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REVIEW

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Algal Bloom Expansion Increases Cyanotoxin Risk in Food

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As advances in global transportation infrastructure make it possible for out of season foods to be available year-round, the need for assessing the risks associated with the food production and expanded distribution are even more important. Risks for foodborne illness are associated with contamination by bacteria, viruses, mold, parasites, natural and synthetic toxins, chemical residues, and conditions that lead to contamination. An increase in the popularity of natural alternatives to pharmaceuticals, herbal remedies and the desire for consuming "super foods" is leading to a change in the dietary patterns of consumers. Similarly, dietary trends are plentiful, with more consumers adopting changes with little medical guidance to dietary plans that are supported by inadequate scientific data. In particular, U.S. consumers are acquiring novel foods that may not be adequately checked for the presence of marine toxins and heat stable toxins in dry or minimally processed foods. Some dry foods cultivated in or processed in regions that may utilize hypoxic agricultural waters high in cyanobacterial or algal contamination. These may perpetuate increased risks for chronic liver, kidney, and neurodegenerative disorders due to intoxication from preventable foodborne agents. Global climate change, which has the effect of potentially expanding the toxic waters into higher latitudes, forecasts an increase in the risk of food contamination with toxins.

INTRODUCTION

Cyanobacteria are microscopic blue-green algae that inhabit all bodies of water, including ocean water and fresh water sources. They are not always green in color and may be red or brown when visible, or free floating in smaller numbers of cells. They increase in abundance and form blooms that encompass filamentous algae and other organisms that act together to grow and produce toxins of concern to human health. Neurotoxins are widely recognized as serious threats to human health and wellbeing. Marine toxins are formed by algae and cyanobacteria that are present in the water. While not all cyanobacteria produce toxins, some are capable of producing toxins under specific environmental conditions. These naturally occurring toxins include microcystins, saxitoxin, anatoxin, ciguatoxin, β-N-methylamino-L-alanine (BMAA†), lipopolysaccharide (LPS) endotoxins, cylindrospermopsin, and nodularins. They occur seasonally based on changes in the composition and temperature of the water,

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†Abbreviations: BMAA, β-N-methylamino-L-alanine; ALS, Amyotrophic Lateral Sclerosis; LPS, lipopolysaccharide; ELISA, Enzyme-Linked Immunosorbent Assay; LC-MS, Liquid Chromatography-Mass Spectrometry.

Keywords: Cyanotoxins, Foodborne illness, Algal blooms, Neurological disorders, Climate

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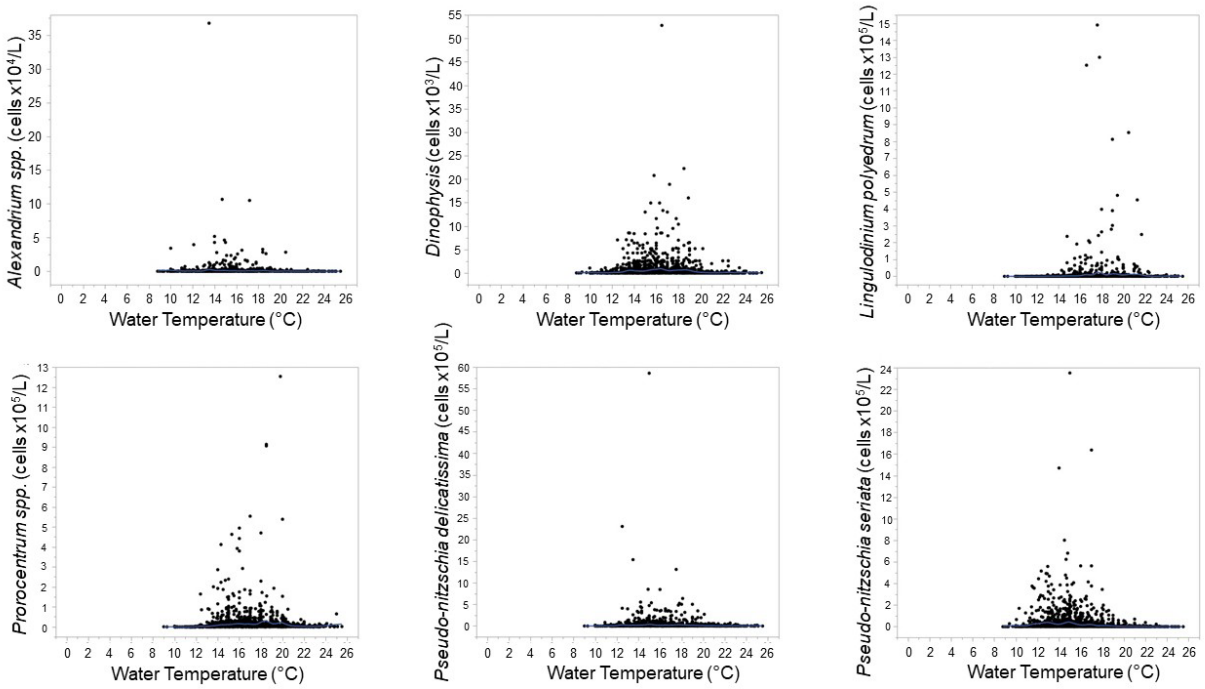

Figure 1. *Alexandrium spp., Dinophysis spp., Lingulodinium polyedrum, Prorocentrum spp., Pseudo-nitzschia delicatissima, Pseudo-nitzschia serriata* species' optimal growth range with respect to temperature. Six scatterplots present the relationship between temperature and the concentration of cells detected in samples of ocean water. Each graph shows a different species or genus, presented in the following order, moving from left to right, then top to bottom: row 1: *Alexandrium spp., Dinophysis spp., Lingulodinium polyedrum*; row 2: *Prorocentrum spp., Pseudo-nitzchia delicatissima, Pseudo-nitzchia serriata*. For each scatterplot, a mean trendline is shown in blue over the datapoints. For each of these graphs, maximum populations are seen in the 12-20°C range of temperatures. Data were collected by the Southern California Coastal Ocean Observing System [5].

flow rates, and the presence of nitrogenous and phosphorous-containing nutrients [1]. Cyanobacteria attach to or accumulate in crustaceans and on the surfaces, fins and gills of fish. They attach to mollusks, shellfish, and kelp, or they form or constitute biofilms, often referred to as surface scum, on the exterior of bivalves like clams, mussels, etc. When seafood, kelp, or freshwater species are contaminated with cyanotoxins, they may retain these toxins within crevices, internal organs, and surfaces. Bioaccumulation and conditions favorable to toxin production move toxins into the food supply at high enough levels to pose a serious threat to human health. Cyanobacterial toxins include non-protein amino acids such as BMAA that have been strongly linked to Parkinsonian symptoms, Amyotrophic Lateral Sclerosis (ALS), and other neurodegenerative disorders.

PREVALENCE

Cyanobacteria are prevalent throughout the earth and credited for being the organisms that created the conditions for future life. While they are bacteria, they are capable of photosynthesis and thus also share the functionality of other phytoplankton. Most species are present in fresh water or briny slow flowing water, producing "blooms" in the presence of higher nutrient levels in warmer climes [1,2]. These blooms create zones where toxins are abundant and may represent one or more types of toxin families. These toxins include hepatotoxins, such as microcystins, nodularins, and cylindrospermopsins, and neurotoxins, such as saxitoxin and antillatoxin. Several prevalence studies from around the world provide insights into the types of species present in bodies of water and the complexities of these communities [1-7]. These organisms are primary producers, often photosynthetic and have served an important role in eutrophication of the planet.

Around the world, a number of species have been identified that produce toxins in ocean waters as well as inland waterways and their benthic waters. Most frequently, the impetus for discovering the presence of these toxins is an investigation into animal toxicosis and not due to preventive monitoring [8]. *Figure 1* includes the cell numbers corresponding to a range of ocean tempera-

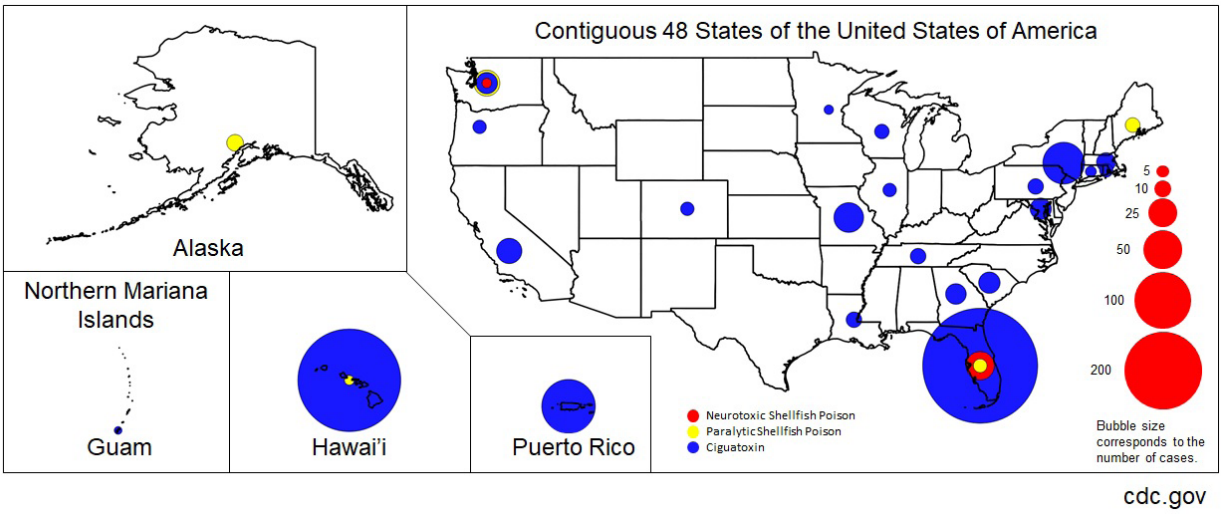

Figure 2. Cases of natural toxins in the United States (1998-2016). A map presents the number of reported cases of neurotoxic shellfish poisoning, paralytic shellfish poison, and ciguatoxin in each state and territory. Number of cases is proportional to the area of the bubble. When multiple types of cases are reported, the bubbles are overlaid, with the largest bubble at the bottom of each stack. While most cases are reported in states with coastlines, several states without coastlines also report cases of seafood-related poisoning. Data were collated by the Centers for Disease Control and Prevention from 1998 to 2016 [32].

tures that support the optimal growth of toxin producing species of algae. These data collected from June 2008 to November 2017 and obtained from the Southern California Coastal Observing System are consistent with optimal temperatures for bloom development at 12 to 20°C across most species [4]. *Alexandrium* is a genus of many species that produce saxitoxin, an algal toxin that is responsible for paralytic shellfish poisoning. *Dinophysis* is another genus that is found in red tide and produces okadaic acid, which is responsible for diarrheic shellfish poisoning. *Lingulodinium polyedrum* produces yessotoxin, which produces symptoms similar to that of paralytic shellfish poisoning. *Prorocentrum* is a genus found in red tide that affects diatoms, reducing the photosynthetic component of the water's plankton and making waters hypoxic. *Pseudo-nitzschia delicatissima* and *Pseudo-nitzschia seriata* are found in harmful algal blooms and produce domoic acid, a neurotoxin that causes amnesic shellfish poisoning [5]. *Anabaena* is a benthic cyanobacteria that has been found to be rapidly responsive to light and oxygen concentrations and potentially able to relocate to more hospitable regions. In light environments, which propel the release of oxygen bubbles due to photosynthesis, *Anabaena* has been found to release the cyanotoxins anatoxin-a and microcystin, which cause respiratory paralysis and chronic liver diseases, respectively [9].

These blooms are generally heavy consumers of nitrogen and phosphorous. Studies have shown that *Microcystis aeruginosa*, a species that is dominant in these blooms contribute to producing hypoxic zones in fresh water systems [10,11] that may lead to the demise of species that would otherwise control these excessive blooms. It is important to note that species such as *Lyngbya wollei, Oscillatoria spp.*, and *Phormidium autumnale* are capable of producing two or more types of toxins and may be able to produce them under different environmental circumstances. This suggests an adaptation or stress response by these cyanobacteria to predatory species or changes in their biosystem that prompt a modulation in defense capacity [8].

A survey of the published literature highlights the presence of high quantities of microcystins in water samples. For example, in Taiwan, a concentration of 8.6 µg/L was detected, the highest ever in their tap water [12]. Microcystins have also been detected in crops, fish and shellfish species around the world with peaks for microcystins noted in rice [13] and fish from China [14] using ELISA (Enzyme-Linked Immunosorbent Assay) and LC-MS (Liquid Chromatography-Mass Spectrometry) methods respectively. Contamination and transportation of these species via microaerosols have also been observed, pointing to non-aqueous means of transfer and contamination. Cyanobacteria genera including *Synechococcus, Synechocystis, Aphanocapsa, Aphanothece, Microcystis, Merismopedia, Woronichinia,* and *Cyanodictyon* were found most commonly in the air over both land and sea in the southwestern Baltic region, of which microcystin-producing *Microcystis* is of most concern to human health [15]. In addition, there have been increasing reports of algal blooms and the detection of BMAA in Australian waters [16-18]. Microcystins are known to be linked to kidney disease, hepatotoxicity leading to organ failure

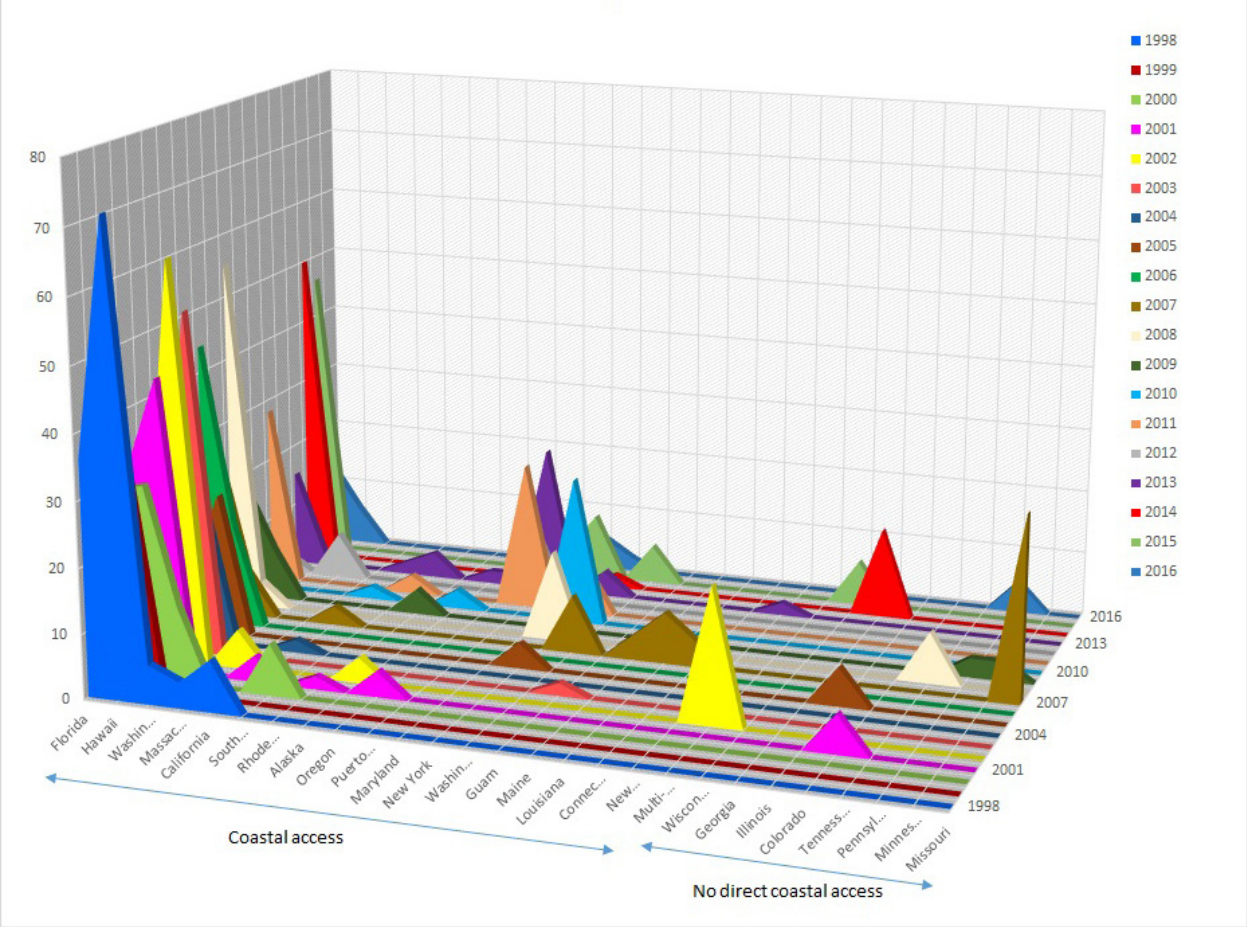

Figure 3. Cases of illness with chronological occurrence and proximity to coast. Number of cases of neurotoxic shellfish poisoning, paralytic shellfish poison, and ciguatoxin combined in each state and territory for each year from 1998 to 2016. States are shown on the x-axis and are grouped into states with coastal access and states without coastal access. On the y-axis, the total number of cases of seafood-related toxin poisoning for each state in each year is plotted. On the z-axis, the years are depicted, with more recent years at the back. While most cases are reported in states with coastlines, several states without coastlines also report cases of seafood-related poisoning. Cases appear to be sporadic in non-coastal states with respect to time. Data were collated by the Centers for Disease Control and Prevention from 1998 to 2016 [32].

[5,19-21], and BMAA has been linked to amyotrophic lateral sclerosis and Parkinsonian disorders [22-25].

MONITORING AND CONTROL

Routine monitoring of algal toxins is either not conducted in some parts of the world or the data are not publicly available. Additionally, the methods for detecting these toxins require expensive equipment, requiring long sample preparation techniques, which are cumbersome, often requiring multiple freeze-thaw cycles [26], or cell lysis to disrupt membranes and to release toxins. Much of the existing techniques are primarily used in water testing at storage, purification, and finishing. While fish and seafood have been included in surveys, plant-based foods and foods harvested from regions that utilize agricultural water from sources primed to contain cyanotoxins have not been studied. There is a need for improved, more mobile, and more rapid methods for detection in a variety of samples, for water as well as food matrices.

The U.S. FDA, European food safety authority, and several Asian food and environmental safety organizations recommend avoiding harvesting seafood, (especially shellfish) during warm summer months when there are known algal blooms taking place, moving harvesting locations and farmed fishing to safer regions and generally monitoring the quality of shellfish between May and August. Ciguatera poisoning is commonly recognized as occurring between 35N and 35S latitude [27]. Increases in temperature, excess nutrients, salt content, and increases in anthropogenic activity have led to a marked increase in the documented cases of cyanobacterial blooms that

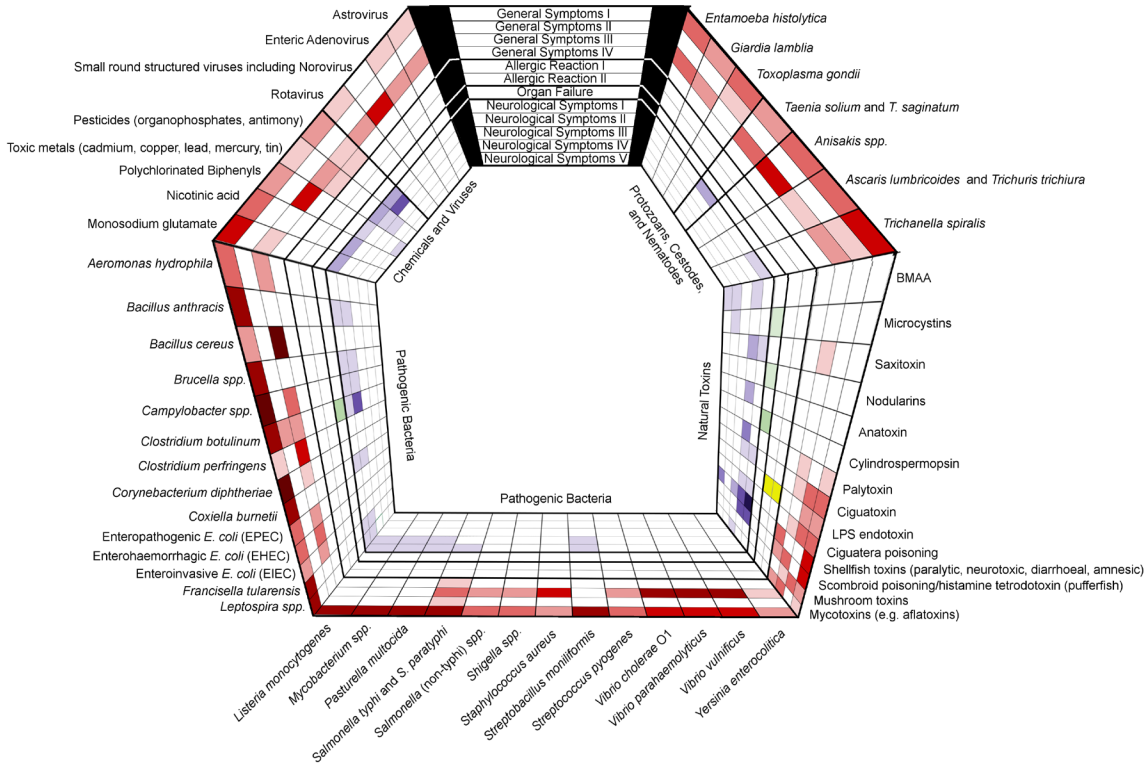

Figure 4. Symptoms associated with their corresponding cause of foodborne illness. Types of symptoms associated with foodborne illnesses. This figure shows data on the symptoms associated with some of the foodborne illnesses caused by viruses, chemicals, pathogenic bacteria, natural toxins, protozoans, cestodes, and nematodes. Illnesses are arranged moving around the outside of the figure, with the information corresponding to a given illness shown as a series of cells from the illness towards the center. The labels for each ring of the figure are broken down into four categories, moving from outside to inside: General Symptoms, Allergic Reaction, Organ Failure, and Neurological Symptoms. These correspond to the colors red, yellow, green, and blue, respectively. The darker the color in a given cell is, the more symptoms in that category belong to that illness. The General Symptoms category shows what generic symptoms are present for a given foodborne illness. General Symptoms I includes fever, headache, malaise, and sore throat. General Symptoms II includes autonomic responses, sores, and rashes. General Symptoms III includes nausea, vomiting, diarrhea, eating and weight issues, and pallor. General Symptoms IV includes bloody diarrhea, hemorrhage, permanent damage, cyanosis, and damage to skin. The Allergic Reaction category is divided into two parts: Allergic Reaction I, which includes topical or gastrointestinal allergic responses, and Allergic Reaction II, which includes respiratory allergic response and anaphylaxis. The third category, Organ Failure, is not divided into smaller categories and includes heart, liver, and kidney illness. The last category, Neurological Symptoms, indicates various neurological effects of diseases. Neurological Symptoms I includes blindness, anxiety, insomnia, and sensory issues. Neurological Symptoms II includes paralysis, difficulty functioning, motor dysfunction, and respiratory paralysis. Neurological Symptoms III includes loss of consciousness, seizure, and coma. Neurological Symptoms IV refers to neurodegenerative diseases. Neurological Symptoms V refers cognitive dysfunction, including memory loss and disorientation. Many of the marine natural toxins shown have no general symptoms associated, meaning it would be hard to identify that the person was ill immediately, while most of them also pose neurological effects of varying seriousness. Data were collated by the World Health Organization [21].

occur on a global basis. Over 25 percent of the reported blooms were toxin producing in Europe, Asia, and America [28]. The Baltic sea region has some of the most spectacular cyanobacterial blooms that while easily visible from the air and from space, pose significant environmental threats, and are being evaluated by teams for surface, sub-surface, and benthic species, nutrient sources and serve as a test ground for a range of monitoring technologies to better assess large scale bloom activity with accuracy [1].

While cyanotoxins have the potential to cause illness, they are not prevalent in all waters populated by cy-

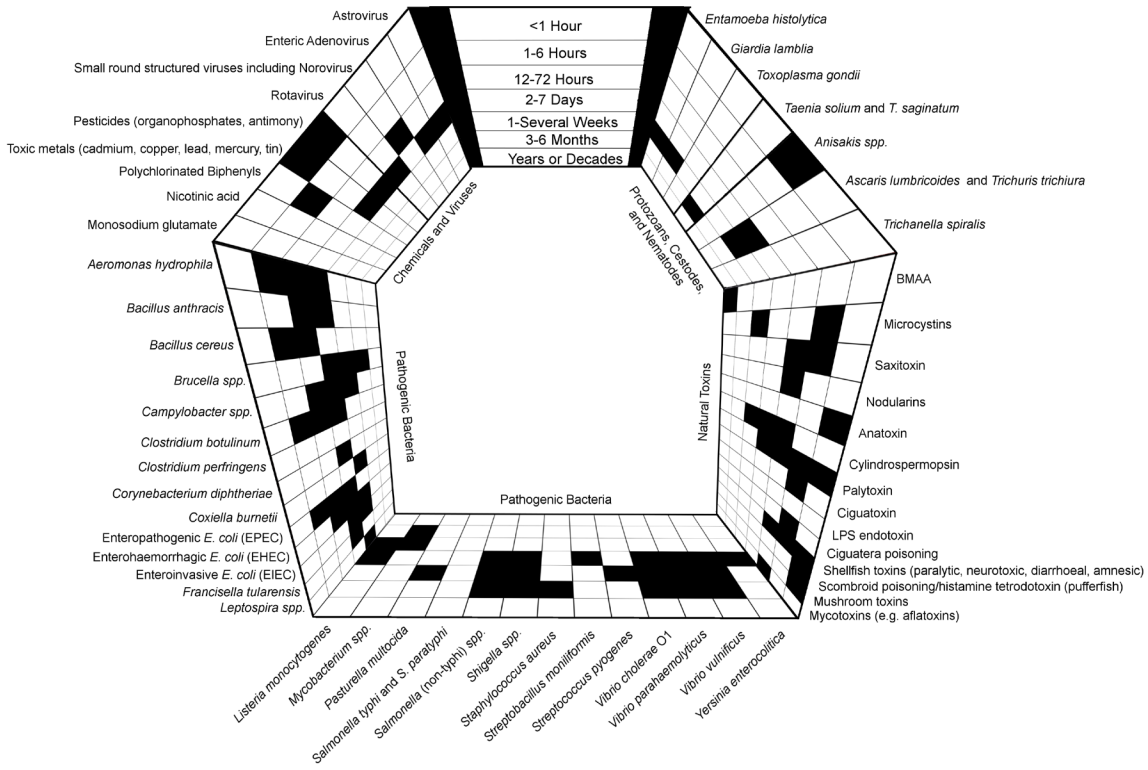

Figure 5. Symptom presentation timeline for each corresponding cause of foodborne illness. Time at which symptoms arise, associated with foodborne illnesses. This figure shows data on the symptoms associated with some of the foodborne illnesses caused by viruses, chemicals, pathogenic bacteria, natural toxins, protozoans, cestodes, and nematodes. Illnesses are arranged moving around the outside of the figure, with the information corresponding to a given illness shown as a series of cells from the illness towards the center. The labels for each ring of the figure are time ranges indicating when symptoms first appear. If a given cell is black, symptoms appear for that illness at the associated point in time. On the outside of the diagram, the shortest time range of less than 1 hour after symptoms is shown, while on the inside of the diagram, the longest time range of years or decades is shown. For natural marine toxins, some of them have symptoms present quickly, while a few like microcystins, cylindrospermopsin, and BMAA can take weeks or years to show indication of certain symptoms. Data were collated by the World Health Organization [21].

anobacteria. In fact, many cyanobacterial species do not produce cyanotoxins. However, the known presence of the minority toxic species prompted Oregon established guidelines for anatoxin-a, cylindrospermopsin, microcystins, and saxitoxins, the most common cyanotoxins, in order to provide limits on how the public may use daily intake of drinking and recreational water and by providing dog-specific guidelines for pet activities [29].

Using solid-phase extraction liquid chromatography mass spectrometry, a group of researchers in Taiwan were able to accurately identify the presence of six microcystins, nodularin, anatoxin-a, and cylindrospermopsin concurrently in various samples of water, and found that it was an appropriate approach for monitoring cyanotoxins [12]. These are also commonly found with *Nodularia spumigena*, *Anabaena spp.*, and *Ananbaena inaequalis* biomasses contributing significantly to the biomass of these communities (10.6 percent to 65.2 percent) during the warm summer months [1]. Because microcystins and nodularin remain potent even after boiling, a boil water advisory isn't an appropriate means of controlling them. An avoidance-based methods is more suitable [30].

ILLNESS

Of the water-borne disease outbreaks in 2009 to 2010, 11 were associated with algal blooms, sickening 61 individuals with dermatologic, gastrointestinal, respiratory, and neurologic symptoms [31]. A common feature of illness associated with harmful algal blooms is lack of clarity in the infection pathway, with some cases being oral and others via respiratory routes or eye- or ear-associated means. In *Figure 2* data from the U.S. Centers for Disease Control and Prevention (CDC) [32] correspond-

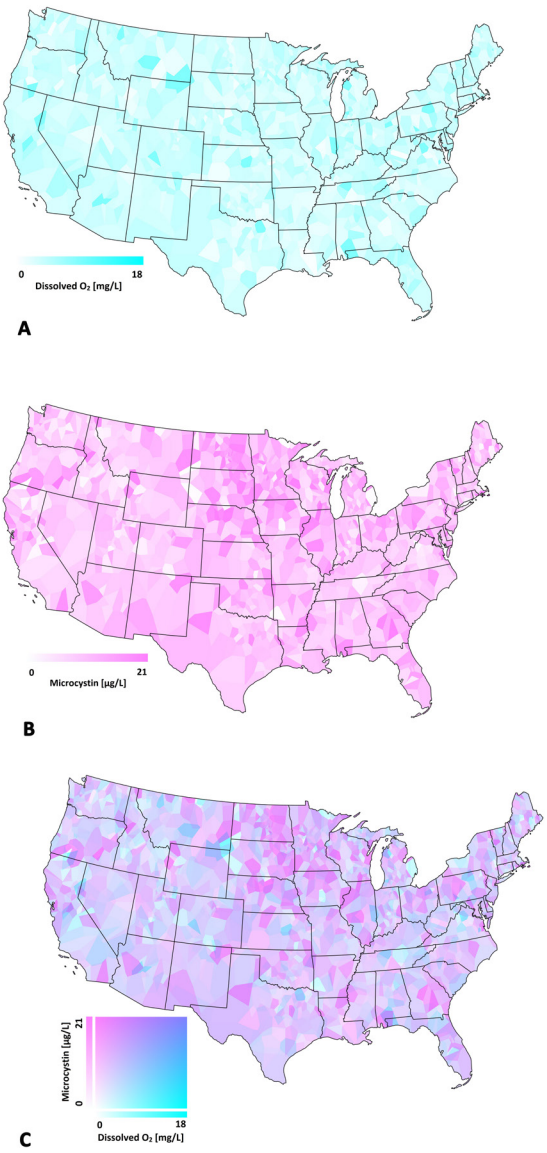

Figure 6. Microcystin concentration and oxygenation of water sources in the United States. Three maps present data on dissolved oxygen concentrations and microcystin concentrations in lakes and river across the United States of America. **(A).** Oxygen concentrations are shown for the contiguous United States, with color at a given point determined by the reported value for the nearest measurement site. The more cyan the color, the higher the reported oxygen concentration. Regions with higher oxygen concentrations are more beneficial to local life, while regions with lower oxygen concentrations are less hospitable to many flora and fauna [3]. **(B).** Microcystin concentrations are shown for the contiguous United States, with color at a given point determined by the reported value for the nearest measurement site. The more magenta the color, the higher the reported microcystin concentration. Regions with lower microcystin concentrations are safe for production of food for human consumption, while regions with higher microcystin concentrations pose greater risks to human health [4]. **(C).** Oxygen and microcystin concentrations are overlaid for the contiguous United States, combining the data of panels A and B of the same figure. Color at a given point is determined by each reported value for the nearest measurement site(s). White represents low concentrations of both oxygen and microcystin. The more cyan the color, the higher the reported oxygen concentration. The more magenta the color, the higher the reported microcystin concentration. Deep blue represents both high oxygen and high microcystin concentrations. Regions represented as cyan are safer for production of food and healthier for local flora and fauna, while regions represented as magenta pose health risks for the production of food and are less hospitable to local flora and fauna. Data were collected by the National Aquatic Resource Surveys [3,4]. See Appendix A.

ing to cases of illness linked to natural toxin are mapped throughout the United States. Most notably illnesses occurring over the 1998 to 2016 period are most commonly linked to the consumption of seafood.

States that have had cases of neurotoxic or paralytic shellfish poisoning, or of ciguatoxin poisoning have bubbles corresponding to the number of cases of that type in that state. These are cases reported between 1998 and 2016.

This figure (*Figure 3*) indicates that disease due to cyanotoxin-contaminated food is mostly a coastal phenomenon, as is expected, yet non-coastal states also have cases of poisoning. This widespread phenomenon can affect many people without warning, although, when viewed in chronological order, no trend over time is apparent, and the prevalence of cases appears to be sporadic in non-coastal states.

Figure 4 assembles key categories of foodborne illnesses based on their symptoms. The diagram is split into four zones, each of which is colored with different colors. In each zone, the outer side refers to more mild symptoms, while the inner side refers to more serious conditions [21]. The outermost red zone, is with respect to general symptoms, ranging from fever and headache on the outside to hemorrhage and cyanosis on the inside. The yellow zone describes allergic response, with the outer half referring to a general reaction, while the inner half deals with anaphylaxis and respiratory issues. The green zone corresponds to organ failure. The innermost blue zone deals with neurological effects, with sensory issues on the outside, paralysis and motor problems further in, then seizure and coma, and finally neurodegeneration and cognitive dysfunction on the inside. Colors in each box represent the number of symptoms that a patient typically presents when affected by the corresponding organism or toxin, where deeper colors represent more marked symptoms and lighter colors corresponding to a lower number of symptoms in each category.

Figure 5 provides a timescale for the occurrence of symptoms that correspond to the illness, ranging from hours on the outside to years on the inside.

Fatal neuromuscular disorders such as Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) have been directly linked to exposure to heavy metals (lead, chromium), pesticides or cyanobacterial toxins such as BMAA [24]. These types of illnesses are difficult to diagnose and may take several years or even decades of exposure for patients to become symptomatic. The risks for natural toxins are thus less easily identifiable and, in many cases, may never be accurately linked to the direct source of contamination or consumption. Rises in kidney and liver disorders are typically noted as a response to toxins.

While cyanobacteria have been well studied, there is little known about the toxicological mechanisms and presence of each toxin in foods [7]. The detrimental health effects of exposure to cyanotoxins are often prevented by avoidance recommendations. For instance, the presence of cyanobacterial cells in recreational waters in excess of a threshold value is generally the cause for avoidance messaging as a means of control.

The maps in *Figure 6* are compilations of data that compare dissolved oxygen values in bodies of water with microcystin concentration. Areas are colored based on reported information from the closest lakes and rivers. *Figure 6a* represents data on oxygen concentrations in water, *Figure 6b* represents data on microcystin concentrations in water, and *Figure 6c* combines both datasets used in *Figure 6a* and *Figure 6b.* White in all three subfigures indicates a low presence of oxygen, microcystin toxin, or both. In *Figure 6a* and *Figure 6c,* the more cyan the color, the more dissolved oxygen there is in the lakes. In *Figure 6b* and *Figure 6c,* the more magenta the color, the more microcystin can be found. In *Figure 6c,* deep blue indicates high quantities of both oxygen and microcystin. Areas that are closer to cyan are more beneficial to local life, while areas that are closer to magenta are less beneficial. Crops grown in magenta areas are more exposed to microcystins. We observe vast regions of magenta in states like Minnesota, Wisconsin, the Dakotas, Illinois, Iowa, and Nebraska [1,2]. These states are the biggest producers of corn and soybean in the U.S. This is worrying, as these are crops that gather harmful toxins and are converted into dry products where algal toxins are not typically much of a concern and tested for. Corn is a major American staple, so many people could potentially be exposed to these toxins in small quantities on a regular basis.

TOXIGENIC EFFECTS

While the data are sparse linking cyanotoxins and organ failures, hepatotoxicity is the primary concern with food and waterborne ingestion of microcystins [33]. Cases of severe neurodegeneration and early death associated with the consumption of BMAA-contaminated sago flour from cycads and the consumption of BMAA-accumulating fruit bats in indigenous populations has been observed [34,35]. Guidelines for drinking water, seafood, and risk assessments that take a preventive approach to mitigate toxigenic effects have been proposed with threshold levels [36] and control by chemical means such as exposure to chlorine [6].

While the understanding of the underlying mechanisms behind cyanotoxin toxicity are yet to be fully understood, progress has been made in characterizing BMAA's toxicity. It has been proposed that BMAA's inappropriate incorporation in protein translation, in place of L-serine, leading to protein misfolding is the mechanism by which

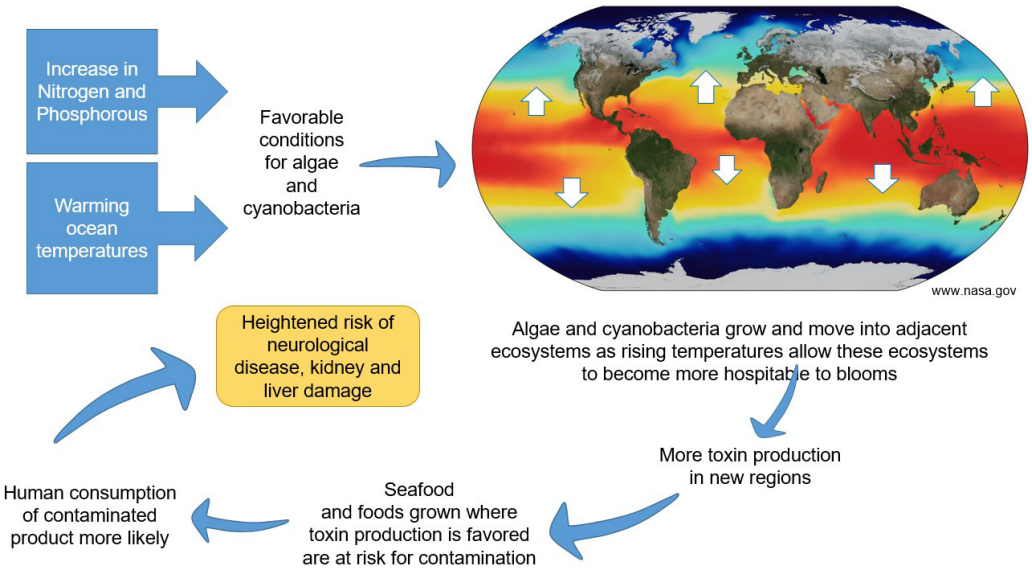

Figure 7. A model of how anthropogenic activity influences risks for downstream health effects. A flowchart representing a model of how anthropogenic phenomena, namely warming ocean temperatures and increased oceanic levels of nitrogen and phosphorous available, can create health problems for humans in general. With the aforementioned phenomena, conditions become more favorable for algae and cyanobacteria to thrive, enabling them to propagate and thrive in higher latitudes than before. This exposes new regions to cyanotoxins and at higher levels, which promotes contamination of seafood and food produced in coexistence with cyanotoxins. This leads to cyanotoxins entering the human food supply, where cyanotoxins have been correlated with higher risk of neurological disease and kidney and liver damage. Map of ocean temperatures was created by NASA [38].

BMAA leads to neurodegeneration. Recently, Onselen and Downing have suggested that BMAA may also perturb enzyme function and associate with commercial proteins to induce cytotoxicity [37].

CONCLUSION

An overall model for how anthropogenic phenomena result in risks to humans is presented in *Figure 7*. Anthropogenic phenomena, such as the introduction of excess nitrogen and phosphorous into water and the upward trend in global temperatures, lead to changes in the populations of algae and cyanobacteria in waters on the planet. Currently, water temperatures that promote cyanobacterial growth are only around the equator [38], but over the next few decades, it is expected that as water temperatures change, conditions will become more conducive to cyanobacterial proliferation. Furthermore, the presence and persistence of cyanobacteria in arid climates and during droughts has been well documented. These organisms, in addition to being resilient, can produce heat-stable toxins that can be carried by inert materials or within dry foods for human consumption. The increase in water temperatures enables toxin-producing algal and cyanobacterial blooms to occur further north and south of the equator, leading to the introduction of the toxins in areas where they previously did not exist. The excess available nitrogen and phosphorous enable quickly-reproducing microorganisms to take over all nutrients in the environment, which leads algae and cyanobacteria to be able to form blooms rapidly while creating hypoxic and toxic water for most native flora and fauna. These two effects cause the native seaweed, fish, and crustaceans to accumulate dangerous quantities of cyanotoxins and algal toxins, which can then enter and endanger human health through the consumption of seafood. In addition, cyanotoxins pose another risk of potentially contaminating dry plant-based foods. These toxins are resilient to boiling and high temperatures, making traditional cooking and food processing methods ineffective or inadequate for denaturing toxins. More studies on the toxicological mechanisms, removal, and control of toxins, as well as detection methods, are necessary. Additionally, the general awareness to symptoms that could flag food and water-borne illnesses in chronically ill patients, and the adoption of improved risk assessment in agricultural systems are needed to better respond to changes in the environment that impact the safety of foods.

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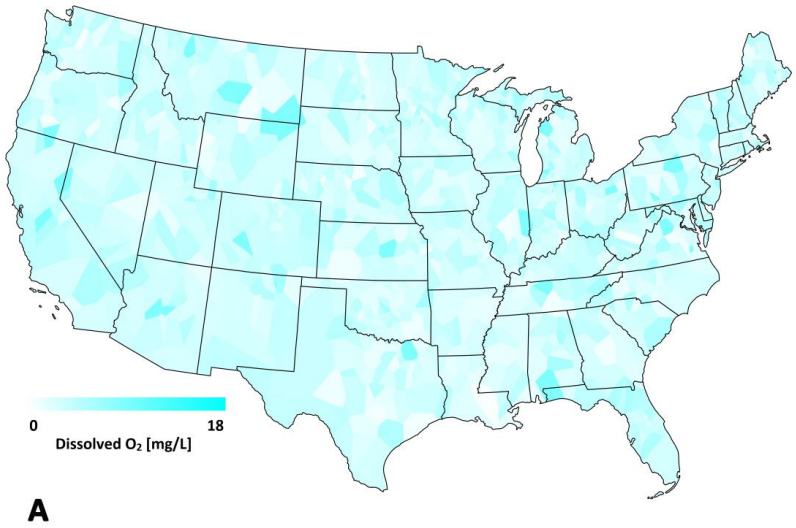
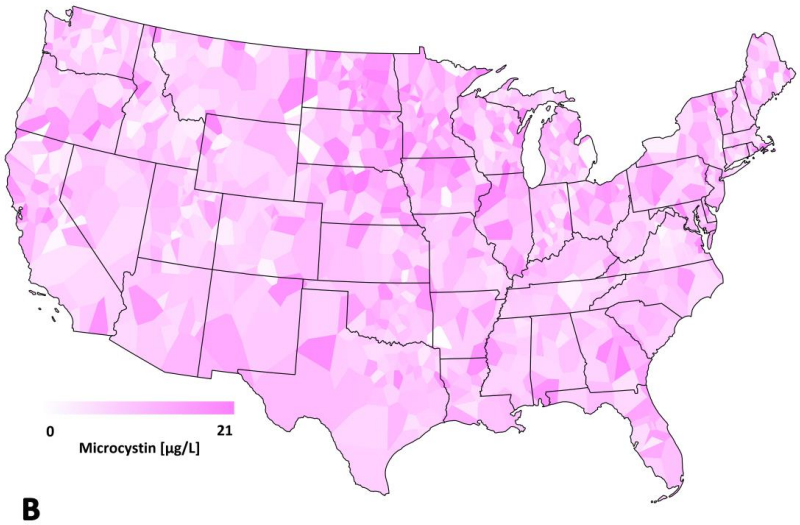
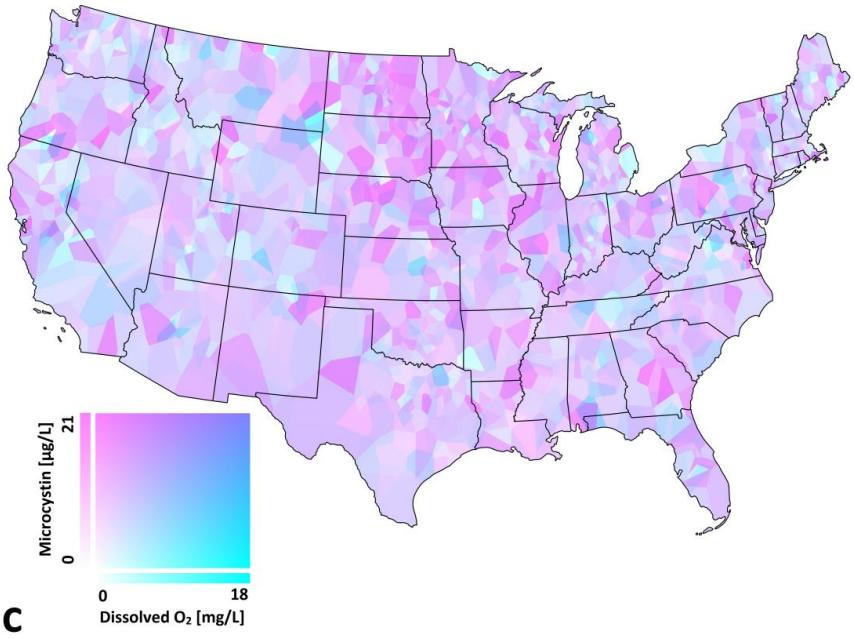
Appendix A.

Figures 6a, 6b, and 6c.





B


Microcystin [µg/L]
21
0
0
18
Dissolved O2 [mg/L]
C