Toxic Cyanobacteria: a Growing Threat to Water and Air Quality

Haley E. Plaas[1,2] and Hans W. Paerl[1,2*]

[1]University of North Carolina at Chapel Hill, Gillings School of Global Public Health, Chapel Hill, NC

[2] University of North Carolina at Chapel Hill, Institute of Marine Sciences, Morehead City, NC

Corresponding Author: Hans W. Paerl, (hans_paerl@unc.edu, (252) 726 6841, Ext. 133,

ORCID: 0000-0003-2211-1011)

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.

Keywords: cyanotoxin, microcystin, spray aerosol, lake spray aerosol, CyanoHABs

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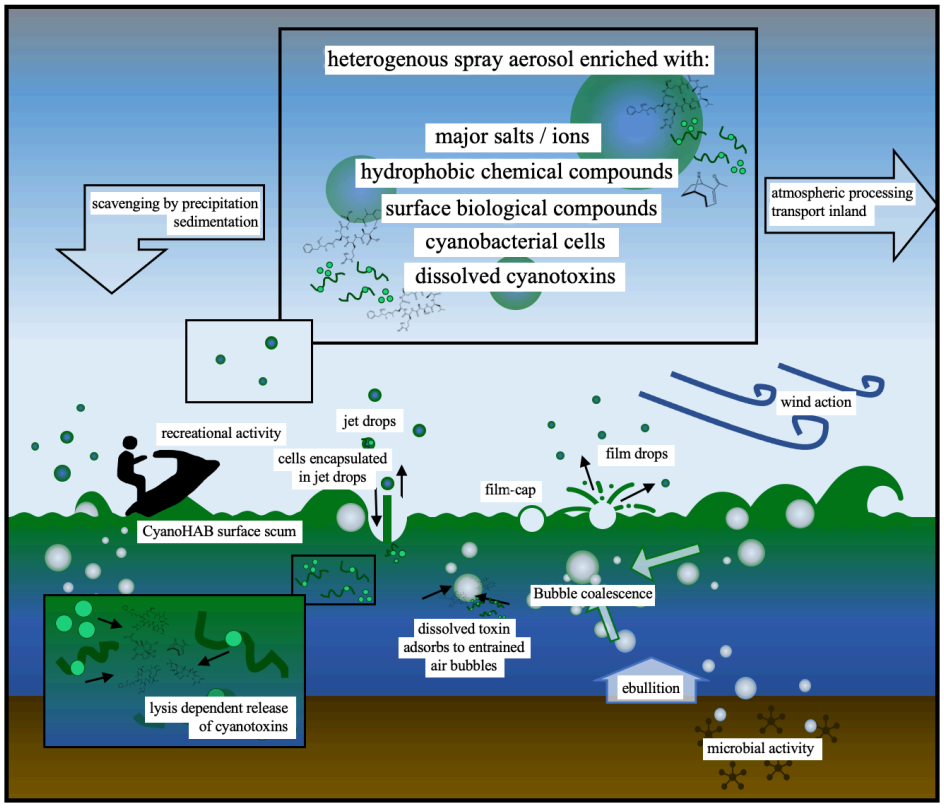

1. Introduction

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 over-enrichment[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 manuscripts 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 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. Less work has evaluated 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. Due to its ubiquitous production, 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 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]

The MC molecule contains D- and L-amino acids, N-methyldehydroalanine (Mdha), and the defining non-proteinogenic 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*-ß-methylaspartic acid (D-MeAsp).[83] The NOD structure varies slightly from MC and consists of an Adda, N-methyldehydrobutyrine (Mdhb), D-*erythro*-ß-methylaspartic 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]

Cylindrospermopsin 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 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 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, ATX-a(s) behaves more similarly to 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, considering 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 rapid photolytic 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 re-suspended 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 whereas the hydrophobic Adda moiety did not interact, but Morris et al. (2000)[120] determined that clay particles

scavenged MC by binding with this moiety. 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 immediately 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

196 produce SSA that can be transported up to 1000 km[144–147] inland at concentrations of 10^3 particles
197 m^{-3}.[148]

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

206 The expected size distributions of film and jet drops ranges from d_a = 0.2-10 µm and d_a =
207 1-200 µm, respectively.[150] However, recent instrumentation improvements reflect a more accurate
208 size distribution may encompass size fractions from nanometers to droplets as large as d_a = 250
209 µm.[153,154] Multiple findings suggest that SSA size distribution is primarily a function of parent
210 bubble size,[134,150,153,157–159] as subsequent film-cap surface area is directly proportional to SSA size
211 distribution.[151] In a review of SSA formation mechanisms, Lewis & Schwartz (2004)[150] concluded
212 that bubbles with radii > 1 mm produce more SSA in the film drop size distribution, while bubbles
213 with radii < 1 mm produce more SSA within the jet drop size distribution. It is speculated that film
214 drops typically contribute to SSA in the fine range while jet drops contribute to SSA in the coarse
215 range.[154] However, given the overlapping size distributions of film and jet drops,[150,152] it is likely
216 that bubbles in natural environments produce a mixture of both film and jet drops. Moreover, mass
217 concentration, or the mass of aerosol per unit volume of air, and size distribution of drops ejected
218 into the atmosphere may grow and shrink dynamically via heterogenous 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, building a better understanding of primary aerosol formation at the air-water interface and how this directly contributes to particle behavior in the atmosphere provides 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

242 relative enrichment in SSA. Hydrophobic metabolites are more readily incorporated into SSA than
243 water soluble organics.[166] This process is well illustrated through the HAB species *K. brevis,* or
244 the Gulf of Mexico red tide. Brevetoxin, a potent neurotoxin produced by *K. brevis*, is frequently
245 detected in SSA during red tides due to its hydrophobic properties.[62,169] At the wave break, fragile
246 *K. brevis* cells lyse, releasing brevetoxin into the water column, where it interacts with air bubbles
247 and is incorporated into SSA.

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

260 **3.2.3 Spatiotemporal controls on SSA**

261 Several meteorological conditions have been investigated to elucidate the impacts of
262 weather on SSA mass concentration, mixing state, and transport. The meteorological variables that
263 control wave action, bubble bursting, and subsequent SSA formation include: wind speed, wind
264 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]

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 $d_a = 180 \pm 20$ nm and a secondary mode at $d_a = 46 \pm 6$ 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

311 composition of LSA varies significantly from SSA, also due to aqueous chemistry, as LSA
312 chemical signatures reflect the major ions of freshwater.[55,56] These unique physiochemical
313 processes attributed to the production of LSA are especially pertinent to consider for aerosol
314 formation in eutrophic waterbodies during frequent and recurrent CyanoHABs.

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

327 **3.2.5 Spray aerosol – a collective term**

328 Due to a lack of data characterizing aerosol produced in estuaries or from sources other
329 than breaking waves, the catch-all term "Spray Aerosol (SA)" is proposed to reference aerosol
330 produced in freshwater, estuarine, or marine ecosystems via bubble bursting processes. While the
331 production of SSA and LSA presumes significant wave action and distinctive chemical signatures,
332 SA could describe primary aerosol emitted in the airsheds of smaller or hydrologically modified
333 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] Secondly, 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) 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. Assessing 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, on-line 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.

Alternatively, more affordable, high-volume samplers which impact aerosol onto filters, stages, or plates, may be paired with complementary real-time aerosol measurements 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 on-line 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 hours and integrating them over a 12-hour 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 collecting aerosol 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 mediums 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 when compared 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 investigating qualities of airborne cyanobacterial communities 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 120V 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 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 μg kg^{-1} in mice) compared 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

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

581 **3.5.3 *In vitro* findings**

582 An *in vitro* study examining the effect of MC-LR on Alveolar type II (ATII) cells, which
583 are present in the lower respiratory tract, revealed significant injury to these tissues when treated
584 with concentrations of ≥ 50 nM MC-LR. Transepithelial electrical resistance in ATII cells was
585 markedly down-regulated in response to MC-LR treatments, indicating the adverse effect of MC-
586 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 hours, 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 sub-lethal 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 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 reaches 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

633 produced in aquatic systems other than the ocean. Moreover, many coastal watersheds are
634 comprised of estuarian continuums, and thus, we recommend the use of the term, “spray aerosol
635 (SA)”, to widely encompass aerosol produced via diverse bubble bursting processes in seawater,
636 freshwater, brackish, or manmade systems.

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

641 *1) The metabolic state of the CyanoHAB.* Cyanobacterial cells are positioned at the surface
642 of the water column, where they may easily interact with entrained air bubbles. The aerosolization
643 of intact cells or cell fragments may be influenced by ecological and morphological characteristics
644 such as cell size, concentration at the surface, or the presence of cell aggregations. The size and
645 morphology of a CyanoHAB cell should be considered as a factor which may influence its
646 incorporation into aerosol.

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

654 CYN, which is proposed to be actively transported outside the cell, may more likely occur
655 in aerosol. However, given that CYN is extremely hydrophilic, we suspect its affinity for air

656 bubbles is likely too low for its significant incorporation into aerosol. We speculate that the
657 cyanotoxins with hydrophobic properties, e.g. MC-LA, ATX-a(s), and STX, are more likely to
658 occur in aerosol when compared to those which are more hydrophilic in nature, e.g. CYN, ATX-
659 a, and homo-ATX-a.

660 *2) The dynamic physicochemical conditions of the ecosystem.* Numerous meteorological
661 conditions should be monitored during CyanoHAB aerosol sampling campaigns. Elevated wind
662 speeds, large fetches, PAR, and RH may influence cyanotoxin aerosol number concentrations and
663 therefore the concentration airborne of cyanotoxins which reach human populations. Our
664 understanding of SA production in freshwater systems and its implications on air quality is in its
665 infancy. At present, it is unclear how physicochemical, ecological, and meteorological factors
666 interact to influence freshwater SA production and mixing state, however, sufficient evidence
667 suggests that wave breaking or alternative bubble bursting processes produce SA which may carry
668 CyanoHAB compounds.

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

677 *3) SA size distribution and its relevance for human exposure.* Though it is unclear whether
678 cyanotoxins are more frequently aerosolized within film or jet drops, CyanoHAB compounds have

679 been detected in aerosol over land, suggesting they exist in respirable size fractions, and therefore
680 may adversely affect human and animal populations living onshore. We speculate that dissolved
681 toxin is more likely enriched in fine SA via film drop formation, whereas intact cells, which are
682 too large to comprise fine aerosol size fractions, are aerosolized via jetting and found in coarse
683 SA. Most CyanoHAB genera are larger than 2.5 μm in diameter, and as such, it is improbable that
684 intact CyanoHAB cells exist in fine aerosol. The average size of a *Microcystis* cell varies from 1.7
685 to 7 μm in diameter,[205,231] which implies that it would settle quickly in aerosol, greatly reducing
686 its relative risk of reaching human lung cells. However, the location in the respiratory tract where
687 cyanotoxins in aerosol are most likely to impact nor the variable toxicity of intra- versus
688 extracellular cyanotoxins in the respiratory tract have been reported.
689 *4) The toxicological effects of cyanotoxins at environmental concentrations.* To date, no
690 toxicological studies have evaluated exposure to MC in aerosol at environmentally relevant
691 concentrations, despite evidence of respirable cyanotoxins in the SA of recreational watersheds.
692 While there have been many case studies to report respiratory irritation in recreational water users
693 during CyanoHABs, current data suggest that acute intoxication via MC inhalation is unlikely, as
694 the highest concentration of MC ever reported in aerosol is 23 ng m^{-3} *in situ*[36] (Table 2), and 50
695 ng m^{-3} in a lab simulation[42] (Table 3). The no-observed-adverse-effect-level (NOAEL) for nasal
696 lesions in mice only occurs at an estimated deposited dose of 3 mg MC kg^{-1} day^{-1}.[226] Therefore,
697 chronic respiratory exposure to concentrations of MC on the magnitude of ~10 ng m^{-3}, including
698 the actual deposited dose *in vivo* at these concentrations, should be explored to fully understand
699 the long term public health risks associated with cyanotoxin inhalation. Moreover, changes in EMT
700 proteins (i.e. C18, OCLD, or ZO-1) or the activation of PI3K/AKt, MAPK, or ERK signaling
701 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.

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Figures

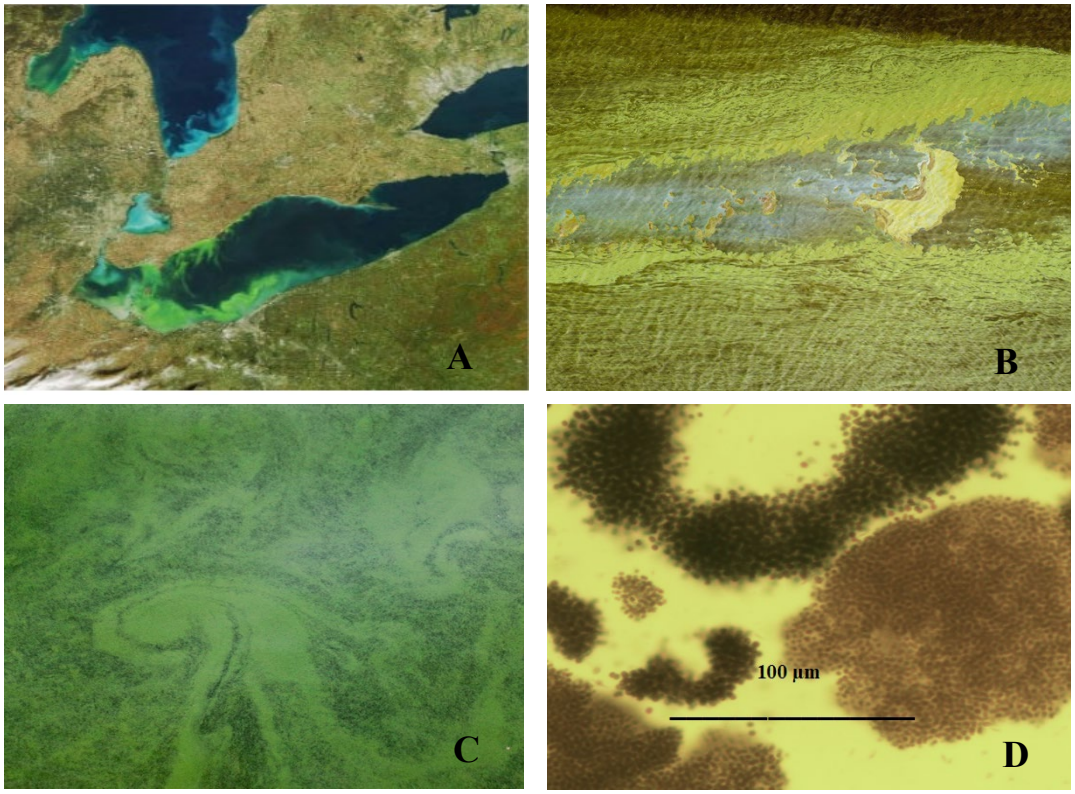

Figure 1. Dense surface cyanobacterial bloom activity; A) a satellite shot of a widespread bloom on western Lake Erie during the Toledo Water Crisis of 2014; B) drone-based photograph of a *Dolichospermum* surface scum on the Chowan River, North Carolina, 2020 (photo: Abe Loven); C) close-up image of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

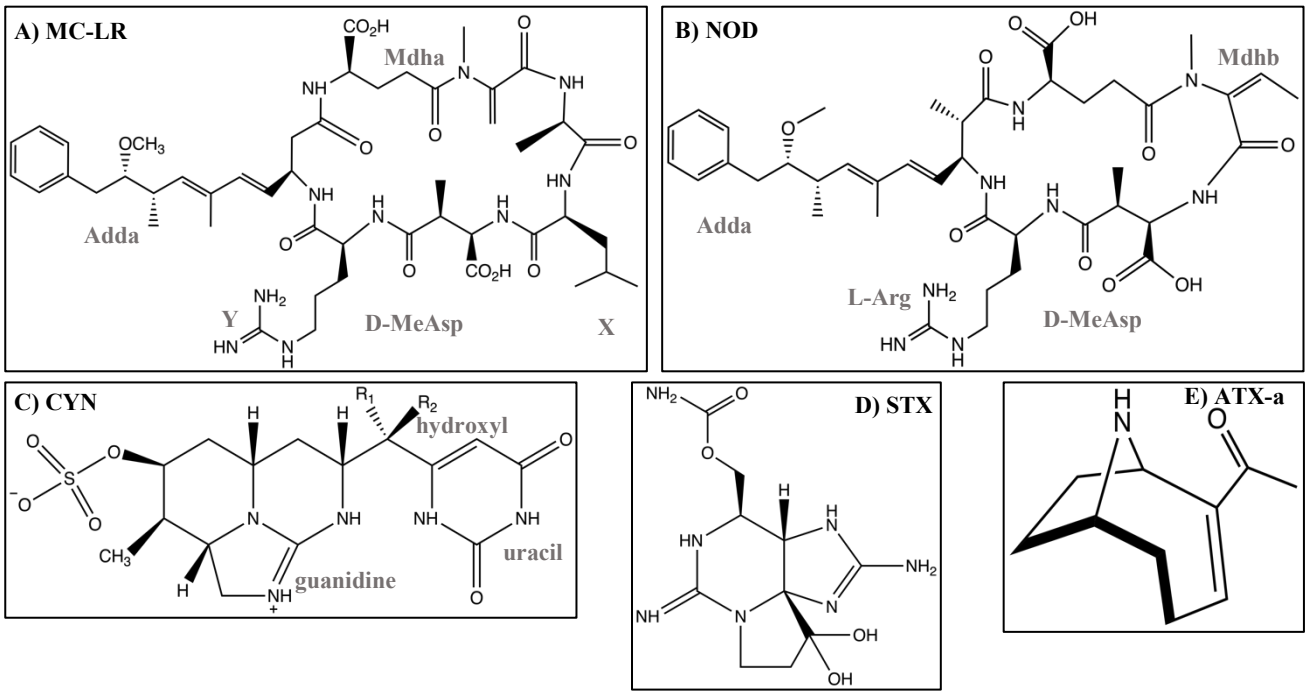

Figure 2. The chemical structures of cyanotoxins with characteristic chemical groups labeled; A) Microcystin-leucine-arginine (MC-LR); B) Nodularin (NOD); C) Cylindrospermopsin (CYN); D) Saxitoxin (STX); E) Anatoxin-a (ATX-a).

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

754

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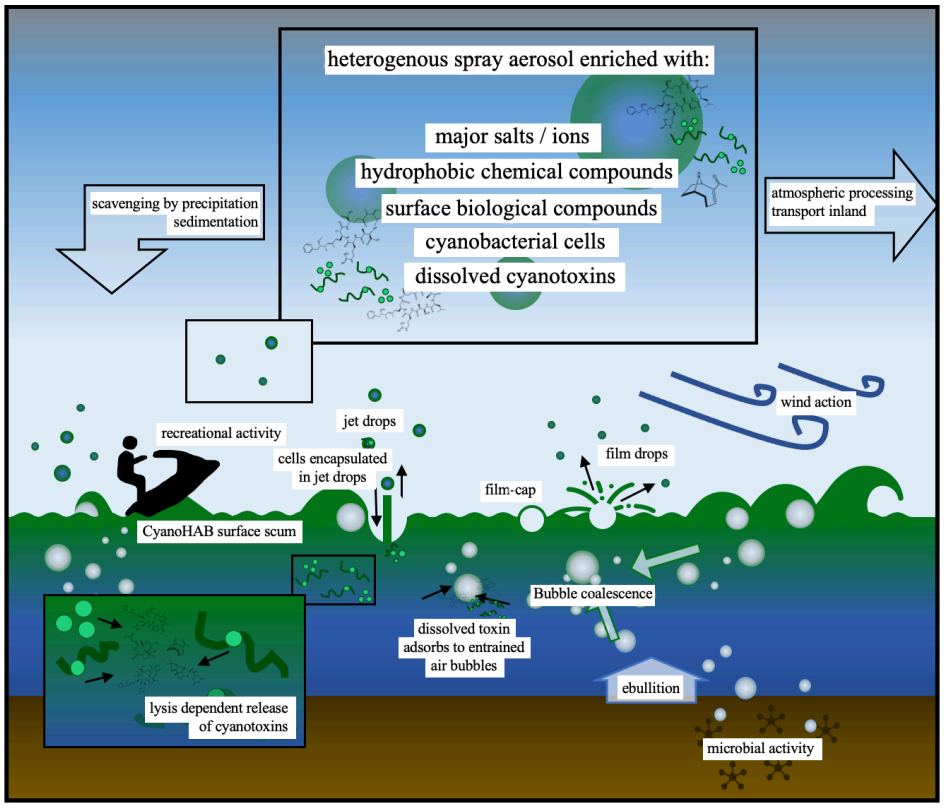

Figure 3. A schematic depicting the proposed mechanisms attributed to cyanotoxin incorporation into spray aerosol.

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] ≤ 0.147µg 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]
pico-cyanobacterial 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 $d_a \leq 3.3$ 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 cells m^{-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

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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	• 23,764-365,011 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 nm 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

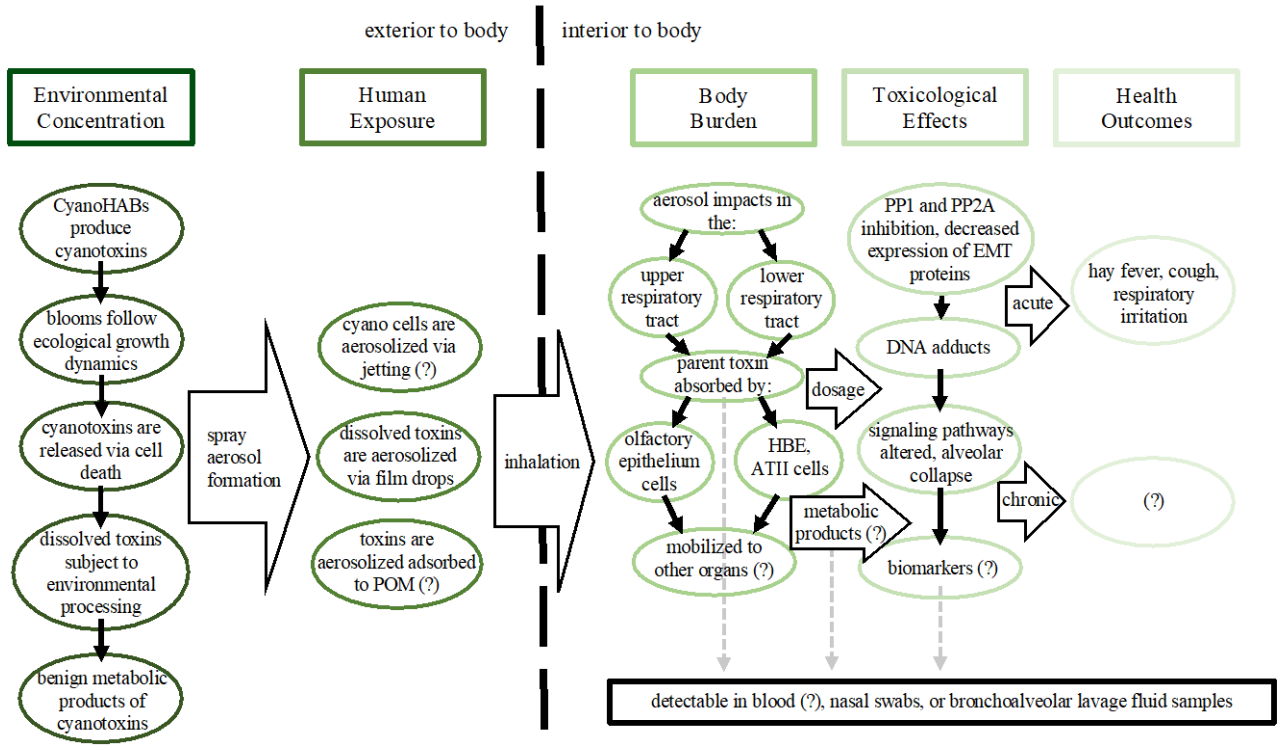

Figure 4. A conceptual diagram depicting the potential pathways which may contribute to adverse health outcomes associated with the inhalation of cyanotoxins. Areas where research is limited, findings are unknown, and more work is necessary are indicated with a question mark.

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