December 7, 2020

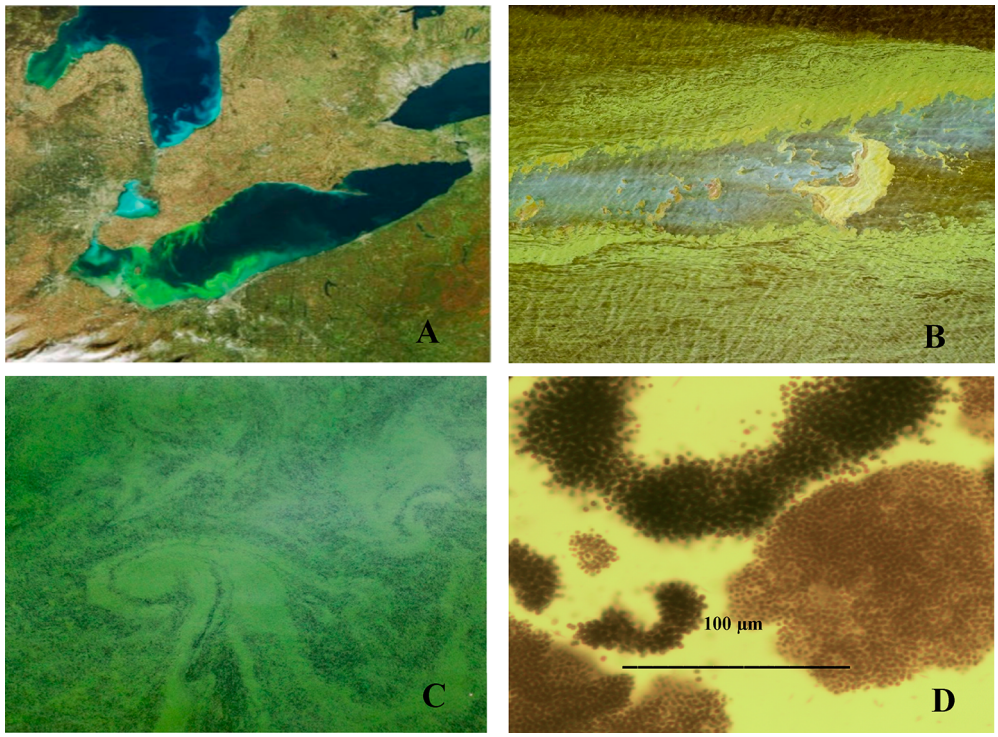


Figure 1. Dense surface cyanobacterial bloom activity; (A) a satellite shot of a widespread bloom on western Lake Erie during the Toledo Water Crisis of 2014; (B) drone-based photograph of a *Dolichospermum* surface scum on the Chowan River, North Carolina, 2020 (photo: Abe Loven); (C) close-up image of a *Microcystis* bloom on Maumee Bay, Lake Erie, Ohio, 2019 (photo: Haley Plaas); (D) photomicrograph of *Microcystis spp.* colonies (photo: Hans Paerl).

cause human respiratory irritation such as hay fever,[40,58,59] and research characterizing algal toxins in aerosol from the marine dinoflagellates *Karenia brevis (K. brevis)*[60−63] and *Ostreopsis* cf. *ovata*[64−67] is common. Little work has been done to evaluate cyanotoxins in aerosol, despite the fact that cyanobacteria dominate airborne algal communities due to their high tolerance for a broad range of atmospheric conditions.[47,68] Airborne cyanobacterial communities can persist in urban environments and are observed in indoor living spaces.[41,44,46,69,70] Individuals living near aquatic ecosystems harboring CyanoHABs may be at an elevated risk of cyanotoxin related health problems, without ever having direct contact with the water. Furthermore, the inhalation of aerosol poses its own noteworthy health risks beyond the toxicological effects of cyanotoxins.[71−78]

Despite known public health threats associated with both exposure to cyanotoxins and the inhalation of aerosol, neither the World Health Organization (WHO) nor the United States (U.S.) Environmental Protection Agency (EPA) have established cyanotoxin inhalation standards. This is largely due to a lack of data characterizing aerosol containing cyanotoxins. Accordingly, the key objectives of this review are to evaluate known mechanisms behind biological incorporation into spray aerosol (SA), compile current data on aerosolized cyanotoxins, and identify knowledge gaps in this interdisciplinary area of research to motivate future studies.

2. METHODS

This critical review utilized the following databases to search the literature: ACS Publications (https://pubs.acs.org/), Google Scholar (https://scholar.google.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Science Direct (https://www.sciencedirect.com/), Taylor and Francis online (https://www.tandfonline.com/), and Web of Science (http://apps.webofknowledge.com/). The primary keywords were searched as follows for each section: for Section 3.1, *cyanotoxin*, *occurrence*, and *fate*, for Section 3.2, *biological*, *sea spray aerosol*, and *lake spray aerosol*, for Sections 3.3 and 3.4, *microcystin*, *aerosol*, *cyanotoxin*, and *harmful algal bloom*, and for Section 3.5, *microcystin*, *inhalation*, and *lung*.

3. RESULTS

Section 3.1 describes the physicochemical processes which affect the transport of cyanotoxins in the environment, as these processes impact cyanotoxin environmental chemistry and incorporation into SA via interactions with entrained air bubbles. Section 3.2 explores the formation mechanisms of SA in aquatic systems and how biological components, including harmful algal bloom (HAB) toxins, are incorporated into SA. Section 3.3 presents a comprehensive overview of the published data which evaluated cyanotoxins and CyanoHAB cells in aerosol. Methods from these studies and other pertinent airborne algae studies are reviewed Section 3.4. Section 3.5 examines the current data on the toxicological effects of MC in human lung models.

3.1. Environmental Fate and Chemistry of Cyanotoxins. *3.1.1. Source, Structure, and Chemistry of Cyanotoxins.* The chemical structure and intrinsic properties of cyanotoxins dictate their reactions and movement in aquatic ecosystems and, therefore, their potential incorporation into aerosol. Most information available on the chemistry, toxicity, and transport of cyanotoxins has focused on MC. MC and NOD are classes of related cyclic peptides with variant amino acid side chains. Both are extremely stable compounds which may persist in the

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

water column for weeks following their release after cell death.[24,79,80] As demonstrated in Table 1, MC is produced by a large majority of the genera discussed, whereas NOD is primarily produced by filamentous genera in estuarine systems.[81,82]

Table 1. Cyanotoxin Production Observed Across Cyanobacterial Genera

Cyanobacterial Genera	ATX	CYN	MC	NOD	STX	References
Anabaenopsis			X			232
Aphanizomenon	X	X	X		X	115
Chrisosporum		X				89,112
Cylindrospermopsis	X	X			X	92,97,233
Cylindrospermum	X		X		X	234
Dolichospermum (ex Anabaena)	X	X	X		X	81,235,236
Fischerella			X			232
Geitlerinema					X	234
Gloeotrichia			X			25
Haplosiphon			X			25
Lyngbya		X			X	96,237,238
Microcystis			X			83,131
Nodularia				X		239,240
Nostoc	X		X	X		82,241,242
Oscillatoria	X	X	X		X	243,244
Phormidium	X		X			82,241,245
Planktothrix	X		X			23,246
Radiocystis			X			25
Raphidiopsis	X	X	X			247
Scytonema			X		X	232
Umezakia		X	X			248

The MC molecule contains D- and L-amino acids, *N*-methyldehydroalanine (Mdha), and the defining nonproteinogenic amino acid side group, 3-amino-9-methoxy-2-6,8-trymethyl-10-phenyldeca-4,6-dienoic acid (Adda) (Figure 2). MC congeners differ primarily at the two L-amino acids (denoted X and Y), but differences are also demonstrated at the Mdha or D-*erythro*-β-methylaspartic acid (D-MeAsp).[83] The NOD structure varies slightly from MC and consists of an Adda, *N*-methyldehydrobutyrine (Mdhb), D-*erythro*-β-methyl-aspartic acid (D-MeAsp), and L-arginine (L-Arg) (Figure 2).[83] Overall, MC and NOD compounds are mildly hydrophilic at typical pH levels in freshwater systems (neutral to mild alkalinity), but MC exhibits increasing hydrophobicity when exposed to acidic conditions.[84] The hydrophobicity of MC (as well as NOD) is driven in part by the Adda moiety and the occurrence of hydrophobic amino acids at each variable side chain;[85,86] such variance in hydrophobicity between congeners, i.e., their relative affinity for air, is important to consider when evaluating their potential incorporation into aerosol. MC congeners with hydrophobic amino acid side chains, e.g., MC-LW (-leucine-tryptophan), have higher octanol−water partitioning coefficients than congeners with less hydrophobic amino acids, e.g., MC-LR (-leucine-arginine).[87]

CYN is a tricyclic alkaloid with a central functional guanidino moiety and a hydroxymethyluracil (Figure 2).[88−90] As a zwitterion, CYN is extremely hydrophilic.[91] *Cylindrospermopsis raciborskii* was the first noted producer of CYN,[92] but additional genera are reported in Table 1.

STX is a trialkyl tetrahydropurine which is chiefly produced by dinoflagellates in marine ecosystems but also by freshwater cyanobacteria (Figure 2).[93,94] Few data sets are available on the occurrence and transport of STX in freshwater systems, but hydrophobic analogues of STX are known to occur within the freshwater cyanobacterium *Lyngbya wollei*.[95] The fate of STX most commonly studied is organismal. A large research focus is placed on the toxicology of STX, as it easily accumulates in

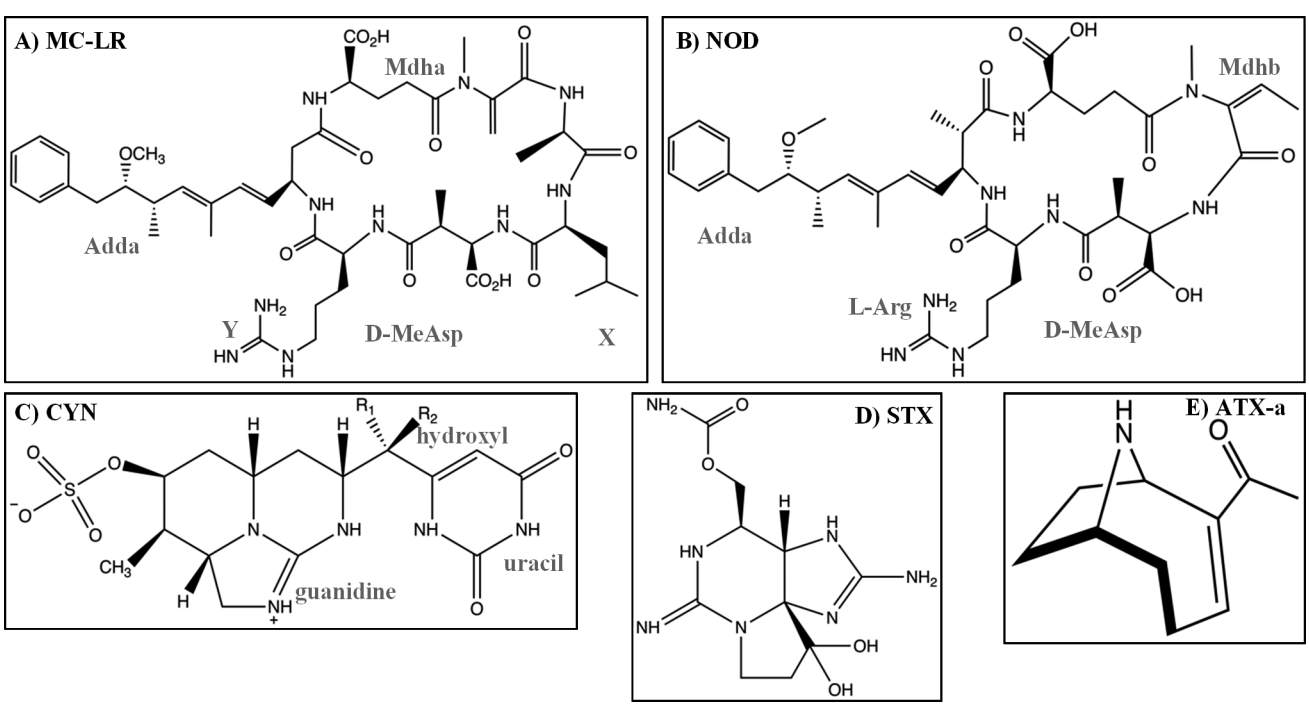


Figure 2. Chemical structures of cyanotoxins with characteristic chemical groups labeled; (A) Microcystin-leucine-arginine (MC-LR); (B) Nodularin (NOD); (C) Cylindrospermopsin (CYN); (D) Saxitoxin (STX); (E) Anatoxin-a (ATX-a).

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

seafood tissues and leads to paralytic shellfish poisoning in human beings.[95−97]

ATX is a group of related secondary amine alkaloids, ATX-a (Figure 2) and homo-ATX-a, as well as the phosphate ester of a cyclic *N*-hydroxyguanidine structure, ATX-a(s).[98−100] Despite their names, ATX-a and ATX-a(s) are structurally dissimilar and therefore exhibit different chemical behaviors. ATX-a and homo-ATX-a are fully soluble in water,[100] but as the only naturally occurring organophosphate, the behavior of ATX-a(s) is more similar to that of organophosphorus insecticides in aquatic ecosystems.[25] ATX-a(s) may adsorb to soils and persist in the environment for long periods of time.[101] Cyanobacterial producers of both ATX and STX are reported in Table 1.

3.1.2. Occurrence of Cyanotoxins in the Environment. Cyanotoxins are largely endotoxins, and their release into the environment is dependent on ambient conditions and bloom growth stage.[94] CyanoHAB cells are typically found in the upper euphotic zone, as many genera maintain buoyancy via gas vesicles to remain surface-active for maximal photosynthetic yields.[102,103] Unlike marine dinoflagellate HABs, CyanoHABs are typically not susceptible to physical forms of cell lysis from breaking wave action or shear stress.[104] CyanoHAB cells only release toxins into the water column during cell senescence,[105,106] lysis through viral activity,[107] or remediation processes such as algaecide treatments,[80] or exposure to heightened salinity along estuarine gradients.[108] In the environment, the dissolved fraction of MC does not usually comprise more than 10% of the bulk toxin concentration,[19,80] and this may also be true for NOD, ATX, and STX.[91,98,109−114] Conversely, CYN can be found at significantly higher proportions in the dissolved form and is proposed to be actively transported outside the cell.[115,116] While the fate of intracellular toxins is controlled by cell physiology, dissolved toxins are subject to processing in the environment. Therefore, consideration of the concentration of dissolved toxins is likely significant when evaluating cyanotoxin transport in aerosol.

3.1.3. Degradation Pathways for Cyanotoxins in the Environment. The bioavailability of and exposure to cyanotoxins in higher organisms is dependent upon site-specific factors. Cyanotoxins are subject to photolysis from sunlight (photosynthetically active radiation (PAR), UV-A, and UV-B), adsorption to sediment or particulate organic matter (POM), or microbial degradation. MC decomposes when exposed to UV light, and under ambient conditions, its half-life is approximately 10 days.[117] Furthermore, photosensitizers such as chlorophyll pigments, humic acid, or fulvic acid must be present for MC and NOD to break down entirely.[118] CYN photolysis occurs less easily *in situ*, as it more strictly requires UV-A sunlight and photosensitizers to degrade effectively.[114,119] Conversely, ATX may undergo rapidphotolytic degradation in the absence of photosensitizers, making its accumulation in sediments or higher organisms less likely.[25,26] Kaminski et al. (2013)[99] found that ATX-a only broke down under high temperatures and UV−B exposure, suggesting it may also persist in the environment for extensive periods.

The biogeochemical characteristics of an ecosystem influence the adsorption of toxins onto POM, such as detritus or plant litter, or suspended minerals and sediments in the water column. MC is potentially scavenged by these particles, protecting it from degradation and transporting it over long distances. MC is possibly resuspended under some conditions, but ultimately, the geochemical fate of MC is not well understood.[120] In a series of eutrophic lakes in Japan, Tsuji et al. (2001)[121] found the hydrophilic moiety of MC bound tightly to sediment but conversely, Morris et al. (2000)[120] determined that clay particles scavenged MC by binding with the hydrophobic Adda. Furthermore, the extent to which MC may adsorb to POM is a function of water pH,[86,122,123] suggesting that site-specific water chemistry is important when considering the ability of cyanotoxins to adsorb to suspended particles or air bubbles for aerosolization.

For MC, NOD, and CYN, the period over which photodegradation occurs in natural settings is lengthy, and their chemistry may disallow them from interaction with suspended sediments. Thus, biotransformation is the proposed dominant pathway for cyanotoxin degradation in natural systems.[124] Cyanotoxins may be degraded by heterotrophic bacteria, as there is evidence of this for MC[125−128] and NOD.[129] However, fewer studies have reported the microbial breakdown of CYN, ATX, or STX.[124] Cyanotoxins may enter the food web via grazing; MC has been demonstrated to bioaccumulate in planktivorous fish, but it does not biomagnify.[130] NOD, CYN, ATX have also been reported in the tissues of fish, but the bioaccumulation of STX is the most pronounced of all cyanotoxins,[25] as it is frequently detected in fish and marine invertebrates.[4,93,97,131,132]

3.2. Aerosol Production at the Air−Water Interface.

3.2.1. Sea Spray Aerosol Formation. One prominent source of airborne cyanobacteria is sea spray aerosol (SSA),[133,134] which is formed at the sea-air interface when water droplets are ejected into the atmosphere. Aerosolization primarily occurs when wind-driven wave action entrains plumes of air bubbles beneath the water.[135,136] Upon reaching the surface, the bubbles burst, ejecting heterogeneous SSA composed of sea salts, water, biological matter, and chemical compounds into the atmosphere.[134,137−140] The fate of SSA in the environment is dependent on multiple factors but notably the aerodynamic diameter (d_a), mass, composition, and oxidation state.[141−143] At the shoreline, breaking waves produce SSA that can be transported up to 1000 km[144−147] inland at concentrations of 10^3 particles m^{-3}.[148]

There are two types of aerosol formed via bubble bursting processes: film and jet drops. When entrained bubbles reach the surface, a thin layer called the film-cap forms atop each bubble. Film drops are produced directly when the film-cap disintegrates and bursts, forming numerous small particles. Jet drops are formed via jetting or when water at the base of a bursting bubble rushes in to fill the exposed cavity, shooting a stream of water upward, which fragments into drops.[137,149−153] An evaluation of the precise formation mechanism of SSA provides valuable insight into the mixing state or variability of chemical components associated in individual SSA particles.[51,152,154−156]

The expected size distributions of film and jet drops range from d_a values of 0.2 to 10 and 1 to 200 μm, respectively.[150] However, recent instrumentation improvements reflect a more accurate size distribution may encompass size fractions from nanometers to droplets as large as d_a = 250 μm.[153,154] Multiple findings suggest that SSA size distribution is primarily a function of parent bubble size,[134,150,153,157−159] as subsequent film-cap surface area is directly proportional to SSA size distribution.[151] In a review of SSA formation mechanisms, Lewis & Schwartz (2004)[150] concluded that bubbles with radii >1 mm produce more SSA in the film drop size distribution,

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

while bubbles with radii <1 mm produce more SSA within the jet drop size distribution. It is speculated that film drops typically contribute to SSA in the fine range while jet drops contribute to SSA in the coarse range.[154] However, given the overlapping size distributions of film and jet drops,[150,152] it is likely that bubbles in natural environments produce a mixture of both film and jet drops. Moreover, mass concentration, or the mass of aerosol per unit volume of air, and size distribution of drops ejected into the atmosphere may grow and shrink dynamically via heterogeneous chemistry,[144,145] equilibration with relative humidity (RH),[150] and accumulation[53] over their lifetime. As such, production mechanism is imperfect as a predictor of SSA size distribution and mass concentration; SSA mixing state is best explained by several interacting physicochemical factors, many of which are regularly indeterminant. However, a better understanding of primary aerosol formation at the air−water interface and how this directly contributes to particle behavior in the atmosphere provide the foundation to investigate potential CyanoHAB incorporation into aerosol.

3.2.2. Biological incorporation into SSA. Surface-active bacteria may be enriched in SSA when compared to bulk seawater.[133] During phytoplankton bloom conditions, the majority of SSA mass is actually composed of biological material.[160] Surface biological activity has long been demonstrated to alter the mixing state of SSA,[160−164] but there remain unexplained interactions between marine biogeochemistry and the physicochemical properties of SSA.[154,163,165,166] Phytoplankton species and their chemical constituents are incorporated into SSA via adsorption to air bubbles in the water column[164] or at the surface microlayer prior to bursting.[167,168] Biological matter is incorporated into SSA in two ways: POM, such as intact or fragmented cells, are encapsulated in jet drops as bioaerosol, and DOM, including biogenic organics such as proteins, enzymes, toxins, saccharides, metabolites, or amino acids, are enriched in film drops.[152,165] Inactive, fragmented cells are preferentially scavenged by entrained bubbles when compared to intact cells.[133] Thus, the phenological state of a bloom may impact the concentration and type of biological material in SSA.[163,166]

For intact cells, adsorption to air bubbles and subsequent aerosolization is influenced by specific phenotypic characteristics,[166] such as exterior membrane hydrophobic sites, morphology, cell concentration at the surface, or other ecological dynamics such as diel cycles and grazing effects.[161] In the case of DOM, the chemical properties of the biogenic compound influence its relative enrichment in SSA. Hydrophobic metabolites are more readily incorporated into SSA than water-soluble organics.[166] This process is well illustrated through the HAB species *K. brevis* or the Gulf of Mexico red tide. Brevetoxin, a potent neurotoxin produced by *K. brevis*, is frequently detected in SSA during red tides due to its hydrophobic properties.[62,169] At the wave break, fragile *K. brevis* cells lyse, releasing brevetoxin into the water column, where it interacts with air bubbles and is incorporated into SSA.

Biogenic compounds are typically a dominant component of fine SSA,[51,170] suggesting film drop formation as the primary source.[134] Jayarathne et al. (2016)[167] found that DOM is specifically enriched in fine SSA, whereas POM is more frequently measured in coarse SSA. This is explained by the drainage of heavier, larger POM (such as live cells) off the film-cap to the bubble base, where it is encapsulated in jet drops. DOM stays suspended in the film-cap and is incorporated into film drops. Conversely, Wang et al. (2017)[152] determined that a suite of intra- and extracellular biological compounds are incorporated into SSA of size distributions from both jet and film drops. Therefore, jet drops cannot be ruled out as a source of biological SSA,[164] but biogenic compounds may be differentially enriched in aerosol when produced via film versus jet drops. This suggests that cyanotoxins may be aerosolized within film or jet drops. At present, we cannot definitively predict the concentration of cyanotoxins that are enriched in aerosol and potentially transported inland.

3.2.3. Spatiotemporal Controls on SSA. Several meteorological conditions have been investigated to elucidate the impacts of weather on SSA mass concentration, mixing state, and transport. The meteorological variables that control wave action, bubble bursting, and subsequent SSA formation include: wind speed, wind direction, atmospheric stability, precipitation, sea and air temperature, RH, sea-state, marine boundary layer height, wave fetch, salinity, and ocean floor and surface topography.[150] These conditions are spatiotemporally dynamic. Their integration poses a challenge to accurately assess SSA production. Air and water temperature, RH, and salinity influence bubble bursting dynamics by altering film-cap thickness and bubble lifetime.[158,159] Precipitation also affects SSA mass concentration, as it scavenges and removes all sizes of SSA via wet deposition.[134,150]

Wind speed and direction most strongly influence SSA formation across regions. SSA concentration is largely a function of elevated wind speeds, which increase wave activity and influence the distance over which SSA may travel (up to hundreds of meters vertically and 10 km downwind of the source).[134,138,139,143,171] SSA number concentrations, or the number of particles per unit volume of air, increase markedly with fetch due to wave field development.[172] Wind direction is especially important to consider with regard to the transport of SSA inland and when forecasting human exposure to SSA. For instance, wind direction is a major predictor of coastal air quality during red tide events. Beach-goers were exposed to significantly lesser concentrations of aerosolized brevetoxin when the wind blew away from shore.[60,169,173]

Other than wind, meteorological controls on SSA formation are based on multiple environmental variables, and thus, the effects vary across regions. Additionally, many of the same environmental conditions influence CyanoHAB ecology and specifically the detection of airborne algae. The most significant environmental factors that may contribute to the dispersal and presence of airborne algae are RH, precipitation, wind speed, and PAR.[46,174] Through air sample cultivation techniques, Sharma et al. (2006)[174] determined that airborne algal communities were more diverse when RH was high (>60%), but abundance was lower. This is likely because humid conditions favored the survival of aquatic algae in aerosol but also promoted the condensation of gaseous H_2O onto hygroscopic algal cell walls, increasing their settling velocity and ultimately decreasing their detection in air. Similarly, precipitation favors the survival of algae in the atmosphere but removes cells via wet deposition. Rainfall and high wind speeds may fragment algal colonies, disperse them within the water column, and generate splashing or capillary wave action, favoring their suspension in the air. Finally, increased sunlight may increase the number of algal particles in the atmosphere because PAR supports maximal cyanobacterial activity at the surface.[174]

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

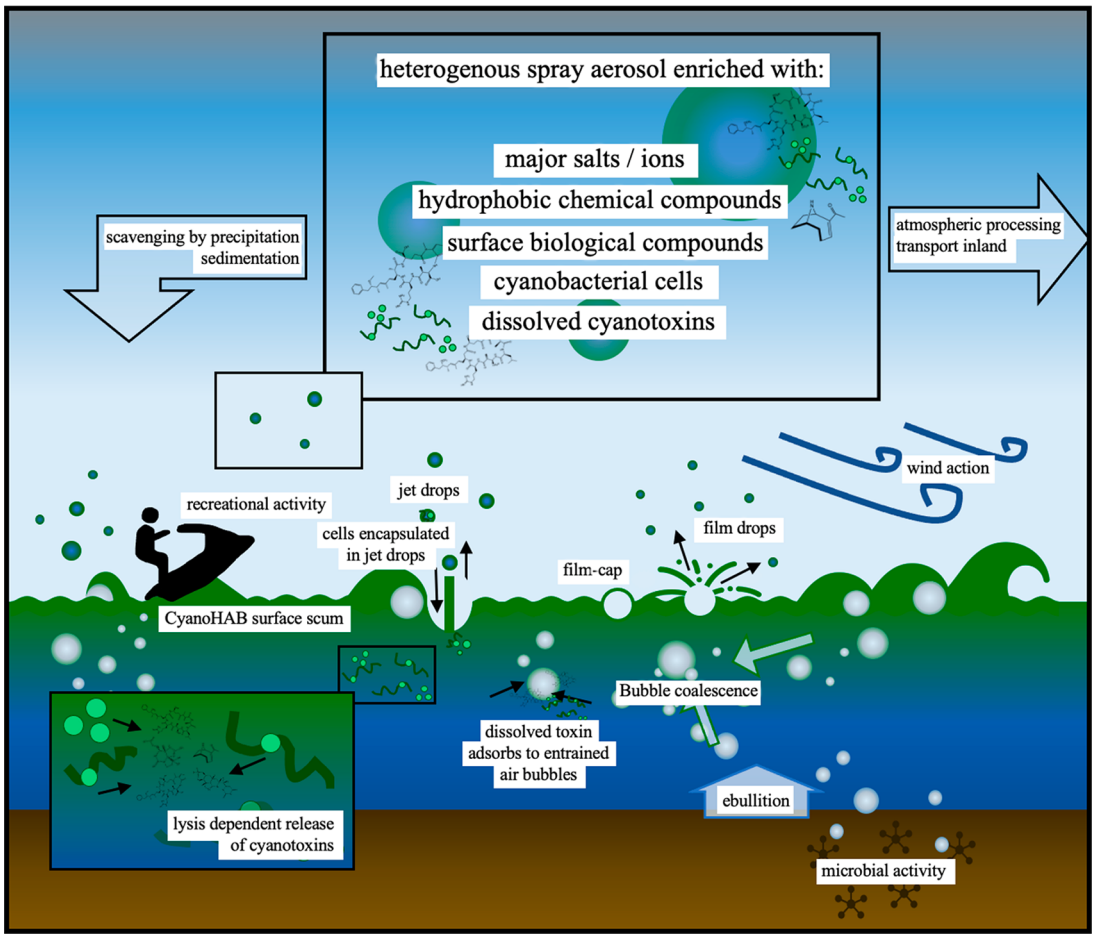


Figure 3. A schematic depicting the proposed mechanisms attributed to cyanotoxin incorporation into spray aerosol.

3.2.4. Lake Spray Aerosol. SA research has recently expanded to examine freshwater aerosol generated via processes similar to SSA. Lake Spray Aerosol (LSA), like SSA, is formed via breaking wave action in the airshed of large lakes and reservoirs. To date, all studies that have characterized LSA were conducted on the Laurentian Great Lakes (U.S. and Canada). LSA may impact Earth's radiative forcing via the production of primary aerosol from waterbodies but on a smaller scale than SSA due to lesser aerosol fluxes.[54−57] Episodic wind events in the northern Great Lakes region are associated with an increase in surface-layer, ultrafine aerosol loads of ∼20%.[175] This study by Chung et al. (2011)[175] found that LSA decreased quickly with increasing altitude (>200 m), limiting ultrafine LSA impacts to a regional scale. Recently however, Olson et al. (2019)[57] found evidence of LSA in altitudes as high as 600 m, suggesting more vertical transport and downwind impacts than previously anticipated. Much work still exists to elucidate the global impact of LSA.

Ambient LSA number concentrations are about one-third that of SSA, and LSA maintains a bimodal size distribution with a primary mode at d_a = 180 ± 20 nm and a secondary mode at d_a = 46 ± 6 nm.[56] The difference in size distribution is a result of water chemistry: lower salt content leads to greater bubble coalescence underwater, producing larger parent bubbles with observed diameters from 250 to 280 μm. This decreases the number of bursting bubbles at the surface and yields a smaller mass concentration of SA mainly comprised of fine aerosol.[56] The chemical composition of LSA varies significantly from SSA, also due to aqueous chemistry, as LSA chemical signatures reflect the major ions of freshwater.[55,56] These unique physiochemical processes attributed to the production of LSA are especially pertinent to consider for aerosol formation in eutrophic waterbodies during frequent and recurrent CyanoHABs.

Despite key differences between SSA and LSA mixing states, biological material can be incorporated via the same mechanisms. Elevated concentrations of cyanobacterial biomass have been demonstrated to alter the mixing state of LSA, increasing biological signatures and shifting size distributions. In a series of LSA generator experiments, May et al. (2018)[39] determined the majority component of LSA is of biological origin during bloom conditions (84 μg/L cyanobacteria), and Olson et al. (2020)[42] found that increased CyanoHAB activity enhanced aerosol production in the ultrafine size range (d_a < 100 nm). A field survey by Slade et al. (2010)[55] detected LSA with similar size distributions near the surface of Lake Michigan, suggesting that LSA produced *in situ* is composed of size fractions which are potentially enriched with MC. Moreover, MC has been detected in LSA generated from other small lakes of the Laurentian Great Lakes region[42] and in California, U.S.,[36] showing that LSA formed during CyanoHABs may pose an emergent threat to public health.[168]

3.2.5. Spray Aerosol: a Collective Term. Due to a lack of data characterizing aerosol produced in estuaries or from sources other than breaking waves, the catch-all term "Spray Aerosol (SA)" is proposed to reference aerosol produced in

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Table 2. Summary of Important Results from *Field-Based* Studies Investigating Cyanotoxins in Aerosol

Cyanobacteria, (cyanotoxin)	Important results from field-based studies	Collection method	Quantification method	Study location	Reference
Microcystis aeruginosa, (MC)	• MMAD peaks at 0.4 and 6.5 μm, RH = 38.4% • MMAD peak at 0.52 μm, RH = 71.7% • MC [aerosol] 0.02−0.08 ng m^{-3}	cascade impactors; personal samplers ([a]Q = 300; 10.6[b]LPM)	ELISA	Bear-Lake, Michigan, U.S.	35
Microcystis aeruginosa, (MC)	• MC [water] 2−5 μg L^{-1}, MC [aerosol] ≤ 0.1 ng m^{-3}, [blood] ≤ 0.147 μg L^{-1} • no respiratory symptom increase in participants following MC exposure	cascade impactors; personal samplers (Q = 300; 10.6 LPM)	ELISA	Michigan, U.S.	37
Microcystis aeruginosa, (MC)	• MMAD peaks at 0.23 and 2.64 μm, RH =[c]n.d. • particulate MC [water] 2−10 μg L^{-1}, bulk MC [water] 15−350 μg L^{-1} • average MC [aerosol] 0.052 ng m^{-3}, maximum 3 ng m^{-3} • MC [nasal swab] ≤ 0.1−5 ng L^{-1} • dominant congener in water and aerosol was MC-LA • no correlation between cell density, MC [water], and [aerosol]	cascade impactors; personal samplers (Q = 300; 10.6 LPM)	ELISA and LC/MS	California, U.S.	36
N. spumigena, (NOD) & *Microcystis sp.*, (MC)	• NOD [aerosol] ≤ 16.2 pg m^{-3}, MC [aerosol] ≤ 1.8 pg m^{-3} • NOD [water] ≤ 9.9 μg L^{-1}, 15% extracellular • MC [water] ≤ 2140 μg L^{-1}, 0.7−45% extracellular	high and low-vol samplers (Q= 1000; 1.2 LPM)	ELISA and LC/MS	South Island, New Zealand	43
n.d., (NOD & MC)	• ENK is an effective internal standard for MC analyses • MC-LA [aerosol] 90−706 fg m^{-3}, MC-LF ≤ 369 fg m^{-3}, MC-LW ≤ 262 fg m^{-3} • low concentrations speculated as result of long-range transport	n.d.	HPLC/(−)ESI-MS/MS	Venice Lagoon, Italy	190
picocyanobacterial genera, (MC)	• 51,964−135,612 picocyanobacterial cells m^{-3} • MC [aerosol] ≤ 13−384 pg m^{-3}, no correlation with cell counts	Gillian BDX-ii samplers (Q = 2 LPM)	ELISA	New England, U.S.	185
Synechococcus, Synechocystis, Aphanocapsa, and *Microcystis* (n.d.)	• open sea, cyanobacterial SSA d_a > 3.3 μm, RH of 63.9−71.3%, onshore, cyanobacterial SSA d_a ≤ 3.3 μm, RH of 39.0−77.1% • surface blooms, PAR, water temperature, phosphorus, and wind speed correlated to increased cyanobacteria in SSA	cascade impactor (Q = 28 LPM) onto agar plates	n.d.	Baltic Sea, Gdynia, Poland	188
pico-cyanobacterial genera (n.d.)	• 2,641−21,324 cellsm^{-3} in Greenland, 2,431−28,355 cells m^{-3} in Antarctica • negative correlation between [aerosol] and wind speed, due to dilution • small-scale turbulence and evaporation may aerosolize picocyanobacteria	Gillian BDX-ii samplers (Q = 2 LPM)	n.d.	Greenland and Antarctica	187

[a]Q= flow rate. [b]LPM = liters per minute. [c]n.d. = not determined.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

freshwater, estuarine, or marine ecosystems via bubble bursting processes. While the production of SSA and LSA presumes significant wave action and distinctive chemical signatures, SA could describe primary aerosol emitted in the airsheds of smaller or hydrologically modified systems such as reservoirs, channels, lakes, and ponds. The consideration of SA production in these systems may prove important for health-related studies, especially in areas with poor water quality where aquatic pollutants are heavily concentrated. SA could also accurately describe aerosol formed via bubble bursting in the airshed of retention ponds such as sewage treatment plants[176] or confined animal feeding operations,[177] which are not discussed herein but have been explored as potential sources of health-related aerosol. More research is needed to consider the public health implications of SA produced via processes other than large wave breaking, especially in eutrophic waters with small fetches where CyanoHAB growth and close-shore recreational activity may be significant, but breaking wave action is less common.

There are additional sources of air−water gas exchange that are also worth consideration as sources of bubble bursting that have not been surveyed as significant contributors to SSA or LSA in the literature. The following processes could also promote SA formation even if on a smaller scale: first, underwater gas emissions via biogeochemical reactions. Microbes in sediments have long been recognized for their production of gas at depth[178] and subsequent atmospheric emissions.[179] This process, known as ebullition, occurs on a global scale. Microbial activity in sediment is estimated to produce 7.5−9 times the amount of gaseous carbon as anthropogenic sources.[180,181] Second, there are several physical disturbances occurring during recreational activity that could lead to bubble bursting in CyanoHAB waters aside from wind driven wave action. When MC occurs in the water column, anthropogenic events that produce SA, like water sporting activities, may facilitate the inhalation of aquatic pollutants.[182,183] Recreational activity may elevate human exposure to respirable aerosol containing MC in waterbodies experiencing CyanoHABs, due to both users' proximity to the blooms and increased physical disturbance at the water's surface.[37] Boating, swimming, and splashing likely leads to additional SA formation. While the quantities of SA emitted from recreation have yet to be formally studied, Backer et al. (2010)[36] did detect MC in the nasal passages of recreational lake users from two lakes during two respective CyanoHABs. Furthermore, the maximal recreational use of water resources coincides with CyanoHAB activity in warm months, serving to compound this effect.[34,36]

The dynamic physicochemical processes explored in Sections 3.1 and 3.2 which may intersect in the natural environment to promote the aerosolization of cyanotoxins is schematically represented in Figure 3.

3.3. Evidence of Airborne CyanoHAB Cells and Compounds. *3.3.1. Picocyanobacteria in Aerosol.* Picocyanobacteria, the smallest cyanobacterial cells (diameter <3 μm),[184] are most commonly detected in aerosol because of their size.[185−187] In the airshed of small lakes around New England, U.S., airborne concentrations of picocyanobacteria were measured in excess of 10^6 cells m^{-3},[185] although the precise mechanism promoting the emission of picocyanobacteria remains unclear. Unlike SSA and LSA number concentrations, picocyanobacterial cell concentration in air is not associated with wind speed and direction, disputing findings that wind driven bubble-mediation is necessary for the incorporation of biological material into SA. Wind dilutes picocyanobacterial cell measurements in the air, rather than increasing numbers as anticipated through increased bubble bursting. This also indicates the potential of an alternative, "passive process" contributing to cyanobacterial aerosolization, such as diffusion, evaporation, air-gas exchange, or small-scale turbulence,[174,185,187] since cyanobacteria are detected in the air on still days. The term "passive process" is used in an attempt to account for multiple unknowns involving the meteorological, ecological, and physicochemical processes which may contribute to the aerosolization of waterborne algae. This underscores the extent of the knowledge gaps which exist in regard to cyanobacterial aerosol communities.

3.3.2. CyanoHAB Cells in Aerosol. Cells, cell fragments, and cyanotoxins from bloom forming genera have been measured in aerosol, including *Cylindrospermum*,[46] *Nodularia*,[43] and *Microcystis*.[35−37,43,46,188] Of the cyanobacteria sourced from waterbodies in a study in Varanasi, India, *Microcystis* was detected year round in aerosol, and *Cylindrospermum* was detected in the late summer, coinciding with a CyanoHAB in a nearby retention pond.[46,174] Current data suggests that the size distribution of CyanoHAB aerosol may range from d_a < 0.1−6.5 μm,[39,42] and differences between reports is likely explained by a number of ambient conditions as explored in section 3, such as RH. Over the open Baltic Sea, Poland, Lewandowska et al. (2017)[188] detected toxigenic cyanobacteria in SSA with d_a> 3.3 μm; however, over land, SSA containing the same genera were significantly smaller in diameter. This is explained by the inertial properties of larger SSA, forcing larger particles to settle out of the air before reaching the shore,[188] or alternatively, particle shrinkage as SA equilibrates to ambient RH over drier land. During CyanoHAB conditions in a small lake in Michigan, U.S., MC was only detected in aerosol onshore, but not over the open lake.[37] This suggests that cyanotoxins can persist in aerosol along the shore and inland, resultant of SA inertia, environmental factors, SA mixing state, and cyanobacterial growth dynamics, as blooms typically accumulate at the edge of a waterbody where they are not easily dispersed by wind.[102] Therefore, respirable cyanotoxins may impact populations living onshore. A comprehensive list of important findings from field campaigns investigating CyanoHAB compounds in aerosol are found in Table 2.

3.3.3. Cyanotoxins in Aerosol. MC is among the most widespread and commonly measured cyanotoxins.[21,30,189] Thus, MC has been the primary cyanotoxin of focus in CyanoHAB aerosol studies, but NOD[43,190] and beta-Methylamino-L-alanine[191] have also been detected in aerosol. In laboratory experiments, MC concentrations in aerosol have ranged from 91 fg m^{-3}[190] to 50 ± 20 ng m^{-3}, the maximum associated with water concentrations of 230 μg L^{-1}.[42] *In situ*, the highest concentration of aerosolized MC ever reported is 23 ng m^{-3}, associated with water concentrations of 5 μg L^{-1}.[36] For NOD, up to 16.2 pg m^{-3} were measured in aerosol, associated with water concentrations of 9.9 μg L^{-1}.[43]

May et al. (2018)[39] found a direct relationship between elevated phycocyanin levels and the enrichment of biological signatures in fine LSA, suggesting that the composition of LSA is altered as result of increased cyanobacterial biomass in the water. In a similar study, Olson et al. (2020)[42] found increased POM and MC in the water column enhanced the production of LSA with d_a < 100 nm. Moreover, congeners containing hydrophobic amino acids, such as MC-LR (-leucine-arginine)

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Table 3. Comprehensive List of Important Findings from Laboratory Experiments Examining CyanoHAB Compounds in Aerosol

Cyanotoxin	Important results from laboratory-based studies	Collection methods	Quantification methods	Aerosol generation method	Reference
MC	• MMAD peaks at 0.03 and 6.06 μm, RH =[a]n.d. • MC [water] 50 μg L^{-1}, yielded [aerosol] of 0.02 ± 0.06 ng m^{-3}	cascade impactors; personal samplers ([b]Q = 300; 10.6[c]LPM)	ELISA	Glass-dispersion tube	35
MC	• 23764−365011 cells m^{-3} • aerosol *not* generated by bubble bursting • evaluated the passive emission of cyanobacterial cells	Gillian BDX-ii samplers (Q = 2 LPM)	ELISA	No mechanical agitations	185
n.d.	• heightened biological signatures in supermicron LSA during HABs, RH ∼ 15% at measurement • phycocyanin fluorescence intensity correlates directly with increased fine LSA production • LSA with strong biological signatures is circular in morphology	ATOFMS	n.d.	Plunging-jet apparatus described in May et al. (2016)[56]	39
MC	• direct association between aqueous POC, MC, and ultrafine LSA production • LSA size distributions resemble POC size distributions: peaks at 46 and 270 nm, RH ∼ 15% • MC [aerosol] ≤ 50 ng m^{-3} • MC-LR [water] of 22.2 μg L^{-1} yielded [aerosol] ≤ 40 ng m^{-3} • plunging-jet apparatus likely lysed cells, MC assumed dissolved • MC-LR and MC-LA enriched by a factor of 830 and 2000 in LSA, respectively • MC-RR only enriched by a factor of 10 • hydrophobic amino acid side chains, e.g., leucine (L), promote the adsorption of dissolved MC onto entrained air bubbles	ATOFMS	LC-MS/MS	Plunging-jet apparatus described in May et al. (2016)[56]	42

[a]n.d. = not determined. [b]Q= flow rate. [c]LPM = liters per minute.

and MC-LA (-leucine-alanine) were preferentially enriched in LSA due to their increased adsorption to air bubbles. The enrichment factors of MC-LR and MC-LA were, respectively, 830 and 2000, relative to bulk seawater, whereas the enrichment factor for MC-RR (arginine-arginine) was only 10.[42] A comprehensive list of important findings from laboratory experiments examining CyanoHAB compounds in aerosol are found in Table 3. Findings from Olson et al. (2020)[42] agree with measurements *in situ*, as Backer et al. (2010)[36] found that MC-LA was the congener most commonly detected in aerosol produced in the airshed of a small lake in California, U.S.. Thus, there is convincing evidence to suggest that the occurrence of dissolved MC contributes directly to the aerosolization of cyanotoxins. However, this is not to conclude that cyanotoxins are exclusively aerosolized in dissolved form, as more data are necessary to support this finding in natural environments. Empirical evidence is currently lacking to demonstrate the conditions under which cyanotoxins are most likely aerosolized, within cells or extracellularly.

3.4. CyanoHAB Aerosol Sampling Methods.

3.4.1. Challenges for Sampling Cyanotoxins and CyanoHAB Cells in Aerosol. Quantifying cyanotoxins in SA is a methodological challenge in field settings. To date, most SA research has focused on the climatic impacts associated with global aerosol production at the air−water interface, and thus, less emphasis has been placed on human exposure potential. There is a pressing need to utilize robust sampling techniques to characterize dynamic SA production *in situ* to analyze the potential public health threats associated with aquatic pollutants in SA. This is not to say the methods explored herein should be avoided entirely but rather that their respective limitations must be considered when designing a study and interpreting results. Specifically, the major issues with regard to CyanoHAB aerosol measurements are (1) identifying the sample source, (2) determining spatiotemporal resolutions, (3) ensuring sample viability, and (4) collection efficiency. Assessment of the complications introduced by each of these issues is of critical importance in designing and executing a field campaign to sample biological matter in SA.

3.4.2. Identifying the Sample Source. Even in remote environments, it is difficult to determine the extent to which an aerosol sample was emitted as SA. In field studies, the source of aerosolized cyanotoxins are largely assumed, based on proximity to the waterbody in question. However, there are several other potential sources of airborne microbial life in the environment,[192−194] therefore necessitating definitive confirmation of the aerosol source. This may be achieved by surveying SA compositional characteristics such as distinct chemical signatures[54,154] or particle size distributions.[56,148] Thus, field-deployable, high-resolution, and real-time particle measurement instruments such as the Atomic Time-of-Flight Mass Spectrometer (ATOFMS) are preferred, as this technology can accurately determine the origin of SA by simultaneously revealing particle composition, diameter, and number concentration. Additionally, online mass spectrometry allows for avoidance of potential artifacts from particle desiccation on filters, sample degradation, and chemical or metabolic reactions over long sample collection periods.[195−197] Such high-resolution technology is very expensive, and to date, all studies which have utilized such equipment to examine CyanoHAB compounds in aerosol have been performed in a laboratory setting,[39,42] which have yet to adequately represent field conditions.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Alternatively, more affordable, high-volume samplers which impact aerosol onto filters, stages, or plates, may be paired with complementary real-time aerosolmeasurements and meteorological conditions.[35−37,43] Mass concentrations can be detected *in situ* with Tapered Element Oscillating Microbalances (TEOM), Beta gauges (BAM), Optical Particle Counters (OPC),[198] or nephelometers,[198,199] while wave activity and SA emissions may be scaled by correlations of wind speed measurements. However, it is important to note that while wind speed may increase SA production, it may also lead to sample dilution and does not account for other sources of bubble bursting.[134,150,187,200]

3.4.3. Determining Spatiotemporal Resolutions. The time and locations spent collecting aerosol should be carefully monitored, as both cyanobacterial blooms and SA production at the air−water interface are highly dynamic. As explored in Section 3.2.3, SA production is greatly influenced by wind speed, direction, and other weather conditions, but these factors may also lead to strong biases in microbial occurrence in aerosol.[174,201,202] Cyanobacterial blooms are also subject to changes based upon weather conditions. Wind and turbulent flows have been demonstrated to disperse surface scums[203,204] which may affect the incorporation of CyanoHAB compounds into SA. Furthermore, under favorable conditions buoyant cyanobacteria become increasingly active at the surface, especially in the early morning, when they rapidly accelerate photosynthetic activity.[103,204,205] Thus, over the course of an aerosol sampling event, the metabolic state of a bloom or surface cell concentration could change markedly, leading to a disproportionate representation of aerosol containing CyanoHAB compounds in a sample. These points also reiterate the benefit of utilizing online mass spectrometry methods when possible, given that such tools allow for real-time spatiotemporal variability to be examined.[195,196]

Confining sampling periods to 1−2 h and integrating them over a 12-h sampling event may work to better understand the time of day when cyanotoxins are most likely to become airborne if limits of detection (LOD) are met. Alternatively, to efficiently capture the ecological processes occurring in the water column, the bloom should be monitored frequently over the course of aerosol collection. Noticeable changes in pH or dissolved oxygen in the water could indicate changes in bloom metabolic state.[205]

3.4.4. Ensuring Sample Viability. If aerosol is being collected over multiple days, sample degradation is always a concern. As aquatic organisms, toxigenic cyanobacteria are unlikely to survive long-term in aerosol or desiccation on an air filter. However, the extended viability of airborne CyanoHAB genera has yet to be formally investigated. As explored in Section 3.1, cyanotoxins are chemically robust; hence, their nuisance in aquatic ecosystems. MC can persist in the environment for weeks to months before fully biodegrading.[24,131] Thus, the loss of toxin sample on a filter is likely to be minimal.

CyanoHAB colonies, e.g., *Microcystis* or *Dolichospermum*, are naturally found in long chains or agglomerates of cells.[206] Upon aerosolization, microbes such as cyanobacteria may exist in an aggregated state, especially during bloom conditions.[194] Moreover, cyanotoxins may adsorb to suspended particles such as sediment, cell fragments, or detritus. Therefore, if impaction breaks up these particles, it may prove difficult to accurately quantify the concentration of cells in aerosol or the true characteristics of the aerosol.

Utilizing "soft" sampling techniques, such as impingement into liquid media, may better preserve sample integrity. However, culture dependent sampling techniques, e.g., impaction onto agar or other nutrient media, significantly underestimate the diversity of microorganisms in aerosol and provide poorly resolved mass concentrations.[194] To avoid cultivation, molecular techniques involving DNA sequencing are better suited as they do not require the continued viability of the sample, and furthermore, this method may offer the ability to better trace the origin via comparison to water sample DNA analyses. Another less abrasive bioaerosol collection method has recently been made possible by the *BioSpot* bioaerosol sampler (Aerosol Devices Inc.).[207−209] This novel technology offers the direct collection of aerosol into water or buffer solution, effectively concentrating the samples with real-time particle size assessment and improved viability. To the best of our knowledge, this instrument has never been used to study biological material in SA. More research is necessary to evaluate the use of the *BioSpot* as an efficacious tool to measure airborne CyanoHAB compounds.

3.4.5. Collection Efficiency. Current findings suggest that high-volume sampling is necessary to meet cyanotoxin LOD in aerosol. The studies which previously utilized low-volume samplers seldom yielded enough biomass to quantify cyanotoxin in aerosol.[35−37,43,185] However, low-volume samplers such as the Gillian BDX-ii (Sensidyne, LP) used in Murby & Haney (2016)[185] and Trout-Haney et al. (2020)[187] are portable and capable of collecting intact cells. If qualities of airborne cyanobacterial communities are being investigated, without a need for sufficient biomass for cyanotoxin quantification, such methods may be useful, as the low flow rate imposes less stress on the cells collected.[41,210] Additionally, low-volume samplers are often battery powered and require much less energy compared to high-volume samplers which generally require at least 120 V electricity. As such, portable, low-volume samplers may prove advantageous for sampling campaigns in remote locations and when meeting LOD is not a concern.

From an analytical perspective, high-resolution cyanotoxin quantification techniques are preferred to commercial kits, such as the enzyme-linked immunosorbent assay (ELISA). ELISA kits tend to overestimate cyanotoxin concentration due to matrix effects,[24] and moreover, their minimum detection limit is 0.1 μg L^{-1}. For aerosol samples on the magnitude of 0.1 pg L^{-1}, the ELISA detection limit is therefore too low and would require intensive sample concentration. While ELISA kits may be useful in rapid water quality monitoring, in order to better investigate the occurrence of cyanotoxin in aerosol, more refined instrumentation is needed. As demonstrated in Gambaro et al. (2012),[190] the higher resolution available through high performance liquid chromatography tandem mass spectrometry (HPLC-MS) approaches more effectively reveal environmentally relevant concentrations of cyanotoxins in aerosol and can further specify isoforms present.

3.5. Toxicological Impacts Associated with CyanoHAB Inhalation. *3.5.1. Epidemiological Outcomes.* Numerous case studies have reported the cytotoxic effects associated with cyanotoxin ingestion, intraperitoneal injection, or dermal contact,[28,33,211−214] but more pertinent to this review, there are many anecdotal reports of respiratory irritation in recreational lake users following exposure to CyanoHABs.[182,215−217] As demonstrated in a systematic review by Stewart et al. (2006),[216] respiratory symptoms are among the most

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

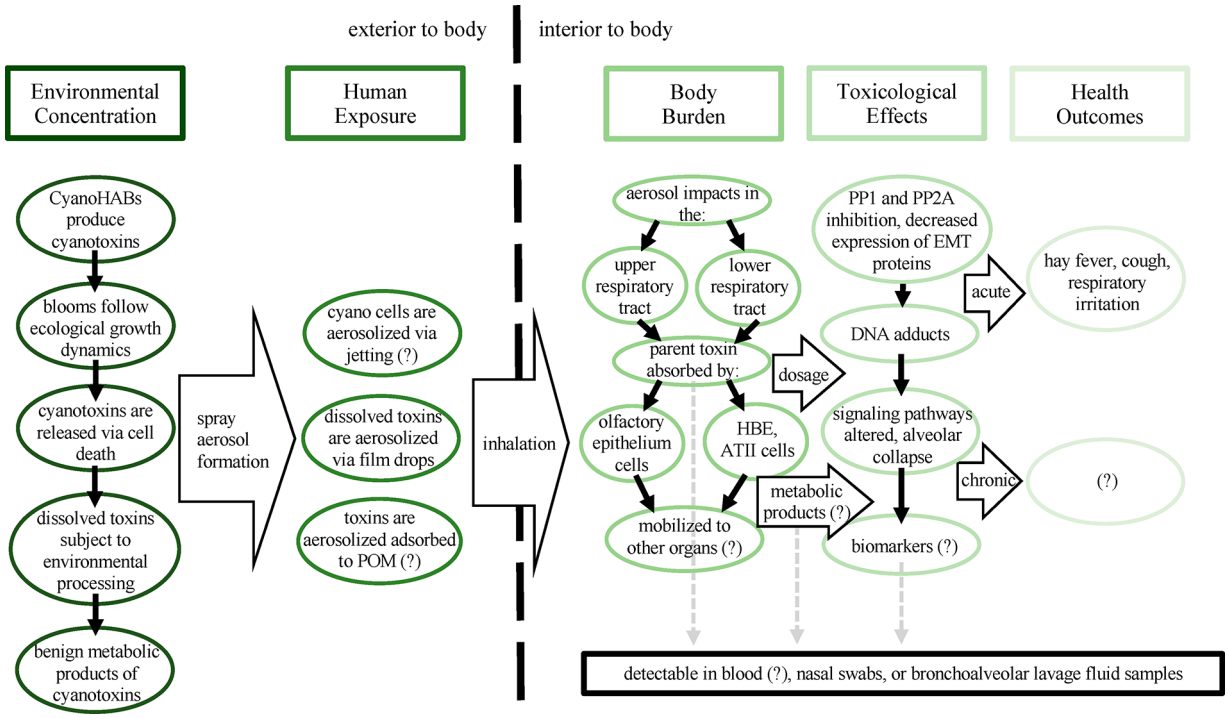


Figure 4. A conceptual diagram depicting the potential pathways which may contribute to adverse health outcomes associated with the inhalation of cyanotoxins. Areas where research is limited, findings are unknown, and more work is necessary are indicated with a question mark.

frequently recorded complaints. Specific respiratory reactions related to CyanoHAB exposure include cough, sore throat, and hay fever, suggesting that the inhalation of cyanobacterial compounds in aerosol may activate inflammatory responses in the human body. In a prospective cohort study conducted in southeastern Queensland and New South Wales, Australia and south Florida, U.S., Stewart et. al (2006)[218] found that study participants were 2.1 (95% CI: 1.1−4.0) times as likely to report mild respiratory symptoms when exposed to CyanoHABs than those who were not exposed. However, concrete evidence to confirm cyanotoxins as the causation of numerous health outcomes including respiratory irritation is often lacking. Most epidemiological investigations in regard to cyanotoxin exposure rely on self-reported activities and symptoms, and therefore, exposures often go underreported or misdiagnosed.[219,220] Studies which have examined cyanotoxin exposure via inhalation failed to detect cyanotoxins in the bloodstream of any participants,[36−38] meaning cyanotoxins may not cross the blood-air barrier in detectable concentrations, or the parent compound is potentially transformed to an unknown metabolite via this uptake route. Ultimately, our epidemiological understanding of the acute and chronic health impacts from CyanoHABs is just beginning.[221]

3.5.2. In Vivo Findings. Current toxicological studies involving the inhalation of cyanotoxins have been limited to MC. MC is a potent inhibitor of serine/threonine type 1 and 2A protein phosphatases (PP1 and PP2A, respectively).[30] Like many other toxins, the median lethal dose (LD_{50}) concentration for MC is lowest when inhaled (43 $\mu g\ kg^{-1}$ in mice) in comparison to other routes of exposure.[222] Furthermore, MC may impact a different suite of organs when assimilated in the respiratory system. While inflammatory responses to MC may extend to lung tissues, the toxin itself less frequently metabolizes to the lung when ingested or absorbed intraperitoneally.[223−225] Thus, direct lung cell exposure to MC must come from the inhalation of aerosol containing cyanobacterial cells or cyanotoxins.

Following acute exposure to MC in aerosol, dose-dependent, microscopic lesions were observed in the nasal cavity of mice; such lesions typically enhance absorption into the bloodstream. However, no hepatoxicity was observed following inhalation, suggesting that MC was not mobilized from the lung to the liver from the respiratory tract,[226] again suggesting that MC may not readily cross the blood-air barrier in the lungs. These results are especially interesting, because in this study, the median mass aerodynamic diameter (MMAD) of the aerosol generated (d_a = 0.53 ± 0.01 μm) should have allowed for deposition in the lower respiratory tract in mice,[226] where blood-oxygen gas exchange occurs.[227] Conversely, Facciponte et al. (2018)[38] found cyanobacteria in the bronchoalveolar lavage fluid of several study participants, suggesting that CyanoHAB cells may be deposited in the lower respiratory tract. The authors speculated the effects of MC inhalation were only noted in the upper respiratory tract due to the presence of protein phosphatase 2A in the olfactory epithelium.[226] However, recently Brózman et al. (2020)[228] found that two types of human bronchial epithelial (HBE) cells express genes encoding organic anion transport proteins that are capable of MC-LR cellular uptake. Moreover, Oliveira et al. (2015)[229] demonstrated that lung tissues were negatively impacted while nasal epithelial cells remained unaffected following intranasal instillation of MC-LR in mice.[229] Thus, exposure assessments should be conducted to evaluate where aerosol containing MC is potentially deposited in human lung cells *in vivo*, perhaps involving aerosol deposition modeling when invasive procedures in human participants such as BAL are impractical.

3.5.3. In Vitro Findings. An *in vitro* study examining the effect of MC-LR on Alveolar type II (ATII) cells, which are present in the lower respiratory tract, revealed significant injury to these tissues when treated with concentrations of ≥50 nM

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

MC-LR. Transepithelial electrical resistance in ATII cells was markedly down-regulated in response to MC-LR treatments, indicating the adverse effect of MC-LR on tight junctions and cell-to-cell communication in the lung.[230] Epithelial-mesenchymal-transition (EMT) proteins were also impacted, as the expression of cytokeratin 18 (C18), cytokeratin 19 (C19), surfactant protein C (SP-C), occludin (OCLN), E-cadherin (CDH1), and tight junction protein-1 (ZO-1) was decreased alongside the upregulation of vimentin (VIM).[230] Activation of phosphoinositide 3-kinase/protein kinase B (PI3K/AKt) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathways were also noted, leading to apoptosis in lung cells.[230] MC-LR also affected cell signaling pathways and growth in HBE cells; after exposure to 20 μM MC-LR, protein adducts were formed in HBE cells *in vitro*,[228] confirming the possible uptake of MC-LR into these cells which exist in the lower respiratory tract. However, no major cytotoxic effects were revealed within 96 h, and only minor disruptions to MAPK (ERK1/2 and p38) activities were reported.[228] Zhao et al. (2016) found more proteins involved in inflammatory response, cytoskeletal functions, and energetic metabolism to be significantly altered following sublethal lung exposure to MC.[225] These findings suggest that changes in the levels of many protein signaling pathways could potentially be monitored as biomarkers for human exposure to MC-LR in aerosol, and a special focus should be placed on monitoring tight junction activity in the lungs. More research utilizing *in vitro* approaches should be conducted to better understand the impact of chronic exposure to airborne cyanotoxins, and furthermore, an emphasis should be placed on examining the cytotoxic effects at environmental concentrations.

4. DISCUSSION AND FUTURE DIRECTION

Diverse lines of evidence suggest that CyanoHAB cells and their chemical constituents are capable of incorporation into SA produced in the airshed of aquatic ecosystems. However, interpreting the physicochemical and ecological controls on the aerosolization of cyanotoxins remains a complex problem. There is a pressing need to further investigate the environmental concentration of cyanotoxins in aerosol, as well as the associated human body burden to determine if cyanotoxin inhalation guidelines should be implemented and where intervention would be best served. Herein, several knowledge gaps were presented regarding the environmental concentration of cyanotoxins in aerosol and the related public health threats (Figure 4).

Largely, the primary form in which cyanotoxins are detected in aerosol is unknown, i.e., intra- or extracellularly. To accurately model the potential dosage of cyanotoxins when inhaled, cyanotoxin concentration and form in aerosol must be determined. We reference publications to suggest that cyanotoxins may be transported in aerosol within intact or fragmented cells, adsorbed to POM or sediments, or dissolved in film or jet drops. Future studies should place a higher emphasis on the potential effects of aerosolized cells since cyanobacterial cells do not easily lyse under ambient conditions; the general lack of dissolved toxins in natural systems may explain the low concentration of cyanotoxins in aerosol reflected in current data. Further investigation should aim to better characterize the form in which cyanotoxins exist in aerosol, as the size, composition, and concentration which reach human populations may vary greatly between dissolved toxins and intact cells. Furthermore, this information must be generated to accurately assess toxin dosages, body burdens, and ultimate public health implications.

There are many studies which have detected toxigenic cyanobacterial genera in the airshed of small freshwater systems such as creeks, lakes, or stormwater ponds, despite the absence of an obvious aerosolization mechanism. We suspect that sources of bubble bursting such as microbial processes or recreational activity could explain the presence of small cyanobacterial cells in the airshed of systems with short fetches, low wave action, and frequent surface scum formations. More research is necessary to better understand the small-scale processes which may promote the emission of primary aerosol from small waterbodies, as there is a growing need to examine SA produced in aquatic systems other than the ocean. We recommend the use of the term, "spray aerosol (SA)", to widely encompass aerosol produced via diverse bubble bursting processes in seawater, freshwater, brackish, or manmade systems.

An effectual approach to characterize aerosol containing cyanotoxins in natural environments must consider (1) the metabolic state of the CyanoHAB, (2) the dynamic physicochemical conditions of the ecosystem, (3) SA size distribution and its relevance for human exposure, and (4) the toxicological effects of cyanotoxins at environmental concentrations.

4.1. Metabolic State of the CyanoHAB. Cyanobacterial cells are positioned at the surface of the water column, where they may easily interact with entrained air bubbles. The aerosolization of intact cells or cell fragments may be influenced by ecological and morphological characteristics such as cell size, concentration at the surface, or the presence of cell aggregations. The size and morphology of a CyanoHAB cell should be considered as a factor which may influence its incorporation into aerosol.

The release of cyanotoxins into the water column increases the fraction of toxin available for chemical interactions with air bubbles. We speculate that processes which promote cell lysis and increase dissolved toxin concentrations, may lead to higher concentrations of toxin in aerosol. CyanoHABs nearing senescence, treated with algaecide, infected with viruses, or occurring along estuarine gradients may contribute most greatly to cyanotoxin enrichment in aerosol, and the period over which toxin degradation occurs could reveal the amount of time dissolved toxin is available for aerosolization.

CYN, which is proposed to be actively transported outside the cell, may more likely be available for incorporation into aerosol. However, given that CYN is extremely hydrophilic, we suspect its affinity for air bubbles is likely too low for its significant incorporation into aerosol. We speculate that the cyanotoxins with hydrophobic properties, e.g., MC-LA, ATX-a(s), and STX, are more likely to occur in aerosol when compared to those which are more hydrophilic in nature, e.g., CYN, ATX-a, and homo-ATX-a.

4.2. Dynamic Physicochemical Conditions of the Ecosystem. Numerous meteorological conditions should be monitored during CyanoHAB aerosol sampling campaigns. Elevated wind speeds, large fetches, PAR, and RH may influence cyanotoxin aerosol number concentrations and therefore the concentration of airborne cyanotoxins which reach human populations. Our understanding of SA production in freshwater systems and its implications on air quality is in its infancy. At present, it is unclear how physicochemical, ecological, and meteorological factors inter-

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

act to influence freshwater SA production and mixing state; however, sufficient evidence suggests that wave breaking or alternative bubble bursting processes produce SA which may carry CyanoHAB compounds.

Regarding CyanoHAB ecology and spatiotemporal dynamics, the seasonality of airborne cyanotoxins should be investigated. Ambient conditions such as precipitation, turbulent flows, and winds blowing away from shore may disperse surface blooms, decreasing the amount of biomass available at the surface for enrichment in aerosol. The hydrodynamics and biogeochemistry of an ecosystem are also important regarding the fate of dissolved toxins in the environment, as these conditions influence the degradation rates and ability of cyanotoxins to adsorb to suspended particulate matter. As such, these dynamic processes should be monitored in attempt to observe the environmental factors which may promote the aerosolization of CyanoHAB compounds.

4.3. SA Size Distribution and Its Relevance for Human Exposure. Though it is unclear whether cyanotoxins are more frequently aerosolized within film or jet drops, CyanoHAB compounds have been detected in aerosol over land, suggesting they exist in respirable size fractions, and therefore may adversely affect human and animal populations living onshore. We speculate that dissolved toxin is more likely enriched in fine SA via film drop formation, whereas intact cells, which are too large to comprise fine aerosol size fractions, are aerosolized via jetting and found in coarse SA. Most CyanoHAB genera are larger than 2.5 μm in diameter, and as such, it is improbable that intact CyanoHAB cells exist in fine aerosol. The average size of a *Microcystis* cell varies from 1.7 to 7 μm in diameter,[205,231] which implies that it would settle quickly in aerosol, greatly reducing its relative risk of reaching human lung cells. However, the location in the respiratory tract where cyanotoxins in aerosol are most likely to impact nor the variable toxicity of intra- versus extracellular cyanotoxins in the respiratory tract have been reported.

4.4. Toxicological Effects of Cyanotoxins at Environmental Concentrations. To date, no toxicological studies have evaluated exposure to MC in aerosol at environmentally relevant concentrations, despite evidence of respirable cyanotoxins in the SA of recreational watersheds. While there have been many case studies to report respiratory irritation in recreational water users during CyanoHABs, current data suggest that acute intoxication via MC inhalation is unlikely, as the highest concentration of MC ever reported in aerosol is 23 ng m^{-3} *in situ*[36] (Table 2) and 50 ng m^{-3} in a lab simulation[42] (Table 3). The no-observed-adverse-effect-level (NOAEL) for nasal lesions in mice only occurs at an estimated deposited dose of 3 mg MC kg^{-1} day^{-1}.[226] Therefore, chronic respiratory exposure to concentrations of MC on the magnitude of ~10 ng m^{-3}, including the actual deposited dose *in vivo* at these concentrations, should be explored to fully understand the long-term public health risks associated with cyanotoxin inhalation. Moreover, changes in EMT proteins (i.e., C18, OCLD, or ZO-1) or the activation of PI3K/AKt, MAPK, or ERK signaling pathways may be useful biomarkers to monitor human exposure to MC during health-related studies. In addition to research elucidating the specific human health outcomes associated with cyanotoxin inhalation, an epidemiological assessment of reported cyanotoxin intoxications via the respiratory tract should be explored. As with red tide, it may be that individuals suffering from respiratory afflictions such as chronic obstructive pulmonary disease and asthma are predisposed to heightened reactions and adverse health outcomes associated with cyanotoxins in aerosol. This information is needed to develop specific and accurate inhalation and air quality exposure guidelines regarding cyanotoxins with special considerations for susceptible populations.

Several knowledge gaps exist regarding the public health risks associated with the inhalation of airborne cyanotoxins. While there is no definitive evidence presented herein to suggest that exposure to cyanotoxins in SA should be immediately regulated, much work remains to evaluate the holistic impacts of CyanoHABs on human respiratory health. Here, we examined current knowledge on cyanotoxin fate in the environment, biological incorporation into SA, existing data on cyanotoxins in SA, relevant collection methods, and the public health concerns with CyanoHAB inhalation. With the expansion of CyanoHABs, the health risks associated with chronic exposure to cyanotoxins will trend upward near systems as large the Laurentian Great Lakes and as small as backyard stormwater ponds. Thus, cyanotoxin incorporation into respirable aerosol may increase across the globe and should be further investigated in order to safeguard the health of human beings, animals, and the environment.

AUTHOR INFORMATION

Corresponding Author

Hans W. Paerl − *University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel Hill, NC 27599, United States; University of North Carolina at Chapel Hill, Institute of Marine Sciences, Morehead City, NC 28557, United States;* orcid.org/0000-0003-2211-1011; Phone: (252) 726 6841, Ext. 133; Email: hans_paerl@unc.edu

Author

Haley E. Plaas − *University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel Hill, NC 27599, United States; University of North Carolina at Chapel Hill, Institute of Marine Sciences, Morehead City, NC 28557, United States;* orcid.org/0000-0001-8823-0457

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.0c06653

Funding

This work is supported in part by the Albemarle Pamlico National Estuary Partnership and North Carolina Sea Grant joint Graduate Fellowship in Estuarine Research (2019-R/MG-1905), and the National Science Foundation Graduate Research Program (2020295001) under which H.E.P. was supported at the time of authorship. Additional support was provided by the National Science Foundation (1840715, 1831096), and the National Institutes of Health (1P01ES028939−01).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Cassandra Gaston and Dr. Kimberly Popendorf for their insightful discussions, Malcolm Barnard, Naomi Chang, Dr. Cassandra Gaston, and Dr. Nathan Hall for their informal peer review, and Kyle Lorey with *South Highland LLC*

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

for his editorial contribution. This work is supported in part by the Albemarle Pamlico National Estuary Partnership and North Carolina Sea Grant joint Graduate Fellowship in Estuarine Research (2019-R/MG-1905), and the National Science Foundation Graduate Research Program (2020295001) under which H.E.P. was supported at the time of authorship. Additional support was provided by the National Science Foundation (1840715, 1831096), and the National Institutes of Health (1P01ES028939-01).

REFERENCES

(1) Burford, M.; Carey, C.; Hamilton, D. P.; Huisman, J.; Paerl, H.; Wood, S.; Wulff, A. Perspective: Advancing the Research Agenda for Improving Understanding of Cyanobacteria in a Future of Global Change. *Harmful Algae* **2020**, *91*, 101601.

(2) Paerl, H. W.; Barnard, M. A. Mitigating the Global Expansion of Harmful Cyanobacterial Blooms: Moving Targets in a Human- and Climatically-Altered World. *Harmful Algae* **2020**, *96*, 101845.

(3) Hisbergues, M.; Christiansen, G.; Rouhiainen, L.; Sivonen, K.; Börner, T. PCR-Based Identification of Microcystin-Producing Genotypes of Different Cyanobacterial Genera. *Arch. Microbiol.* **2003**, *180* (6), 402−410.

(4) Van Dolah, F. M. Marine Algal Toxins: Origins, Health Effects, and Their Increased Occurrence. *Environ. Health Perspect.* **2000**, *108*, 133−141 March.

(5) Paerl, H. W.; Xu, H.; McCarthy, M. J.; Zhu, G.; Qin, B.; Li, Y.; Gardner, W. S. Controlling Harmful Cyanobacterial Blooms in a Hyper-Eutrophic Lake (Lake Taihu, China): The Need for a Dual Nutrient (N & P) Management Strategy. *Water Res.* **2011**, *45* (5), 1973−1983.

(6) Paerl, H. W.; Hall, N. S.; Calandrino, E. S. Controlling Harmful Cyanobacterial Blooms in a World Experiencing Anthropogenic and Climatic-Induced Change. *Sci. Total Environ.* **2011**, *409*, 1739−1745 April 15.

(7) Paerl, H. W.; Havens, K. E.; Hall, N. S.; Otten, T. G.; Zhu, M.; Xu, H.; Zhu, G.; Qin, B. Mitigating a Global Expansion of Toxic Cyanobacterial Blooms: Confounding Effects and Challenges Posed by Climate Change. *Mar. Freshwater Res.* **2020**, *71* (5), 579.

(8) Paerl, H. W.; Otten, T. G. Blooms Bite the Hand That Feeds Them. *Science*. American Association for the Advancement of Science 2013; pp 433−434. DOI: 10.1126/science.1245276.

(9) Paerl, H. W.; Whitall, D. R. Anthropogenically-Derived Atmospheric Nitrogen Deposition, Marine Eutrophication and Harmful Algal Bloom Expansion: Is There a Link? *Ambio* **1999**, *28* (4), 307−311.

(10) Visser, P. M.; Verspagen, J. M. H.; Sandrini, G.; Stal, L. J.; Matthijs, H. C. P.; Davis, T. W.; Paerl, H. W.; Huisman, J. How Rising CO2 and Global Warming May Stimulate Harmful Cyanobacterial Blooms. *Harmful Algae* **2016**, *54*, 145−159.

(11) Huisman, J.; Codd, G. A.; Paerl, H. W.; Ibelings, B. W.; Verspagen, J. M. H.; Visser, P. M. Cyanobacterial Blooms. *Nat. Rev. Microbiol.* **2018**, *16* (8), 471−483.

(12) Mantzouki, E.; Lürling, M.; Fastner, J.; de Senerpont Domis, L.; Wilk-Woźniak, E.; Koreivienė, J.; Seelen, L.; Teurlincx, S.; Verstijnen, Y.; Krztoń, W.; Walusiak, E.; Karosienė, J.; Kasperoviienė, J.; Savadova, K.; Vitonytė, I.; Cillero-Castro, C.; Budzynska, A.; Goldyn, R.; Kozak, A.; Rosińska, J.; Szeląg-Wasielewska, E.; Domek, P.; Jakubowska-Krepska, N.; Kwasizur, K.; Messyasz, B.; Pełechata, A.; Pełechaty, M.; Kokocinski, M.; García-Murcia, A.; Real, M.; Romans, E.; Noguero-Ribes, J.; Duque, D. P.; Fernández-Morán, E.; Karakaya, N.; Häggqvist, K.; Demir, N.; Beklioğlu, M.; Filiz, N.; Levi, E. E.; Iskin, U.; Bezirci, G.; Tavşanoğlu, Ü. N.; Özhan, K.; Gkelis, S.; Panou, M.; Fakioglu, Ö.; Avagianos, C.; Kaloudis, T.; ćelik, K.; Yilmaz, M.; Marcé, R.; Catalán, N.; Bravo, A. G.; Buck, M.; Colom-Montero, W.; Mustonen, K.; Pierson, D.; Yang, Y.; Raposeiro, P. M.; GonĆalves, V.; Antoniou, M. G.; Tsiarta, N.; McCarthy, V.; Perello, V. C.; Feldmann, T.; Laas, A.; Panksep, K.; Tuvikene, L.; Gagala, I.; Mankiewicz-Boczek, J.; YağcÑ, M. A.; ćÑnar, ï.; ćapkÑn, K.; YağcÑ, A.; Cesur, M.; Bilgin, F.; Bulut, C.; Uysal, R.; Obertegger, U.; Boscaini, A.; Flaim, G.; Salmaso, N.; Cerasino, L.; Richardson, J.; Visser, P. M.; Verspagen, J. M. H.; Karan, T.; Soylu, E. N.; MaraşlÑoğlu, F.; Napiórkowska-Krzebietke, A.; Ochocka, A.; Pasztaleniec, A.; Antão-Geraldes, A. M.; Vasconcelos, V.; Morais, J.; Vale, M.; Köker, L.; AkĆaalan, R.; Albay, M.; ŠpoljarićMaronić, D.; Stević, F.; čuna Pfeiffer, T.; Fonvielle, J.; Straile, D.; Rothhaupt, K. O.; Hansson, L. A.; Urrutia-Cordero, P.; Bláha, L.; GeriĆ, R.; Fránková, M.; KoĆer, M. A. T.; Alp, M. T.; Remec-Rekar, S.; Elersek, T.; Triantis, T.; Zervou, S. K.; Hiskia, A.; Haande, S.; Skjelbred, B.; Madrecka, B.; Nemova, H.; Drastichova, I.; Chomova, L.; Edwards, C.; Sevindik, T. O.; Tunca, H.; Önem, B.; Aleksovski, B.; Krstić, S.; Vucelić, I. B.; Nawrocka, L.; Salmi, P.; Machado-Vieira, D.; De Oliveira, A. G.; Delgado-Martín, J.; García, D.; Cereijo, J. L.; Gomà, J.; Trapote, M. C.; Vegas-Vilarrúbia, T.; Obrador, B.; Grabowska, M.; Karpowicz, M.; Chmura, D.; Úbeda, B.; Gálvez, J. Á.; Özen, A.; Christoffersen, K. S.; Warming, T. P.; Kobos, J.; Mazur-Marzec, H.; Pérez-Martínez, C.; Ramos-Rodríguez, E.; Arvola, L.; Alcaraz-Párraga, P.; Toporowska, M.; Pawlik-Skowronska, B.; Niedźwiecki, M.; Pćczuła, W.; Leira, M.; Hernández, A.; Moreno-Ostos, E.; Blanco, J. M.; Rodríguez, V.; Montes-Pérez, J. J.; Palomino, R. L.; Rodríguez-Pérez, E.; Carballeira, R.; Camacho, A.; Picazo, A.; Rochera, C.; Santamans, A. C.; Ferriol, C.; Romo, S.; Soria, J. M.; Dunalska, J.; Sieńska, J.; Szymański, D.; Kruk, M.; Kostrzewska-Szlakowska, I.; Jasser, I.; čutinić, P.; Gligora UdoviĆ, M.; Plenković-Moraj, A.; Frąk, M.; Bańkowska-Sobczak, A.; Wasilewicz, M.; Özkan, K.; Maliaka, V.; Kangro, K.; Grossart, H. P.; Paerl, H. W.; Carey, C. C.; Ibelings, B. W. Temperature Effects Explain Continental Scale Distribution of Cyanobacterial Toxins. *Toxins (Basel)*. 2018, *10* (4). DOI: 10.3390/toxins10040156.

(13) O'Neil, J. M.; Davis, T. W.; Burford, M. A.; Gobler, C. J. The Rise of Harmful Cyanobacteria Blooms: The Potential Roles of Eutrophication and Climate Change. *Harmful Algae* **2012**, *14*, 313−334.

(14) Chorus, I. Toxic Cyanobacteria in Water - A Guide to Their Public Health Consequences, Monitoring and Management; 1999.

(15) Carmichael, W. W.; Boyer, G. L. Health Impacts from Cyanobacteria Harmful Algae Blooms: Implications for the North American Great Lakes. *Harmful Algae* **2016**, *54*, 194−212.

(16) Chapra, S. C.; Boehlert, B.; Fant, C.; Bierman, V. J.; Henderson, J.; Mills, D.; Mas, D. M. L.; Rennels, L.; Jantarasami, L.; Martinich, J.; Strzepek, K. M.; Paerl, H. W. Climate Change Impacts on Harmful Algal Blooms in U.S. Freshwaters: A Screening-Level Assessment. *Environ. Sci. Technol.* **2017**, *51* (16), 8933−8943.

(17) Bullerjahn, G. S.; McKay, R. M.; Davis, T. W.; Baker, D. B.; Boyer, G. L.; D'Anglada, L. V.; Doucette, G. J.; Ho, J. C.; Irwin, E. G.; Kling, C. L.; Kudela, R. M.; Kurmayer, R.; Michalak, A. M.; Ortiz, J. D.; Otten, T. G.; Paerl, H. W.; Qin, B.; Sohngen, B. L.; Stumpf, R. P.; Visser, P. M.; Wilhelm, S. W. Global Solutions to Regional Problems: Collecting Global Expertise to Address the Problem of Harmful Cyanobacterial Blooms. A Lake Erie Case Study. *Harmful Algae* **2016**, *54*, 223−238.

(18) Qin, B.; Zhu, G.; Gao, G.; Zhang, Y.; Li, W.; Paerl, H. W.; Carmichael, W. W. A Drinking Water Crisis in Lake Taihu, China: Linkage to Climatic Variability and Lake Management. *Environ. Manage.* **2010**, *45* (1), 105−112.

(19) Ueno, Y.; Nagata, S.; Tsutsumi, T.; Hasegawa, A.; Watanabe, M. F.; Park, H. D.; Chen, G. G.; Yu, S. Z. Detection of Microcystins, a Blue-Green Algal Hepatotoxin, in Drinking Water Sampled in Haimen and Fusui, Endemic Areas of Primary Liver Cancer in China, by Highly Sensitive Immunoassay. *Carcinogenesis* **1996**, *17* (6), 1317−1321.

(20) Westrick, J. A.; Szlag, D. A Cyanotoxin Primer for Drinking Water Professionals. *J. - Am. Water Works Assoc.* **2018**, *110*, E1−E16.

(21) Otten, T. G.; Paerl, H. W. Health Effects of Toxic Cyanobacteria in U.S. Drinking and Recreational Waters: Our Current Understanding and Proposed Direction. *Current environmental health reports*. Springer March 1, 2015; pp 75−84. DOI: 10.1007/s40572-014-0041-9.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

(22) Pearson, L. A.; Dittmann, E.; Mazmouz, R.; Ongley, S. E.; D'Agostino, P. M.; Neilan, B. A. The Genetics, Biosynthesis and Regulation of Toxic Specialized Metabolites of Cyanobacteria. *Harmful Algae* **2016**, *54*, 98−111.
(23) Wood, S. A.; Rueckert, A.; Hamilton, D. P.; Cary, S. C.; Dietrich, D. R. Switching Toxin Production on and off: Intermittent Microcystin Synthesis in a Microcystis Bloom. *Environ. Microbiol. Rep.* **2011**, *3* (1), 118−124.
(24) Schmidt, J. R.; Wilhelm, S. W.; Boyer, G. L. The Fate of Microcystins in the Environment and Challenges for Monitoring. *Toxins*. MDPI AG 2014; pp 3354−3387. DOI: 10.3390/toxins6123354.
(25) Buratti, F. M.; Manganelli, M.; Vichi, S.; Stefanelli, M.; Scardala, S.; Testai, E.; Funari, E. Cyanotoxins: Producing Organisms, Occurrence, Toxicity, Mechanism of Action and Human Health Toxicological Risk Evaluation. *Arch. Toxicol.* **2017**, *91* (3), 1049−1130.
(26) Funari, E.; Testai, E. Human Health Risk Assessment Related to Cyanotoxins Exposure. *Crit. Rev. Toxicol.* **2008**, *38* (2), 97−125.
(27) Wood, R. Acute Animal and Human Poisonings from Cyanotoxin Exposure - A Review of the Literature. *Environ. Int.* **2016**, *91*, 276−282.
(28) Drobac, D.; Tokodi, N.; Simeunović, J.; Baltić, V.; Stanić, D.; SvirČev, Z. Human Exposure to Cyanotoxins and Their Effects on Health. *Arh. Hig. Rada Toksikol.* **2013**, *64* (2), 305−316.
(29) Lee, J.; Lee, S.; Jiang, X. Cyanobacterial Toxins in Freshwater and Food: Important Sources of Exposure to Humans. *Annu. Rev. Food Sci. Technol.* **2017**, *8* (1), 281−304.
(30) Dawson, R. The Toxicology of Microcystins. *Toxicon* **1998**, *36* (7), 953−962.
(31) Codd, G. A.; Ward, C. J.; Bell, S. G. Cyanobacterial Toxins: Occurrence, Modes of Action, Health Effects and Exposure Routes. In *Archives of toxicology. Supplement. = Archiv für Toxikologie. Supplement*; Springer: Berlin, Heidelberg, 1997; Vol. *19*, pp 399−410. DOI: 10.1007/978-3-642-60682-3_38.
(32) Carvalho, G. M. C.; Oliveira, V. R.; Casquilho, N. V.; Araujo, A. C. P.; Soares, R. M.; Azevedo, S. M. F. O.; Pires, K. M. P.; ValenCa, S. S.; Zin, W. A. Pulmonary and Hepatic Injury after Sub-Chronic Exposure to Sublethal Doses of Microcystin-LR. *Toxicon* **2016**, *112*, 51−58.
(33) Giannuzzi, L.; Sedan, D.; Echenique, R.; Andrinolo, D. An Acute Case of Intoxication with Cyanobacteria and Cyanotoxins in Recreational Water in Salto Grande Dam, Argentina. *Mar. Drugs* **2011**, *9* (11), 2164−2175.
(34) Vidal, F.; Sedan, D.; D'Agostino, D.; Cavalieri, M. L.; Mullen, E.; Parot Varela, M. M.; Flores, C.; Caixach, J.; Andrinolo, D. Recreational Exposure during Algal Bloom in Carrasco Beach, Uruguay: A Liver Failure Case Report. *Toxins (Basel)*. 2017, *9* (9). DOI: 10.3390/toxins9090267.
(35) Cheng, Y.; Yue, Z.; Irvin, C.; Kirkpatrick, B.; Backer, L. Characterization of Aerosols Containing Microcystin. *Mar. Drugs* **2007**, *5* (4), 136−150.
(36) Backer, L. C.; McNeel, S. V.; Barber, T.; Kirkpatrick, B.; Williams, C.; Irvin, M.; Zhou, Y.; Johnson, T. B.; Nierenberg, K.; Aubel, M.; LePrell, R.; Chapman, A.; Foss, A.; Corum, S.; Hill, V. R.; Kieszak, S. M.; Cheng, Y.-S. S. Recreational Exposure to Microcystins during Algal Blooms in Two California Lakes. *Toxicon* **2010**, *55* (5), 909−921.
(37) Backer, L. C.; Carmichael, W.; Kirkpatrick, B.; Williams, C.; Irvin, M.; Zhou, Y.; Johnson, T.; Nierenberg, K.; Hill, V.; Kieszak, S.; Cheng, Y.-S. Recreational Exposure to Low Concentrations of Microcystins During an Algal Bloom in a Small Lake. *Mar. Drugs* **2008**, *6* (2), 389−406.
(38) Facciponte, D. N.; Bough, M. W.; Seidler, D.; Carroll, J. L.; Ashare, A.; Andrew, A. S.; Tsongalis, G. J.; Vaickus, L. J.; Henegan, P. L.; Butt, T. H.; Stommel, E. W. Identifying Aerosolized Cyanobacteria in the Human Respiratory Tract: A Proposed Mechanism for Cyanotoxin-Associated Diseases. *Sci. Total Environ.* **2018**, *645*, 1003−1013.
(39) May, N. W.; Olson, N. E.; Panas, M.; Axson, J. L.; Tirella, P. S.; Kirpes, R. M.; Craig, R. L.; Gunsch, M. J.; China, S.; Laskin, A.; Ault, A. P.; Pratt, K. A. Aerosol Emissions from Great Lakes Harmful Algal Blooms. *Environ. Sci. Technol.* **2018**, *52* (2), 397−405.
(40) Sharma, N. K.; Rai, A. K. Allergenicity of Airborne Cyanobacteria Phormidium Fragile and Nostoc Muscorum. *Ecotoxicol. Environ. Saf.* **2008**, *69* (1), 158−162.
(41) Wiśniewska, K.; Lewandowska, A. U.; Śliwińska-Wilczewska, S. The Importance of Cyanobacteria and Microalgae Present in Aerosols to Human Health and the Environment - Review Study. *Environment International*. Elsevier Ltd October 1, 2019; p 104964. DOI: 10.1016/j.envint.2019.104964.
(42) Olson, N. E.; Cooke, M. E.; Shi, J. H.; Birbeck, J. A.; Westrick, J. A.; Ault, A. P. Harmful Algal Bloom Toxins in Aerosol Generated from Inland Lake Water. *Environ. Sci. Technol.* **2020**, *54* (8), 4769−4780.
(43) Wood, S. A.; Dietrich, D. R. Quantitative Assessment of Aerosolized Cyanobacterial Toxins at Two New Zealand Lakes. *J. Environ. Monit.* **2011**, *13* (6), 1617−1624.
(44) Després, V.; Huffman, J. A.; Burrows, S. M.; Hoose, C.; Safatov, A.; Buryak, G.; Fröhlich-Nowoisky, J.; Elbert, W.; Andreae, M.; Pöschl, U.; Jaenicke, R. Primary Biological Aerosol Particles in the Atmosphere: A Review. *Tellus, Ser. B* **2012**, *64* (1), 15598.
(45) Fröhlich-Nowoisky, J.; Kampf, C. J.; Weber, B.; Huffman, J. A.; Pöhlker, C.; Andreae, M. O.; Lang-Yona, N.; Burrows, S. M.; Gunthe, S. S.; Elbert, W.; Su, H.; Hoor, P.; Thines, E.; Hoffmann, T.; Després, V. R.; Pöschl, U. Bioaerosols in the Earth System: Climate, Health, and Ecosystem Interactions. *Atmos. Res.* **2016**, *182*, 346−376.
(46) Sharma, N. K.; Singh, S.; Rai, A. K. Diversity and Seasonal Variation of Viable Algal Particles in the Atmosphere of a Subtropical City in India. *Environ. Res.* **2006**, *102* (3), 252−259.
(47) Sharma, N. K.; Singh, S. Differential Aerosolization of Algal and Cyanobacterial Particles in the Atmosphere. *Indian J. Microbiol.* **2010**, *50* (4), 468−473.
(48) Broady, P. A. Diversity, Distribution and Dispersal of Antarctic Terrestrial Algae. *Biodivers. Conserv.* **1996**, *5* (11), 1307−1335.
(49) Brown, R. M.; Larson, D. A.; Bold, H. C. Airborne Algae: Their Abundance and Heterogeneity. *Science (Washington, DC, U. S.)* **1964**, *143* (3606), 583−585.
(50) Tesson, S. V. M.; Skjøth, C. A.; Šantl-Temkiv, T.; Löndahl, J. Airborne Microalgae: Insights, Opportunities, and Challenges. *Appl. Environ. Microbiol.*. American Society for Microbiology April 1, 2016; pp 1978−1991. DOI: 10.1128/AEM.03333-15.
(51) Gantt, B.; Meskhidze, N. The Physical and Chemical Characteristics of Marine Primary Organic Aerosol: A Review. *Atmos. Chem. Phys.* **2013**, *13* (8), 3979−3996.
(52) Hasenecz, E. S.; Kaluarachchi, C. P.; Lee, H. D.; Tivanski, A. V.; Stone, E. A. Saccharide Transfer to Sea Spray Aerosol Enhanced by Surface Activity, Calcium, and Protein Interactions. *ACS Earth Sp. Chem.* **2019**, *3* (11), 2539−2548.
(53) Russell, L. M.; Pandis, S. N.; Seinfeld, J. H. Aerosol Production and Growth in the Marine Boundary Layer. *J. Geophys. Res.* **1994**, *99* (D10), 20989−21003.
(54) Axson, J. L.; May, N. W.; Colón-Bernal, I. D.; Pratt, K. A.; Ault, A. P. Lake Spray Aerosol: A Chemical Signature from Individual Ambient Particles. *Environ. Sci. Technol.* **2016**, *50* (18), 9835−9845.
(55) Slade, J. H.; Vanreken, T. M.; Mwaniki, G. R.; Bertman, S.; Stirm, B.; Shepson, P. B. Aerosol Production from the Surface of the Great Lakes. *Geophys. Res. Lett.* 2010, *37* (18). DOI: 10.1029/2010GL043852.
(56) May, N. W.; Axson, J. L.; Watson, A.; Pratt, K. A.; Ault, A. P. Lake Spray Aerosol Generation: A Method for Producing Representative Particles from Freshwater Wave Breaking. *Atmos. Meas. Tech.* **2016**, *9* (9), 4311−4325.
(57) Olson, N. E.; May, N. W.; Kirpes, R. M.; Watson, A. E.; Hajny, K. D.; Slade, J. H.; Shepson, P. B.; Stirm, B. H.; Pratt, K. A.; Ault, A. P. Lake Spray Aerosol Incorporated into Great Lakes Clouds. *ACS Earth Sp. Chem.* 2019, *3* (12) acsearthspacechem.9b00258. DOI: 10.1021/acsearthspacechem.9b00258.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

(58) Heise, H. A. Symptoms of Hay Fever Caused by Algae. *J. Allergy* **1949**, *20* (5), 383−385.
(59) Heise, H. A. Symptoms of Hay Fever Caused by Algae. II. Microcystis, Another Form of Algae Producing Allergenic Reactions. *J. Allergy* **1951**, *9* (1), 100−101.
(60) Abraham, W. M.; Bourdelais, A. J.; Ahmed, A.; Serebriakov, I.; Baden, D. G. Effects of Inhaled Brevetoxins in Allergic Airways: Toxin-Allergen Interactions and Pharmacologic Intervention. *Environ. Health Perspect.* **2005**, *113* (5), 632−637.
(61) Pierce, R. H.; Henry, M. S.; Blum, P. C.; Hamel, S. L.; Kirkpatrick, B.; Cheng, Y. S.; Zhou, Y.; Irvin, C. M.; Naar, J.; Weidner, A.; Fleming, L. E.; Backer, L. C.; Baden, D. G. Brevetoxin Composition in Water and Marine Aerosol along a Florida Beach: Assessing Potential Human Exposure to Marine Biotoxins. *Harmful Algae* **2005**, *4* (6), 965−972.
(62) Pierce, R.; Henry, M.; Proffitt, L. S. Red Tide Toxin (Brevetoxin) Enrichment in Marine Aerosol. *Toxic Mar. Phytoplankt.* 1990, No. Elsevier: pp Amsterdam, (pg. 397−402).
(63) Walsh, J. J.; Lenes, J. M.; Weisberg, R. H.; Zheng, L.; Hu, C.; Fanning, K. A.; Snyder, R.; Smith, J. More Surprises in the Global Greenhouse: Human Health Impacts from Recent Toxic Marine Aerosol Formations, Due to Centennial Alterations of World-Wide Coastal Food Webs. *Mar. Pollut. Bull.*. Elsevier Ltd March 15, 2017; pp 9−40. DOI: 10.1016/j.marpolbul.2016.12.053.
(64) Casabianca, S.; Casabianca, A.; Riobó, P.; Franco, J. M.; Vila, M.; Penna, A. Quantification of the Toxic Dinoflagellate Ostreopsis Spp. by QPCR Assay in Marine Aerosol. *Environ. Sci. Technol.* **2013**, *47* (8), 3788−3795.
(65) Ciminiello, P.; Dell'Aversano, C.; Iacovo, E.; Dello Fattorusso, E.; Forino, M.; Tartaglione, L.; Benedettini, G.; Onorari, M.; Serena, F.; Battocchi, C.; Casabianca, S.; Penna, A. First Finding of Ostreopsis Cf. Ovata Toxins in Marine Aerosols. *Environ. Sci. Technol.* **2014**, *48* (6), 3532−3540.
(66) Pavaux, A.-S.; Berdalet, E.; Lemée, R. Chemical Ecology of the Benthic Dinoflagellate Genus Ostreopsis: Review of Progress and Future Directions. *Front. Mar. Sci.* **2020**, *7*, 7.
(67) Vila, M.; Abós-Herràndiz, R.; Isern-Fontanet, J.; Àlvarez, J.; Berdalet, E. Establishing the Link between Ostreopsis Cf. Ovata Blooms and Human Health Impacts Using Ecology and Epidemiology. *Sci. Mar.* **2016**, *80* (S1), 107−115.
(68) Sharma, N. K.; Rai, A. K.; Singh, S.; Brown, R. M. Airborne Algae: Their Present Status and Relevance. *Journal of Phycology*. John Wiley & Sons, Ltd: August 1, 2007; pp 615−627. DOI: 10.1111/j.1529-8817.2007.00373.x.
(69) Lang-Yona, N.; Lehahn, Y.; Herut, B.; Burshtein, N.; Rudich, Y. Marine Aerosol as a Possible Source for Endotoxins in Coastal Areas. *Sci. Total Environ.* **2014**, *499* (1), 311−318.
(70) Berstein, L. I.; Safferman, R. S. Viable Algae in House Dust. *Nature* **1970**, *227* (5260), 851−852.
(71) Dockery, D. W.; Pope, C. A.; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G.; Speizer, F. E. An Association between Air Pollution and Mortality in Six U.S. Cities. *N. Engl. J. Med.* **1993**, *329* (24), 1753−1759.
(72) Pope, C. A.; Dockery, D. W. Health Effects of Fine Particulate Air Pollution: Lines That Connect. *J. Air Waste Manage. Assoc.* **2006**, *56* (6), 709−742.
(73) Dockery, D. W.; Pope, C. A. Acute Respiratory Effects of Particulate Air Pollution. *Annu. Rev. Public Health* **1994**, *15* (1), 107−132.
(74) Samet, J. M.; Dominici, F.; Curriero, F. C.; Coursac, I.; Zeger, S. L. Fine Particulate Air Pollution and Mortality in 20 U.S. Cities, 1987−1994. *N. Engl. J. Med.* **2000**, *343* (24), 1742−1749.
(75) Jerrett, M.; Burnett, R. T.; Arden Pope, C.; Ito, K.; Thurston, G.; Krewski, D.; Shi, Y.; Calle, E.; Thun, M. Long-Term Ozone Exposure and Mortality. *N. Engl. J. Med.* **2009**, *360* (11), 1085−1095.
(76) Baccarelli, A.; Wright, R. O.; Bollati, V.; Tarantini, L.; Litonjua, A. A.; Suh, H. H.; Zanobetti, A.; Sparrow, D.; Vokonas, P. S.; Schwartz, J. Rapid DNA Methylation Changes after Exposure to Traffic Particles. *Am. J. Respir. Crit. Care Med.* **2009**, *179* (7), 572−578.
(77) Hoek, G.; Krishnan, R. M.; Beelen, R.; Peters, A.; Ostro, B.; Brunekreef, B.; Kaufman, J. D. Long-Term Air Pollution Exposure and Cardio-Respiratory Mortality: A Review. *Environmental Health: A Global Access Science Source*. 2013. DOI: 10.1186/1476-069X-12-43.
(78) Kim, K. H.; Kabir, E.; Kabir, S. A Review on the Human Health Impact of Airborne Particulate Matter. *Environment International*. Elsevier Ltd January 1, 2015; pp 136−143. DOI: 10.1016/j.envint.2014.10.005.
(79) Birbeck, J. A.; Westrick, J. A.; O'neill, G. M.; Spies, B.; Szlag, D. C. Comparative Analysis of Microcystin Prevalence in Michigan Lakes by Online Concentration Lc/Ms/Ms and Elisa. *Toxins* **2019**, *11* (1), 13.
(80) Jones, G. J.; Orr, P. T. Release and Degradation of Microcystin Following Algicide Treatment of a Microcystis Aeruginosa Bloom in a Recreational Lake, as Determined by HPLC and Protein Phosphatase Inhibition Assay. *Water Res.* **1994**, *28* (4), 871−876.
(81) Carmichael, W. W.; Eschedor, J. T.; Patterson, G. M.; Moore, R. E. Toxicity and Partial Structure of a Hepatotoxic Peptide Produced by the Cyanobacterium Nodularia Spumigena Mertens Emend. LS75 from New Zealand. *Appl. Environ. Microbiol.* **1988**, *54* (9), 2257−2263.
(82) Catherine, Q.; Susanna, W.; Isidora, E.-S.; Mark, H.; Aurélie, V.; Jean-FranÇois, H. A Review of Current Knowledge on Toxic Benthic Freshwater Cyanobacteria - Ecology, Toxin Production and Risk Management. *Water Res.* **2013**, *47* (15), 5464−5479.
(83) Rinehart, K. L.; Harada, K. I.; Namikoshi, M.; Chen, C.; Harvis, C. A.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasley, V. R.; Dahlem, A. M.; Carmichael, W. W. Nodularin, Microcystin, and the Configuration of Adda. *J. Am. Chem. Soc.* **1988**, *110* (25), 8557−8558.
(84) McCord, J.; Lang, J. R.; Hill, D.; Chernoff, N.; Strynar, M. PH Dependent Octanol-Water Partitioning Coefficients of Microcystin Congeners. *J. Water Health* **2018**, *16* (3), 340−345.
(85) Bouaïcha, N.; Miles, C. O.; Beach, D. G.; Labidi, Z.; Djabri, A.; Benayache, N. Y.; Nguyen-Quang, T. Structural Diversity, Characterization and Toxicology of Microcystins. *Toxins* **2019**, *11* (12), 714.
(86) de Maagd, P. G.-J.; Hendriks, A. J.; Seinen, W.; Sijm, D. T. H. M. PH-Dependent Hydrophobicity of the Cyanobacteria Toxin Microcystin-LR. *Water Res.* **1999**, *33* (3), 677−680.
(87) Ward, C. J.; Codd, G. A. Comparative Toxicity of Four Microcystins of Different Hydrophobicities to the Protozoan, Tetrahymena Pyriformis. *J. Appl. Microbiol.* **1999**, *86* (5), 874−882.
(88) Banker, R.; Carmeli, S.; Werman, M.; Teltsch, B.; Porat, R.; Sukenik, A. Uracil Moiety Is Required for Toxicity of the Cyanobacterial Hepatotoxin Cylindrospermopsin. *J. Toxicol. Environ. Health, Part A* **2001**, *62* (4), 281−288.
(89) Banker, R.; Teltsch, B.; Sukenik, A.; Carmeli, S. 7-Epicylindrospermopsin, a Toxic Minor Metabolite of the Cyanobacterium Aphanizomenon Ovalisporum from Lake Kinneret, Israel. *J. Nat. Prod.* **2000**, *63* (3), 387−389.
(90) Ohtani, I.; Moore, R. E.; Runnegar, M. T. C. Cylindrospermopsin: A Potent Hepatotoxin from the Blue-Green Alga Cylindrospermopsis Raciborskii. *J. Am. Chem. Soc.* **1992**, *114* (20), 7941−7942.
(91) Norris, R. L. G.; Eaglesham, G. K.; Shaw, G. R.; Senogles, P.; Chiswell, R. K.; Smith, M. J.; Davis, B. C.; Seawright, A. A.; Moore, M. R. Extraction and Purification of the Zwitterions Cylindrospermopsin and Deoxycylindrospermopsin from Cylindrospermopsis Raciborskii. *Environ. Toxicol.* **2001**, *16* (5), 391−396.
(92) Bourke, A. T. C.; Hawes, R. B.; Neilson, A.; Stallman, N. D. An Outbreak of Hepato-Enteritis (the Palm Island Mystery Disease) Possibly Caused by Algal Intoxication. *Toxicon* **1983**, *21*, 45−48.
(93) Cusick, K.; Sayler, G. An Overview on the Marine Neurotoxin, Saxitoxin: Genetics, Molecular Targets, Methods of Detection and Ecological Functions. *Mar. Drugs* **2013**, *11* (12), 991−1018.
(94) Pearson, L.; Mihali, T.; Moffitt, M.; Kellmann, R.; Neilan, B. On the Chemistry, Toxicology and Genetics of the Cyanobacterial Toxins, Microcystin, Nodularin, Saxitoxin and Cylindrospermopsin.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Marine Drugs. MDPI AG May 10, 2010; pp 1650−1680. DOI: 10.3390/md8051650.
(95) Wiese, M.; D'Agostino, P. M.; Mihali, T. K.; Moffitt, M. C.; Neilan, B. A. Neurotoxic Alkaloids: Saxitoxin and Its Analogs. *Mar. Drugs* **2010**, *8* (7), 2185−2211.
(96) Foss, A. J.; Phlips, E. J.; Yilmaz, M.; Chapman, A. Characterization of Paralytic Shellfish Toxins from Lyngbya Wollei Dominated Mats Collected from Two Florida Springs. *Harmful Algae* **2012**, *16*, 98−107.
(97) Lagos, N.; Onodera, H.; Zagatto, P. A.; Andrinolo, D.; Azevedo, S. M. F. Q.; Oshima, Y. The First Evidence of Paralytic Shellfish Toxins in the Freshwater Cyanobacterium Cylindrospermopsis Raciborskii, Isolated from Brazil. *Toxicon* **1999**, *37* (10), 1359−1373.
(98) Sivonen, K.; Himberg, K.; Luukkainen, R.; Niemelä, S. I.; Poon, G. K.; Codd, G. A. Preliminary Characterization of Neurotoxic Cyanobacteria Blooms and Strains from Finland. *Toxic. Assess.* **1989**, *4* (3), 339−352.
(99) Kaminski, A.; Bober, B.; Lechowski, Z.; Bialczyk, J. Determination of Anatoxin-a Stability under Certain Abiotic Factors. *Harmful Algae* **2013**, *28*, 83−87.
(100) Wonnacott, S.; Gallagher, T. The Chemistry and Pharmacology of Anatoxin-a and Related Homotropanes with Respect to Nicotinic Acetylcholine Receptors. *Marine Drugs*. Multidisciplinary Digital Publishing Institute (MDPI) 2006; pp 228−254. DOI: 10.3390/md403228.
(101) Ragnarsdottir, K. V. Environmental Fate and Toxicology of Organophosphate Pesticides. *J. Geol. Soc.* **2000**, *157* (4), 859−876.
(102) Paerl, W. W.; Ustach, J. F. Blue-green Algal Scums: An Explanation for Their Occurrence during Freshwater Blooms. *Limnol. Oceanogr.* **1982**, *27* (2), 212−217.
(103) Walsby, A. E.; Hayes, P. K.; Boje, R.; Stal, L. J. The Selective Advantage of Buoyancy Provided by Gas Vesicles for Planktonic Cyanobacteria in the Baltic Sea. *New Phytol.* **1997**, *136* (3), 407−417.
(104) Moisander, P. H.; Hench, J. L.; Kononen, K.; Paerl, H. W. Small-Scale Shear Effects on Heterocystous Cyanobacteria. *Limnol. Oceanogr.* **2002**, *47* (1), 108−119.
(105) Park, H. D.; Iwami, C.; Watanabe, M. F.; Harada, K. I.; Okino, T.; Hayashi, H. Temporal Variabilities of the Concentrations of Intra- and Extracellular Microcystin and Toxic Microcystis Species in a Hypertrophie Lake, Lake Suwa, Japan (1991−1994). *Environ. Toxicol. Water Qual.* **1998**, *13* (1), 61−72.
(106) Paerl, H. W.; Otten, T. G. Harmful Cyanobacterial Blooms: Causes, Consequences, and Controls. *Microb. Ecol.* **2013**, *65* (4), 995−1010.
(107) McKindles, K. M.; Manes, M. A.; DeMarco, J. R.; McClure, A.; McKay, R. M.; Davis, T. W.; Bullerjahn, G. S. Dissolved Microcystin Release Coincident with Lysis of a Microcystis -Dominated Bloom in Western Lake Erie Attributed to a Novel Cyanophage. *Appl. Environ. Microbiol.* 2020. DOI: 10.1128/aem.01397-20.
(108) Bormans, M.; Amzil, Z.; Mineaud, E.; Brient, L.; Savar, V.; Robert, E.; Lance, E. Demonstrated Transfer of Cyanobacteria and Cyanotoxins along a Freshwater-Marine Continuum in France. *Harmful Algae* **2019**, *87*, 101639.
(109) Lehtimäki, J.; Moisander, P.; Sivonen, K.; Kononen, K. Growth, Nitrogen Fixation, and Nodularin Production by Two Baltic Sea Cyanobacteria. *Appl. Environ. Microbiol.* **1997**, *63* (5), 1647−1656.
(110) Rapala, J.; Lahti, K.; Sivonen, K.; Niemelä, S. I. Biodegradability and Adsorption on Lake Sediments of Cyanobacterial Hepatotoxins and Anatoxin-a. *Lett. Appl. Microbiol.* **1994**, *19* (6), 423−428.
(111) Spoof, L.; Berg, K. A.; Rapala, J.; Lahti, K.; Lepistö, L.; Metcalf, J. S.; Codd, G. A.; Meriluoto, J. First Observation of Cylindrospermopsin in Anabaena Lapponica Isolated from the Boreal Environment (Finland). *Environ. Toxicol.* **2006**, *21* (6), 552−560.
(112) Cirés, S.; Wörmer, L.; Timón, J.; Wiedner, C.; Quesada, A. Cylindrospermopsin Production and Release by the Potentially Invasive Cyanobacterium Aphanizomenon Ovalisporum under Temperature and Light Gradients. *Harmful Algae* **2011**, *10* (6), 668−675.
(113) Shaw, G. R.; Sukenik, A.; Livne, A.; Chiswell, R. K.; Smith, M. J.; Seawright, A. A.; Norris, R. L.; Eaglesham, G. K.; Moore, M. R. Blooms of the Cylindrospermopsin Containing Cyanobacterium, Aphanizomenon Ovalisporum (Fofti), in Newly Constructed Lakes, Queensland, Australia. *Environ. Toxicol.* **1999**, *14* (1), 167−177.
(114) Wörmer, L.; Huerta-Fontela, M.; Cirés, S.; Carrasco, D.; Quesada, A. Natural Photodegradation of the Cyanobacterial Toxins Microcystin and Cylindrospermopsin. *Environ. Sci. Technol.* **2010**, *44* (8), 3002−3007.
(115) Preußel, K.; Stüken, A.; Wiedner, C.; Chorus, I.; Fastner, J. First Report on Cylindrospermopsin Producing Aphanizomenon Flos-Aquae (Cyanobacteria) Isolated from Two German Lakes. *Toxicon* **2006**, *47* (2), 156−162.
(116) Rzymski, P.; Poniedziałek, B. In Search of Environmental Role of Cylindrospermopsin: A Review on Global Distribution and Ecology of Its Producers. *Water Res.* **2014**, *66*, 320−337.
(117) Tsuji, K.; Watanuki, T.; Kondo, F.; Watanabe, M. F.; Suzuki, S.; Nakazawa, H.; Suzuki, M.; Uchida, H.; Harada, K. I. Stability of Microcystins from Cyanobacteria-II. Effect of UV Light on Decomposition and Isomerization. *Toxicon* **1995**, *33* (12), 1619−1631.
(118) Welker, M.; Steinberg, C. Rates of Humic Substance Photosensitized Degradation of Microcystin-LR in Natural Waters. *Environ. Sci. Technol.* **2000**, *34* (16), 3415−3419.
(119) Chiswell, R. K.; Shaw, G. R.; Eaglesham, G.; Smith, M. J.; Norris, R. L.; Seawright, A. A.; Moore, M. R. Stability of Cylindrospermopsin, the Toxin from the Cyanobacterium, Cylindrospermopsis Raciborskii: Effect of PH, Temperature, and Sunlight on Decomposition. *Environ. Toxicol.* **1999**, *14* (1), 155−161.
(120) Morris, R. J.; Williams, D. E.; Luu, H. A.; Holmes, C. F. B.; Andersen, R. J.; Calvert, S. E. The Adsorption of Microcystin-LR by Natural Clay Particles. *Toxicon* **2000**, *38* (2), 303−308.
(121) Tsuji, K.; Masui, H.; Uemura, H.; Mori, Y.; Harada, K. I. Analysis of Microcystins in Sediments Using MMPB Method. *Toxicon* **2001**, *39* (5), 687−692.
(122) Liu, G.; Qian, Y.; Dai, S.; Feng, N. Adsorption of Microcystin LR and LW on Suspended Particulate Matter (SPM) at Different PH. *Water, Air, Soil Pollut.* **2008**, *192* (1−4), 67−76.
(123) Munusamy, T.; Hu, Y. L.; Lee, J. F. Adsorption and Photodegradation of Microcystin-LR onto Sediments Collected from Reservoirs and Rivers in Taiwan: A Laboratory Study to Investigate the Fate, Transfer, and Degradation of Microcystin-LR. *Environ. Sci. Pollut. Res.* **2012**, *19* (6), 2390−2399.
(124) Corbel, S.; Mougin, C.; Bouaïcha, N. Cyanobacterial Toxins: Modes of Actions, Fate in Aquatic and Soil Ecosystems, Phytotoxicity and Bioaccumulation in Agricultural Crops. *Chemosphere* **2014**, *96*, 1−15.
(125) Bourne, D. G.; Jones, G. J.; Blakeley, R. L.; Jones, A.; Negri, A. P.; Riddles, P. Enzymatic Pathway for the Bacterial Degradation of the Cyanobacterial Cyclic Peptide Toxin Microcystin LR. *Appl. Environ. Microbiol.* **1996**, *62* (11), 4086−4094.
(126) Ho, L.; Hoefel, D.; Saint, C. P.; Newcombe, G. Isolation and Identification of a Novel Microcystin-Degrading Bacterium from a Biological Sand Filter. *Water Res.* **2007**, *41* (20), 4685−4695.
(127) Okano, K.; Shimizu, K.; Kawauchi, Y.; Maseda, H.; Utsumi, M.; Zhang, Z.; Neilan, B. A.; Sugiura, N. Characteristics of a Microcystin-Degrading Bacterium under Alkaline Environmental Conditions. *J. Toxicol.* **2009**, *2009*, 1−8.
(128) Okano, K.; Shimizu, K.; Maseda, H.; Kawauchi, Y.; Utsumi, M.; Itayama, T.; Zhang, Z.; Sugiura, N. Whole-Genome Sequence of the Microcystin-Degrading Bacterium Sphingopyxis Sp. Strain C-1. *Genome Announc.* 2015, *3* (4). DOI: 10.1128/genomeA.00838-15.
(129) Imanishi, S.; Kato, H.; Mizuno, M.; Tsuji, K.; Harada, K. I. Bacterial Degradation of Microcystins and Nodularin. *Chem. Res. Toxicol.* **2005**, *18* (3), 591−598.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

(130) Ibelings, B. W.; Chorus, I. Accumulation of Cyanobacterial Toxins in Freshwater "Seafood" and Its Consequences for Public Health: A Review. *Environ. Pollut.*. Elsevier: November 1, 2007; pp 177−192. DOI: 10.1016/j.envpol.2007.04.012.
(131) Carmichael, W. W. The Cyanotoxins. In *Incorporating in Plant Pathology - Classic Papers*; Elsevier: 1997; pp 211−256. DOI: 10.1016/S0065-2296(08)60282-7.
(132) Cirés, S.; Delgado, A.; González-Pleiter, M.; Quesada, A. Temperature Influences the Production and Transport of Saxitoxin and the Expression of Sxt Genes in the Cyanobacterium Aphanizomenon Gracile. *Toxins* **2017**, *9* (10), 322.
(133) Aller, J. Y.; Kuznetsova, M. R.; Jahns, C. J.; Kemp, P. F. The Sea Surface Microlayer as a Source of Viral and Bacterial Enrichment in Marine Aerosols. *J. Aerosol Sci.* **2005**, *36* (5−6), 801−812.
(134) De Leeuw, G.; Andreas, E. L.; Anguelova, M. D.; Fairall, C. W.; Lewis, E. R.; O'Dowd, C.; Schulz, M.; Schwartz, S. E. Production Flux of Sea Spray Aerosol. *Rev. Geophys.* **2011**, *49* (2), RG2001.
(135) Deane, G. B.; Stokes, M. D. Scale Dependence of Bubble Creation Mechanisms in Breaking Waves. *Nature* **2002**, *418* (6900), 839−844.
(136) Deane, G. B.; Stokes, M. D. Air Entrainment Processes and Bubble Size Distributions in the Surf Zone. *J. Phys. Oceanogr.* **1999**, *29* (7), 1393−1403.
(137) Kientzler, C. F.; Arons, A. B.; Blanchard, D. C.; Woodcock, A. H. Photographic Investigation of the Projection of Droplets by Bubbles Bursting at a Water Surface. *Tellus* **1954**, *6* (1), 1−7.
(138) Monahan, E. C. Sea Spray as a Function of Low Elevation Wind Speed. *J. Geophys. Res.* **1968**, *73* (4), 1127−1137.
(139) Monahan, E. C.; Fairall, C. W.; Davidson, K. L.; Boyle, P. J. Observed Inter-relations between 10m Winds, Ocean Whitecaps and Marine Aerosols. *Q. J. R. Meteorol. Soc.* **1983**, *109* (460), 379−392.
(140) Moore, D. J.; Mason, B. J. The Concentration, Size Distribution and Production Rate of Large Salt Nuclei over the Oceans. *Q. J. R. Meteorol. Soc.* **1954**, *80* (346), 583−590.
(141) Riemer, N.; Ault, A. P.; West, M.; Craig, R. L.; Curtis, J. H. Aerosol Mixing State: Measurements, Modeling, and Impacts. *Reviews of Geophysics*. Blackwell Publishing Ltd June 21, 2019; pp 187−249. DOI: 10.1029/2018RG000615.
(142) Seinfeld, J. H.; Pandis, S. N. Atmospheric Chemistry and Physics. *Atmos. Chem. Phys.* **2006**, *5* (1), 139−152.
(143) Kunz, G. J.; De Leeuw, G.; Becker, E.; O'Dowd, C. D. Lidar Observations of Atmospheric Boundary Layer Structure and Sea Spray Aerosol Plumes Generation and Transport at Mace Head, Ireland (PARFORCE Experiment). *J. Geophys. Res. Atmos.* 2002, *107* (19). DOI: 10.1029/2001JD001240.
(144) Bondy, A. L.; Wang, B.; Laskin, A.; Craig, R. L.; Nhliziyo, M. V.; Bertman, S. B.; Pratt, K. A.; Shepson, P. B.; Ault, A. P. Inland Sea Spray Aerosol Transport and Incomplete Chloride Depletion: Varying Degrees of Reactive Processing Observed during SOAS. *Environ. Sci. Technol.* **2017**, *51* (17), 9533−9542.
(145) Gard, E. E.; Kleeman, M. J.; Gross, D. S.; Hughes, L. S.; Allen, J. O.; Morrical, B. D.; Fergenson, D. P.; Dienes, T.; Gälli, M. E.; Johnson, R. J.; Cass, G. R.; Prather, K. A. Direct Observation of Heterogeneous Chemistry in the Atmosphere. *Science (Washington, DC, U. S.)* **1998**, *279* (5354), 1184−1187.
(146) May, N. W.; Gunsch, M. J.; Olson, N. E.; Bondy, A. L.; Kirpes, R. M.; Bertman, S. B.; China, S.; Laskin, A.; Hopke, P. K.; Ault, A. P.; Pratt, K. A. Unexpected Contributions of Sea Spray and Lake Spray Aerosol to Inland Particulate Matter. *Environ. Sci. Technol. Lett.* **2018**, *5* (7), 405−412.
(147) Manders, A. M. M.; Schaap, M.; Querol, X.; Albert, M. F. M. A.; Vercauteren, J.; Kuhlbusch, T. A. J.; Hoogerbrugge, R. Sea Salt Concentrations across the European Continent. *Atmos. Environ.* **2010**, *44* (20), 2434−2442.
(148) Clarke, A.; Kapustin, V.; Howell, S.; Moore, K. Sea-Salt Size Distributions from Breaking Waves: Implications for Marine Aerosol Production and Optical Extinction Measurements during SEAS*. *J. Atmos. Ocean. Technol.* **2003**, *20* (10), 1362−1374.
(149) Blanchard, D. C.; Woodcock, A. H. Bubble Formation and Modification in the Sea and Its Meteorological Significance. *Tellus* **1957**, *9* (2), 145−158.
(150) Lewis, E. R.; Schwartz, S. E. Sea Salt Aerosol Production: Mechanisms, Methods, Measurements and Models—A Critical Review. In *Geophysical Monograph Series; Geophysical Monograph Series*; American Geophysical Union: Washington, D. C., 2004; Vol. *152*, pp 1−408. DOI: 10.1029/152GM01.
(151) Spiel, D. E. On the Births of Film Drops from Bubbles Bursting on Seawater Surfaces. *J. Geophys. Res. Ocean.* **1998**, *103* (C11), 24907−24918.
(152) Wang, X.; Deane, G. B.; Moore, K. A.; Ryder, O. S.; Stokes, M. D.; Beall, C. M.; Collins, D. B.; Santander, M. V.; Burrows, S. M.; Sultana, C. M.; Prather, K. A. The Role of Jet and Film Drops in Controlling the Mixing State of Submicron Sea Spray Aerosol Particles. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114* (27), 6978−6983.
(153) Wu, J. Production Functions of Film Drops by Bursting Bubbles. *J. Phys. Oceanogr.* **2001**, *31* (11), 3249−3257.
(154) Collins, D. B.; Zhao, D. F.; Ruppel, M. J.; Laskina, O.; Grandquist, J. R.; Modini, R. L.; Stokes, M. D.; Russell, L. M.; Bertram, T. H.; Grassian, V. H.; Deane, G. B.; Prather, K. A. Direct Aerosol Chemical Composition Measurements to Evaluate the Physicochemical Differences between Controlled Sea Spray Aerosol Generation Schemes. *Atmos. Meas. Tech.* **2014**, *7* (11), 3667−3683.
(155) Prather, K. A.; Bertram, T. H.; Grassian, V. H.; Deane, G. B.; Stokes, M. D.; DeMott, P. J.; Aluwihare, L. I.; Palenik, B. P.; Azam, F.; Seinfeld, J. H.; Moffet, R. C.; Molina, M. J.; Cappa, C. D.; Geiger, F. M.; Roberts, G. C.; Russell, L. M.; Ault, A. P.; Baltrusaitis, J.; Collins, D. B.; Corrigan, C. E.; Cuadra-Rodriguez, L. A.; Ebben, C. J.; Forestieri, S. D.; Guasco, T. L.; Hersey, S. P.; Kim, M. J.; Lambert, W. F.; Modini, R. L.; Mui, W.; Pedler, B. E.; Ruppel, M. J.; Ryder, O. S.; Schoepp, N. G.; Sullivan, R. C.; Zhao, D. Bringing the Ocean into the Laboratory to Probe the Chemical Complexity of Sea Spray Aerosol. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110* (19), 7550−7555.
(156) Gaston, C. J.; Furutani, H.; Guazzotti, S. A.; Coffee, K. R.; Bates, T. S.; Quinn, P. K.; Aluwihare, L. I.; Mitchell, B. G.; Prather, K. A. Unique Ocean-Derived Particles Serve as a Proxy for Changes in Ocean Chemistry. *J. Geophys. Res.* **2011**, *116* (D18), D18310.
(157) Cipriano, R. J.; Blanchard, D. C. Bubble and Aerosol Spectra Produced by a Laboratory 'Breaking Wave.'. *J. Geophys. Res.* **1981**, *86* (C9), 8085.
(158) Lhuissier, H.; Villermaux, E. Bursting Bubble Aerosols. *J. Fluid Mech.* **2012**, *696*, 5−44.
(159) Poulain, S.; Villermaux, E.; Bourouiba, L. Ageing and Burst of Surface Bubbles. *J. Fluid Mech.* **2018**, *851*, 636−671.
(160) O'Dowd, C. D.; Facchini, M. C.; Cavalli, F.; Ceburnis, D.; Mircea, M.; Decesari, S.; Fuzzi, S.; Young, J. Y.; Putaud, J. P. Biogenically Driven Organic Contribution to Marine Aerosol. *Nature* **2004**, *431* (7009), 676−680.
(161) Blanchard, D. C. The Ejection of Drops from the Sea and Their Enrichment with Bacteria and Other Materials: A Review. *Estuaries* **1989**, *12* (3), 127−137.
(162) Blanchard, D. C.; Syzdek, L. D. Concentration of Bacteria in Jet Drops from Bursting Bubbles. *J. Geophys. Res.* **1972**, *77* (27), 5087−5099.
(163) Collins, D. B.; Ault, A. P.; Moffet, R. C.; Ruppel, M. J.; Cuadra-Rodriguez, L. A.; Guasco, T. L.; Corrigan, C. E.; Pedler, B. E.; Azam, F.; Aluwihare, L. I.; Bertram, T. H.; Roberts, G. C.; Grassian, V. H.; Prather, K. A. Impact of Marine Biogeochemistry on the Chemical Mixing State and Cloud Forming Ability of Nascent Sea Spray Aerosol. *J. Geophys. Res. Atmos.* **2013**, *118* (15), 8553−8565.
(164) Fuentes, E.; Coe, H.; Green, D.; De Leeuw, G.; McFiggans, G. Laboratory-Generated Primary Marine Aerosol via Bubble-Bursting and Atomization. *Atmos. Meas. Tech.* **2010**, *3* (1), 141−162.
(165) Schiffer, J. M.; Mael, L. E.; Prather, K. A.; Amaro, R. E.; Grassian, V. H. Sea Spray Aerosol: Where Marine Biology Meets Atmospheric Chemistry. *ACS Cent. Sci.* **2018**, *4* (12), 1617−1623.
(166) Wang, X.; Sultana, C. M.; Trueblood, J.; Hill, T. C. J.; Malfatti, F.; Lee, C.; Laskina, O.; Moore, K. A.; Beall, C. M.; McCluskey, C. S.;

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Cornwell, G. C.; Zhou, Y.; Cox, J. L.; Pendergraft, M. A.; Santander, M. V.; Bertram, T. H.; Cappa, C. D.; Azam, F.; DeMott, P. J.; Grassian, V. H.; Prather, K. A. Microbial Control of Sea Spray Aerosol Composition: A Tale of Two Blooms. *ACS Cent. Sci.* **2015**, *1* (3), 124−131.

(167) Jayarathne, T.; Sultana, C. M.; Lee, C.; Malfatti, F.; Cox, J. L.; Pendergraft, M. A.; Moore, K. A.; Azam, F.; Tivanski, A. V.; Cappa, C. D.; Bertram, T. H.; Grassian, V. H.; Prather, K. A.; Stone, E. A. Enrichment of Saccharides and Divalent Cations in Sea Spray Aerosol during Two Phytoplankton Blooms. *Environ. Sci. Technol.* **2016**, *50* (21), 11511−11520.

(168) Marks, R.; Górecka, E.; McCartney, K.; Borkowski, W. Rising Bubbles as Mechanism for Scavenging and Aerosolization of Diatoms. *J. Aerosol Sci.* **2019**, *128*, 79−88.

(169) Cheng, Y. S.; McDonald, J. D.; Kracko, D.; Irvin, C. M.; Zhou, Y.; Pierce, R. H.; Henry, M. S.; Bourdelaisa, A.; Naar, J.; Baden, D. G. Concentration and Particle Size of Airborne Toxic Algae (Brevetoxin) Derived from Ocean Red Tide Events. *Environ. Sci. Technol.* **2005**, *39* (10), 3443−3449.

(170) Bigg, E. K.; Leck, C. The Composition of Fragments of Bubbles Bursting at the Ocean Surface. *J. Geophys. Res.* **2008**, *113* (D11), D11209.

(171) Wilson, T. W.; Ladino, L. A.; Alpert, P. A.; Breckels, M. N.; Brooks, I. M.; Browse, J.; Burrows, S. M.; Carslaw, K. S.; Huffman, J. A.; Judd, C.; Kilthau, W. P.; Mason, R. H.; McFiggans, G.; Miller, L. A.; Najera, J. J.; Polishchuk, E.; Rae, S.; Schiller, C. L.; Si, M.; Temprado, J. V.; Whale, T. F.; Wong, J. P. S.; Wurl, O.; Yakobi-Hancock, J. D.; Abbatt, J. P. D.; Aller, J. Y.; Bertram, A. K.; Knopf, D. A.; Murray, B. J. A Marine Biogenic Source of Atmospheric Ice-Nucleating Particles. *Nature* **2015**, *525* (7568), 234−238.

(172) Laussac, S.; Piazzola, J.; Tedeschi, G.; Yohia, C.; Canepa, E.; Rizza, U.; Van Eijk, A. M. J. Development of a Fetch Dependent Sea-Spray Source Function Using Aerosol Concentration Measurements in the North-Western Mediterranean. *Atmos. Environ.* **2018**, *193*, 177−189.

(173) Backer, L. C.; Kirkpatrick, B.; Fleming, L. E.; Cheng, Y. S.; Pierce, R.; Bean, J. A.; Clark, R.; Johnson, D.; Wanner, A.; Tamer, R.; Zhou, Y.; Baden, D. G. Occupational Exposure to Aerosolized Brevetoxins during Florida Red Tide Events: Effects on a Healthy Worker Population. *Environ. Health Perspect.* **2005**, *113* (5), 644−649.

(174) Sharma, N. K.; Rai, A. K.; Singh, S. Meteorological Factors Affecting the Diversity of Airborne Algae in an Urban Atmosphere. *Ecography (Cop.).* **2006**, *29* (5), 766−772.

(175) Chung, S. H.; Basarab, B. M.; Vanreken, T. M. Regional Impacts of Ultrafine Particle Emissions from the Surface of the Great Lakes. *Atmos. Chem. Phys.* **2011**, *11* (24), 12601−12615.

(176) Hsiao, T. C.; Lin, A. Y. C.; Lien, W. C.; Lin, Y. C. Size Distribution, Biological Characteristics and Emerging Contaminants of Aerosols Emitted from an Urban Wastewater Treatment Plant. *J. Hazard. Mater.* **2020**, *388*, 121809.

(177) Yan, H.; Zhang, L.; Guo, Z.; Zhang, H.; Liu, J. Production Phase Affects the Bioaerosol Microbial Composition and Functional Potential in Swine Confinement Buildings. *Animals* 2019, *9* (3). DOI: 10.3390/ani9030090.

(178) Barnes, R. O.; Goldberg, E. D. Methane Production and Consumption in Anoxic Marine Sediments. *Geology* **1976**, *4* (5), 297.

(179) Donelan, M. A.; Wanninkhof, R. Gas Transfer at Water Surfaces-Concepts and Issues. *In Geophysical Monograph Series* **2013**, *127*, 1−10.

(180) Crowther, T. W.; Glick, H. B.; Covey, K. R.; Bettigole, C.; Maynard, D. S.; Thomas, S. M.; Smith, J. R.; Hintler, G.; Duguid, M. C.; Amatulli, G.; Tuanmu, M.-N.; Jetz, W.; Salas, C.; Stam, C.; Piotto, D.; Tavani, R.; Green, S.; Bruce, G.; Williams, S. J.; Wiser, S. K.; Huber, M. O.; Hengeveld, G. M.; Nabuurs, G.-J.; Tikhonova, E.; Borchardt, P.; Li, C.-F.; Powrie, L. W.; Fischer, M.; Hemp, A.; Homeier, J.; Cho, P.; Vibrans, A. C.; Umunay, P. M.; Piao, S. L.; Rowe, C. W.; Ashton, M. S.; Crane, P. R.; Bradford, M. A. Mapping Tree Density at a Global Scale. *Nature* **2015**, *525* (7568), 201−205.

(181) Dutta, H.; Dutta, A. The Microbial Aspect of Climate Change. *Energy, Ecol. Environ.* **2016**, *1* (4), 209−232.

(182) Codd, G.; Bell, S.; Kaya, K.; Ward, C.; Beattie, K.; Metcalf, J. Cyanobacterial Toxins, Exposure Routes and Human Health. *Eur. J. Phycol.* **1999**, *34* (4), 405−415.

(183) Massey, I. Y.; Yang, F.; Ding, Z.; Yang, S.; Guo, J.; Tezi, C.; Al-Osman, M.; Kamegni, R. B.; Zeng, W. Exposure Routes and Health Effects of Microcystins on Animals and Humans: A Mini-Review. *Toxicon* **2018**, *151*, 156−162.

(184) Jasser, I.; Callieri, C. Picocyanobacteria. In *Handbook of Cyanobacterial Monitoring and Cyanotoxin Analysis*; John Wiley & Sons, Ltd: Chichester, UK, 2017; pp 19−27. DOI: 10.1002/9781119068761.ch3.

(185) Murby, A. L.; Haney, J. F. Field and Laboratory Methods to Monitor Lake Aerosols for Cyanobacteria and Microcystins. *Aerobiologia (Bologna).* **2016**, *32* (3), 395−403.

(186) Sahu, N.; Tangutur, A. D. Airborne Algae: Overview of the Current Status and Its Implications on the Environment. *Aerobiologia*. Kluwer Academic Publishers 2015; pp 89−97. DOI: 10.1007/s10453-014-9349-z.

(187) Trout-Haney, J. V.; Heindel, R. C.; Virginia, R. A. Picocyanobacterial Cells in Near-Surface Air above Terrestrial and Freshwater Substrates in Greenland and Antarctica. *Environ. Microbiol. Rep.* **2020**, *12*, 1758−2229 12832.

(188) Lewandowska, A. U.; Śliwińska-Wilczewska, S.; Woźniczka, D. Identification of Cyanobacteria and Microalgae in Aerosols of Various Sizes in the Air over the Southern Baltic Sea. *Mar. Pollut. Bull.* **2017**, *125* (1−2), 30−38.

(189) Paerl, H. W. Mitigating Toxic Planktonic Cyanobacterial Blooms in Aquatic Ecosystems Facing Increasing Anthropogenic and Climatic Pressures. *Toxins*. MDPI AG February 8, 2018. DOI: 10.3390/toxins10020076.

(190) Gambaro, A.; Barbaro, E.; Zangrando, R.; Barbante, C. Simultaneous Quantification of Microcystins and Nodularin in Aerosol Samples Using High-Performance Liquid Chromatography/Negative Electrospray Ionization Tandem Mass Spectrometry. *Rapid Commun. Mass Spectrom.* **2012**, *26* (12), 1497−1506.

(191) Banack, S. A.; Caller, T.; Henegan, P.; Haney, J.; Murby, A.; Metcalf, J. S.; Powell, J.; Alan, P.; Stommel, E. Detection of Cyanotoxins, β-N-Methylamino-L-Alanine and Microcystins, from a Lake Surrounded by Cases of Amyotrophic Lateral Sclerosis. *Toxins* **2015**, *7* (2), 322−336.

(192) Adams, R. I.; Miletto, M.; Taylor, J. W.; Bruns, T. D. Dispersal in Microbes: Fungi in Indoor Air Are Dominated by Outdoor Air and Show Dispersal Limitation at Short Distances. *ISME J.* **2013**, *7* (7), 1262−1273.

(193) Bowers, R. M.; McLetchie, S.; Knight, R.; Fierer, N. Spatial Variability in Airborne Bacterial Communities across Land-Use Types and Their Relationship to the Bacterial Communities of Potential Source Environments. *ISME J.* **2011**, *5* (4), 601−612.

(194) Šantl-Temkiv, T.; Sikoparija, B.; Maki, T.; Carotenuto, F.; Amato, P.; Yao, M.; Morris, C. E.; Schnell, R.; Jaenicke, R.; Pöhlker, C.; DeMott, P. J.; Hill, T. C. J.; Huffman, J. A. Bioaerosol Field Measurements: Challenges and Perspectives in Outdoor Studies. *Aerosol Sci. Technol.* **2020**, *54*, 520−546.

(195) Gard, E.; Mayer, J. E.; Morrical, B. D.; Dienes, T.; Fergenson, D. P.; Prather, K. A. Real-Time Analysis of Individual Atmospheric Aerosol Particles: Design and Performance of a Portable ATOFMS. *Anal. Chem.* **1997**, *69* (20), 4083−4091.

(196) Pratt, K. A.; Prather, K. A. Mass Spectrometry of Atmospheric Aerosols-Recent Developments and Applications. Part II: On-Line Mass Spectrometry Techniques. *Mass Spectrom. Rev.* **2012**, *31*, 17−48 January.

(197) DeCarlo, P. F.; Kimmel, J. R.; Trimborn, A.; Northway, M. J.; Jayne, J. T.; Aiken, A. C.; Gonin, M.; Fuhrer, K.; Horvath, T.; Docherty, K. S.; Worsnop, D. R.; Jimenez, J. L. Field-Deployable, High-Resolution, Time-of-Flight Aerosol Mass Spectrometer. *Anal. Chem.* **2006**, *78* (24), 8281−8289.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

(198) Sousan, S.; Koehler, K.; Thomas, G.; Park, J. H.; Hillman, M.; Halterman, A.; Peters, T. M. Inter-Comparison of Low-Cost Sensors for Measuring the Mass Concentration of Occupational Aerosols. *Aerosol Sci. Technol.* **2016**, *50* (5), 462−473.
(199) Wang, Z.; Wang, D.; Peng, Z. R.; Cai, M.; Fu, Q.; Wang, D. Performance Assessment of a Portable Nephelometer for Outdoor Particle Mass Measurement. *Environ. Sci. Process. Impacts* **2018**, *20* (2), 370−383.
(200) Zábori, J.; Matisans, M.; Krejci, R.; Nilsson, E. D.; Ström, J. Artificial Primary Marine Aerosol Production: A Laboratory Study with Varying Water Temperature, Salinity, and Succinic Acid Concentration. *Atmos. Chem. Phys.* **2012**, *12* (22), 10709.
(201) Uetake, J.; Tobo, Y.; Uji, Y.; Hill, T. C. J.; DeMott, P. J.; Kreidenweis, S. M.; Misumi, R. Seasonal Changes of Airborne Bacterial Communities Over Tokyo and Influence of Local Meteorology. *Front. Microbiol.* **2019**, *10* (JULY), 1572.
(202) Du, P.; Du, R.; Ren, W.; Lu, Z.; Fu, P. Seasonal Variation Characteristic of Inhalable Microbial Communities in PM2.5 in Beijing City, China. *Sci. Total Environ.* **2018**, *610−611*, 308−315.
(203) Hozumi, A.; Ostrovsky, I.; Sukenik, A.; Gildor, H. Turbulence Regulation of Microcystis Surface Scum Formation and Dispersion during a Cyanobacteria Bloom Event. *Inland Waters* **2020**, *10* (1), 51−70.
(204) Reynolds, C. S.; Walsby, A. E. Water-Blooms. *Biol. Rev.* **1975**, *50* (4), 437−481.
(205) Reynolds, C. S. The Ecology of Phytoplankton; 2006. DOI: 10.1017/CBO9780511542145.
(206) Watson, S.; Whitton, B.; Higgins, S. H. P.; Brooks, B.; Wehr, J. Harmful Algal Blooms; 2015.
(207) Lednicky, J.; Pan, M.; Loeb, J.; Hsieh, H.; Eiguren-Fernandez, A.; Hering, S.; Fan, Z. H.; Wu, C. Y. Highly Efficient Collection of Infectious Pandemic Influenza H1N1 Virus (2009) through Laminar-Flow Water Based Condensation. *Aerosol Sci. Technol.*. Taylor and Francis Inc. July 2, 2016; pp i−iv. DOI: 10.1080/02786826.2016.1179254.
(208) Pan, M.; Bonny, T. S.; Loeb, J.; Jiang, X.; Lednicky, J. A.; Eiguren-Fernandez, A.; Hering, S.; Fan, Z. H.; Wu, C.-Y. Collection of Viable Aerosolized Influenza Virus and Other Respiratory Viruses in a Student Health Care Center through Water-Based Condensation Growth. *mSphere* 2017, *2* (5). DOI: 10.1128/msphere.00251-17.
(209) Nieto-Caballero, M.; Savage, N.; Keady, P.; Hernandez, M. High Fidelity Recovery of Airborne Microbial Genetic Materials by Direct Condensation Capture into Genomic Preservatives. *J. Microbiol. Methods* **2019**, *157*, 1−3.
(210) Fröhlich-Nowoisky, J.; Pickersgill, D. A.; Després, V. R.; Pöschl, U. High Diversity of Fungi in Air Particulate Matter. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (31), 12814−12819.
(211) SvirČev, Z.; Drobac, D.; Tokodi, N.; Mijović, B.; Codd, G. A.; Meriluoto, J. Toxicology of Microcystins with Reference to Cases of Human Intoxications and Epidemiological Investigations of Exposures to Cyanobacteria and Cyanotoxins. *Arch. Toxicol.*. Springer Verlag February 1, 2017; pp 621−650. DOI: 10.1007/s00204-016-1921-6.
(212) Azevedo, S. M. F. O.; Carmichael, W. W.; Jochimsen, E. M.; Rinehart, K. L.; Lau, S.; Shaw, G. R.; Eaglesham, G. K. Human Intoxication by Microcystins during Renal Dialysis Treatment in Caruaru—Brazil. *Toxicology* **2002**, *181−182*, 441−446.
(213) Soares, R. M.; Yuan, M.; Servaites, J. C.; Delgado, A.; Magalhães, V. F.; Hilborn, E. D.; Carmichael, W. W.; Azevedo, S. M. F. O. Sublethal Exposure from Microcystins to Renal Insufficiency Patients in Rio de Janeiro, Brazil. *Environ. Toxicol.* **2006**, *21* (2), 95−103.
(214) Saadi, O.; El Esterman, A. J.; Cameron, S.; Roder, D. M. Murray River Water, Raised Cyanobacterial Cell Counts, and Gastrointestinal and Dermatological Symptoms. *Med. J. Aust.* **1995**, *162* (3), 122−125.
(215) Chorus, I.; Falconer, I. R.; Salas, H. J.; Bartram, J. Health Risks Caused by Freshwater Cyanobacteria in Recreational Waters. *J. Toxicol. Environ. Health, Part B* **2000**, *3*, 323−347.
(216) Stewart, I.; Webb, P. M.; Schluter, P. J.; Shaw, G. R. Recreational and Occupational Field Exposure to Freshwater Cyanobacteria - A Review of Anecdotal and Case Reports, Epidemiological Studies and the Challenges for Epidemiologic Assessment. *Environ. Health* **2006**, *5*, 6 March 24.
(217) Pilotto, L. S.; Douglas, R. M.; Burch, M. D.; Cameron, S.; Beers, M.; Rouch, G. J.; Robinson, P.; Kirk, M.; Cowie, C. T.; Hardiman, S.; Moore, C.; Attewell, R. G. Health Effects of Exposure to Cyanobacteria (Blue-Green Algae) during Recreational Water-Related Activities. *Aust. N. Z. J. Public Health* **1997**, *21* (6), 562−566.
(218) Stewart, I.; Webb, P. M.; Schluter, P. J.; Fleming, L. E.; Burns, J. W.; Gantar, M.; Backer, L. C.; Shaw, G. R. Epidemiology of Recreational Exposure to Freshwater Cyanobacteria - An International Prospective Cohort Study. *BMC Public Health* **2006**, *6* (1), 93.
(219) Backer, L. C.; Manassaram-Baptiste, D.; LePrell, R.; Bolton, B. Cyanobacteria and Algae Blooms: Review of Health and Environmental Data from the Harmful Algal Bloom-Related Illness Surveillance System (HABISS) 2007−2011. *Toxins* **2015**, *7* (4), 1048−1064.
(220) Hilborn, E. D.; Beasley, V. R. One Health and Cyanobacteria in Freshwater Systems: Animal Illnesses and Deaths Are Sentinel Events for Human Health Risks. *Toxins*. MDPI AG April 20, 2015; pp 1374−1395. DOI: 10.3390/toxins7041374.
(221) Backer, L. C. Cyanobacterial Harmful Algal Blooms (CyanoHABs): Developing a Public Health Response. *Lake Reservoir Manage.* **2002**, *18* (1), 20−31.
(222) Creasia, D. A. Acute Inhalation Toxicity of Microcystin-LR with Mice. *Toxicon 28*, 605. Toxicon 1990, 28 (605).
(223) Soares, R. M.; Cagido, V. R.; Ferraro, R. B.; Meyer-Fernandes, J. R.; Rocco, P. R. M.; Zin, W. A.; Azevedo, S. M. F. O. Effects of Microcystin-LR on Mouse Lungs. *Toxicon* **2007**, *50* (3), 330−338.
(224) Carvalho, G. M. C.; Oliveira, V. R.; Soares, R. M.; Azevedo, S. M. F. O.; Lima, L. M.; Barreiro, E. J.; ValenĆa, S. S.; Saldiva, P. H. N.; Faffe, D. S.; Zin, W. A. Can LASSBio 596 and Dexamethasone Treat Acute Lung and Liver Inflammation Induced by Microcystin-LR? *Toxicon* **2010**, *56* (4), 604−612.
(225) Li, X.; Xu, L.; Zhou, W.; Zhao, Q.; Wang, Y. Chronic Exposure to Microcystin-LR Affected Mitochondrial DNA Maintenance and Caused Pathological Changes of Lung Tissue in Mice. *Environ. Pollut.* **2016**, *210*, 48−56.
(226) Benson, J. M.; Hutt, J. A.; Rein, K.; Boggs, S. E.; Barr, E. B.; Fleming, L. E. The Toxicity of Microcystin LR in Mice Following 7 Days of Inhalation Exposure. *Toxicon* **2005**, *45* (6), 691−698.
(227) Geiser, M.; Kreyling, W. G. Deposition and Biokinetics of Inhaled Nanoparticles. *Particle and Fibre Toxicology*. January 20, 2010. DOI: 10.1186/1743-8977-7-2.
(228) Brózman, O.; Kubickova, B.; Babica, P.; Laboha, P. Microcystin-LR Does Not Alter Cell Survival and Intracellular Signaling in Human Bronchial Epithelial Cells. *Toxins (Basel)*. 2020, *12* (3). DOI: 10.3390/toxins12030165.
(229) Oliveira, V. R.; Mancin, V. G. L.; Pinto, E. F.; Soares, R. M.; Azevedo, S. M. F. O.; Macchione, M.; Carvalho, A. R.; Zin, W. A. Repeated Intranasal Exposure to Microcystin-LR Affects Lungs but Not Nasal Epithelium in Mice. *Toxicon* **2015**, *104*, 14−18.
(230) Wang, C.; Gu, S.; Yin, X.; Yuan, M.; Xiang, Z.; Li, Z.; Cao, H.; Meng, X.; Hu, K.; Han, X. The Toxic Effects of Microcystin-LR on Mouse Lungs and Alveolar Type II Epithelial Cells. *Toxicon* **2016**, *115*, 81−88.
(231) Hu, H.; Wei, Y. The Freshwater Algae of China. *Systematics, Taxonomy and Ecology.* **2006**, 1−1023.
(232) Paerl, H. W.; Otten, T. G.; Kudela, R. Mitigating the Expansion of Harmful Algal Blooms Across the Freshwater-to-Marine Continuum. *Environ. Sci. Technol.* **2018**, *52* (10), 5519−5529.
(233) Saker, M. L.; Griffiths, D. J. The Effect of Temperature on Growth and Cylindrospermopsin Content of Seven Isolates of Cylindrospermopsis Raciborskii (Nostocales, Cyanophyceae) from Water Bodies in Northern Australia. *Phycologia* **2000**, *39* (4), 349−354.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

(234) Borges, H. L. F.; Branco, L. H. Z.; Martins, M. D.; Lima, C. S.; Barbosa, P. T.; Lira, G. A. S. T.; Bittencourt-Oliveira, M. C.; Molica, R. J. R. Cyanotoxin Production and Phylogeny of Benthic Cyanobacterial Strains Isolated from the Northeast of Brazil. *Harmful Algae* **2015**, *43*, 46−57.
(235) Henriksen, P.; Carmichael, W. W.; An, J.; Moestrup, Ø. Detection of an Anatoxin-a(s)-like Anticholinesterase in Natural Blooms and Cultures of Cyanobacteria/Blue-Green Algae from Danish Lakes and in the Stomach Contents of Poisoned Birds. *Toxicon* **1997**, *35* (6), 901−913.
(236) Sivonen, K.; Niemelä, S. I.; Niemi, R. M.; Lepistö, L.; Luoma, T. H.; Räsänen, L. A. Toxic Cyanobacteria (Blue-Green Algae) in Finnish Fresh and Coastal Waters. *Hydrobiologia* **1990**, *190* (3), 267−275.
(237) Carmichael, W.; Evans, W. R.; Yin, Q. Q.; Bell, P.; Moczydlowski, E. Evidence for Paralytic Shellfish Poisons in the Freshwater Cyanobacterium Lyngbya Wollei (Farlow Ex Gomont) Comb. Nov. *Appl. Environ. Microbiol.* **1997**, *63* (8), 3104LP−3110.
(238) Seifert, M.; McGregor, G.; Eaglesham, G.; Wickramasinghe, W.; Shaw, G. First Evidence for the Production of Cylindrospermopsin and Deoxy-Cylindrospermopsin by the Freshwater Benthic Cyanobacterium, Lyngbya Wollei (Farlow Ex Gomont) Speziale and Dyck. *Harmful Algae* **2007**, *6* (1), 73−80.
(239) Ploug, H. Cyanobacterial Surface Blooms Formed by Aphanizomenon Sp. and Nodularia Spumigena in the Baltic Sea: Small-Scale Fluxes, PH, and Oxygen Microenvironments. *Limnol. Oceanogr.* **2008**, *53* (3), 914−921.
(240) Stal, L. J.; Albertano, P.; Bergman, B.; Bröckel, K.; von Gallon, J. R.; Hayes, P. K.; Sivonen, K.; Walsby, A. E. BASIC: Baltic Sea Cyanobacteria. An Investigation of the Structure and Dynamics of Water Blooms of Cyanobacteria in the Baltic Sea—Responses to a Changing Environment. *Cont. Shelf Res.* **2003**, *23* (17), 1695−1714.
(241) Fetscher, A. E.; Howard, M. D. A.; Stancheva, R.; Kudela, R. M.; Stein, E. D.; Sutula, M. A.; Busse, L. B.; Sheath, R. G. Wadeable Streams as Widespread Sources of Benthic Cyanotoxins in California, USA. *Harmful Algae* **2015**, *49*, 105−116.
(242) Gehringer, M. M.; Adler, L.; Roberts, A. A.; Moffitt, M. C.; Mihali, T. K.; Mills, T. J. T.; Fieker, C.; Neilan, B. A. Nodularin, a Cyanobacterial Toxin, Is Synthesized in Planta by Symbiotic Nostoc Sp. *ISME J.* **2012**, *6* (10), 1834−1847.
(243) Ruiz, M.; Galanti, L.; Ruibal, A. L.; Rodriguez, M. I.; Wunderlin, D. A.; Amé, M. V. First Report of Microcystins and Anatoxin-a Co-Occurrence in San Roque Reservoir (Córdoba, Argentina). *Water, Air, Soil Pollut.* **2013**, *224* (6), 1−17.
(244) Shams, S.; Capelli, C.; Cerasino, L.; Ballot, A.; Dietrich, D. R.; Sivonen, K.; Salmaso, N. Anatoxin-a Producing Tychonema (Cyanobacteria) in European Waterbodies. *Water Res.* **2015**, *69*, 68−79.
(245) Wood, S. A.; Selwood, A. I.; Rueckert, A.; Holland, P. T.; Milne, J. R.; Smith, K. F.; Smits, B.; Watts, L. F.; Cary, C. S. First Report of Homoanatoxin-a and Associated Dog Neurotoxicosis in New Zealand. *Toxicon* **2007**, *50* (2), 292−301.
(246) Wood, S. A.; Heath, M. W.; Holland, P. T.; Munday, R.; McGregor, G. B.; Ryan, K. G. Identification of a Benthic Microcystin-Producing Filamentous Cyanobacterium (Oscillatoriales) Associated with a Dog Poisoning in New Zealand. *Toxicon* **2010**, *55* (4), 897−903.
(247) Li, R.; Carmichael, W. W.; Brittain, S.; Eaglesham, G. K.; Shaw, G. R.; Liu, Y.; Watanabe, M. M. First Report of the Cyanotoxins Cylindrospermopsin and Deoxycylindrospermopsin from Raphidiopsis Curvata (Cyanobacteria). *J. Phycol.* **2001**, *37* (6), 1121−1126.
(248) Harada, K.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terao, K. Isolation of Cylindrospermopsin from a Cyanobacterium Umezakia Natans and Its Screening Method. *Toxicon* **1994**, *32* (1), 73−84.

https://dx.doi.org/10.1021/acs.est.0c06653
Environ. Sci. Technol. XXXX, XXX, XXX−XXX