Oregon Harmful Algae Bloom Surveillance (HABS) Program

Public Health Advisory Guidelines
Harmful Algae Blooms in Freshwater Bodies

Oregon Health Authority

Public Health Division
Center for Health Protection
Environmental Public Health Section

Updated May, 2016

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Introduction

Cyanobacteria, also known as blue-green algae, are commonly found in many fresh and saltwater environments around the world. Some cyanobacteria species are referred to as toxigenic because they have the potential to produce toxins that can harm people, pets and wildlife.

Some Oregon water bodies are monitored for cyanobacterial harmful blooms (cyanoHABs). The number of waterbodies monitored is affected by available local, state, and federal resources and the costs associated with sampling. Historically the decision-making process for issuing and lifting health advisories varied according to the managing jurisdiction of a specific water body. In 2009, the Oregon Health Authority Public Health Division (OPHD) assumed responsibility for the decision-making process and for issuing and lifting public health advisories when cyanoHABs are detected.

The OPHD is working to gain a better understanding about the occurrence of cyanoHABs in Oregon and their impact on human health. Funding for Oregon's Harmful Algae Bloom program was through a five-year federal grant from the U.S. Centers for Disease Control and Prevention (CDC). That grant ceased in September of 2013. Currently program staff implement the highest priority activities such as the issuing and lifting of advisories with no funding.

OPHD program objectives:

- Track freshwater cyanoHABs with data provided by partner agencies
- Track cases of human and animal illnesses related to cyanoHABs
- Enter environmental and health data for OPHD tracking
- Build capacity of our partners to monitor water bodies in a scientifically sound manner with the goal of protecting public health
- Provide technical assistance to partner agencies to assess health risks associated with algal toxins
- Educate and inform the public regarding health risks due to cyanoHABs

Background

The advisory process guidelines in this document were developed and are modified based on the most current national data and references, and on monitoring data received from our waterbody partners and stakeholders.

These guidelines are used to educate the public and our partners about how and when OPHD issues and lifts public health advisories. Public health advisories help to inform the public of the health risks associated with exposure to potentially toxic cyanobacteria in Oregon's recreational fresh waters.

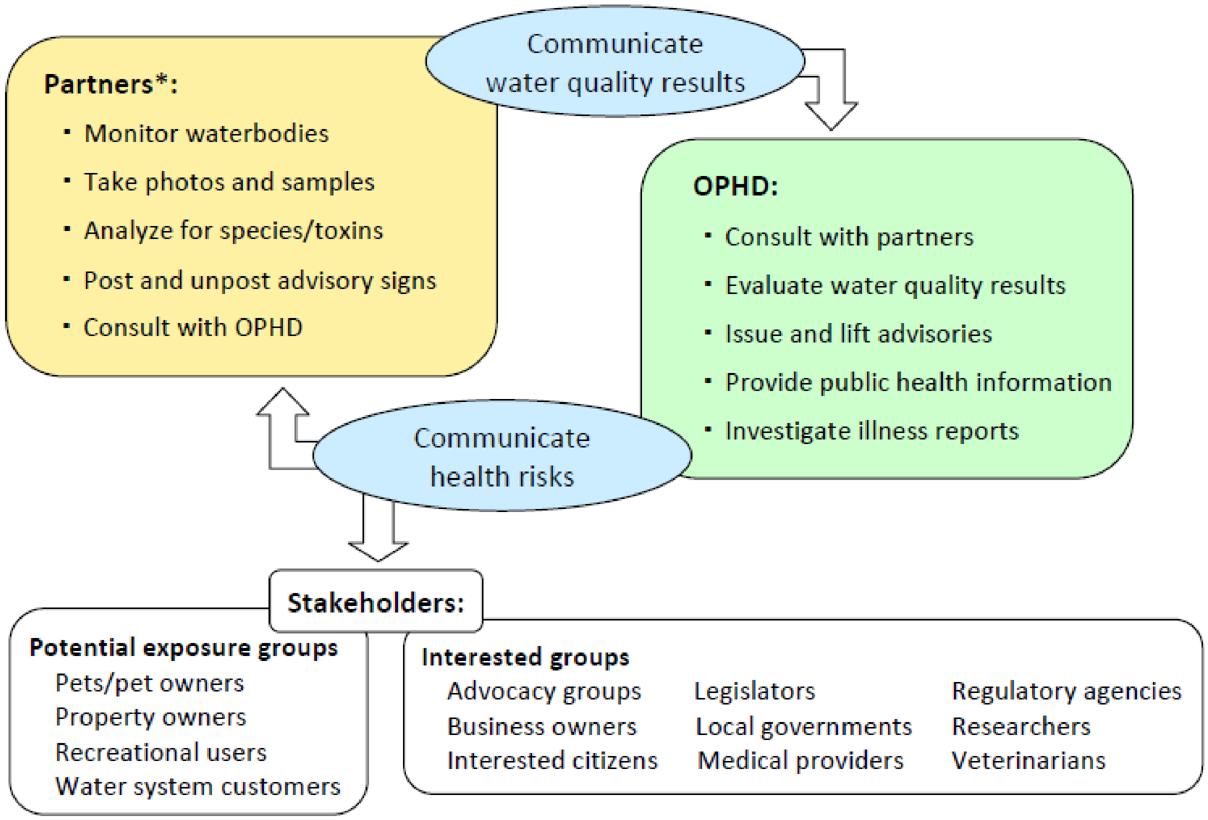
OPHD authority for public health and safety fall under Title 36, Oregon Revised Statute (ORS), Chapter 431.035 to 431.530.

CyanoHAB Coordination Process

Specific actions are involved in monitoring, responding to and communicating information about cyanoHAB blooms.

Coordination among the OPHD and its partners and stakeholders is paramount to complete the advisory process from identification and sampling of a bloom to notifying the public of an advisory. Figure 1 depicts the flow of activities among all entities involved in cyanoHAB incidents.

Figure 1. Activities involved in monitoring and responding to cyanoHABs



*Oregon Department of Environmental Quality, U.S. Forest Service, U.S. Army Corps of Engineers and other waterbody managers.

The main roles of the OPHD are to issue and lift health advisories based on water quality data provided by partners and to provide risk communication.

Partners in this effort include the Oregon Department of Environmental Quality, U.S. Forest Service, U.S. Army Corps of Engineers and other waterbody managers.

For the purposes of the OPHD public health advisory process, stakeholders are classified in two sub-groups:

- Exposure: Those with a greater risk of illness from cyanoHABs through recreational activities. Exposure can occur through ingestion, inhalation or skin contact with contaminated water. More information regarding potential routes of exposure is provided in Appendix C.

- Interest: Those with varying levels of need, involvement or interest in program operations or policies, are affected by the program or are intended users of program outcomes/findings.

Table 1.Roles and Responsibilities for Monitoring and Responding to a CyanoHAB

Activity	*Lead role*	*Assist*
Monitor	Partners monitor water bodies through on-site observations for evidence of cyanoHABs	OPHD provides guidance for establishing a monitoring program
Collect water samples	Partners use scientifically acceptable methods to obtain water samples	OPHD provides guidance on sampling techniques
Analyze samples	Partners contract with laboratories that are qualified to perform the required analyses	OPHD provides a list of laboratories with appropriate analytic capabilities
Issue or lift advisories	OPHD evaluates data and compares test results to established criteria to determine if an advisory should be issued or lifted	OPHD informs local health departments before issuing or lifting advisories
Communicate advisory information	OPHD informs general public through advisory news releases, GovDelivery messages, broadcast and print media, an automated electronic list-serv, a toll-free hotline and the HABs website	Partners and local health departments inform constituents of health advisory status through news releases and signage
Ongoing communication between the OPHD and partners occurs throughout the bloom season regarding advisory decisions, bloom information, water quality data and illness reports.		

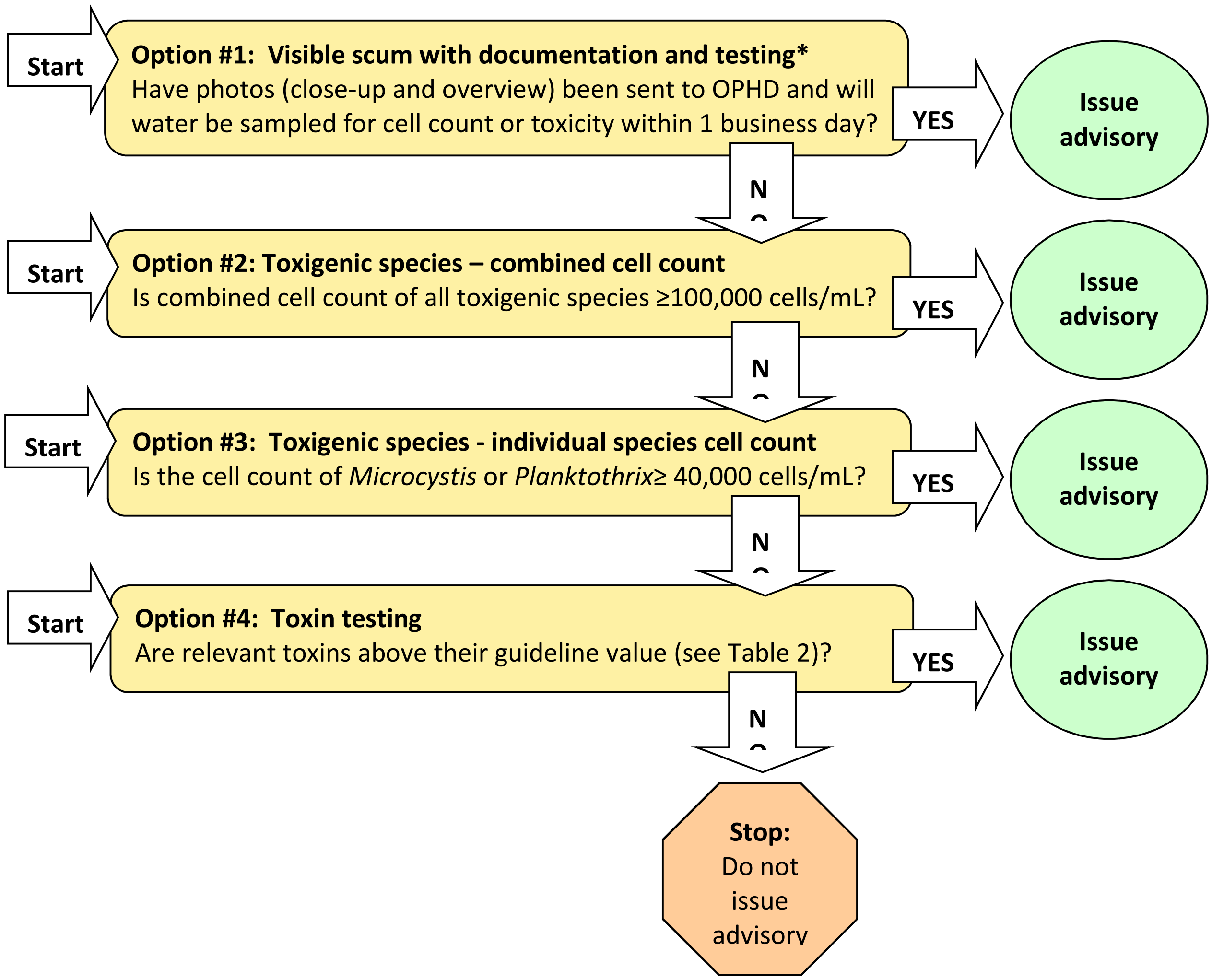
Criteria for Issuing a Public Health Advisory

OPHD is responsible for the decision-making and communication process of issuing and lifting public health advisories. While waiting for the OPHD advisory process, local management may post educational signs as a precautionary measure to alert the public of the potential health risks associated with using the water during a cyanoHAB.

OPHD criteria for issuing a public health advisory depend on the method selected. Options are:

- Visible scum (with supporting photographs and water analysis)
- Cell counts
- Toxicity levels
- Combinations of two or all three of these options.

Figure 2. OPHD process for issuing public health advisories for a cyanoHAB



Scum is defined as a visible mass of blue-green algae or cyanobacteria in stagnant or slow moving water. Scum accumulations of the greatest concern are those occurring at or near recreational access points.

OPHD guideline values for cyanobacterial cell counts and toxins are based on the World Health Organization risk categories and research in the field. More information regarding the rationale used to help determine when advisories should be posted is provided in Appendix A.

Additional Guidance on Toxin Based Monitoring Program: Option 4

Toxin testing provides the most accurate information in terms of protecting public health. Toxin testing also results in health advisory decisions that are based on actual human health risk rather than potential health risk.

Because cyanobacteria often do not produce toxins, even when present in concentrations above OPHD's guideline values, it is anticipated that Option 4 will result in fewer and shorter duration public health advisories for a given water body. However, laboratory costs when using Option 4 are higher than those for Options 1 through 3.

OPHD's cyanotoxin guideline values, listed in Table 2, are the basis for determining whether an advisory will be issued under Option 4. The OPHD Sampling Guidelines document contains detailed information on how to conduct a toxin-based monitoring program.

Table 2. Health advisory guideline values for cyanotoxins in Oregon recreational waters (µg/L)

Guideline Value:	*Anatoxin-A*	*Cylindrospermopsin*	*Saxitoxin*	*Microcystin*
	20	20	10*	10

*Note that the guideline values for cylindrospermopsin and saxitoxin have changed from the previous values of 6 and 100 µg/L. See Appendix B for the detailed rationale behind these changes.

OPHD has also developed dog-specific guideline values. They are for informational purposes only and are not to be used as a basis for issuing public health advisories. These guideline values can be found in Appendix C.

Special note: *Aphanizomenon flos-aquae* exemption from cyanotoxin-producing genus list

Aphanizomenon flos-aque (AFA) is a species of cyanobacteria commonly found in Oregon's fresh waters. Although some studies have shown this species to produce toxins in other parts of the world, subsequent evaluations of that work show that the species either was or likely was misidentified.

For the purpose of issuing public health advisories, AFA is excluded from calculation of combined cell counts of toxigenic species. Other species of the genus *Aphanizomenon*, such as *A. gracile*, have been demonstrated to produce cyanotoxins. In recognition of this exemption the toxigenic genus list presented in Appendix B, Table B-1 describes *Aphanizomenon (Except A. flos-aquae)*.

Criteria for Lifting a Public Health Advisory

Table 3 summarizes the lifting criteria for advisories issued based on the type of monitoring that led to the advisory.

Table 3. Criteria for lifting advisories

Monitoring option used to generate advisory	*Lifting criteria*
Option 1: Visible Scum	Initial cell count or toxin results below threshold
Options 2 and 3: Cell counts	Cell counts and toxin results below threshold
Option 4: Toxin based monitoring	Toxin results below threshold

Cyanobacteria can release their toxins during bloom formation and as the bloom is declining, and toxins can take some time to degrade once released. It is possible to have cell counts below advisory thresholds and still have toxins present. Therefore, to reduce the risk of exposure to the public, toxin analysis must be completed to lift an advisory.

If an advisory is issued based on Option 1 (visible scum) and initial sample results verify that either cell counts or toxins are below guideline values, OPHD will immediately lift the advisory. In this case OPHD advises continued visual assessment of the bloom and resampling if a change in bloom conditions is observed.

If an advisory is issued based on Options 2 or 3 (cell counts above threshold value), OPHD will lift advisories when tests show that cell counts and toxin concentrations are below the guideline values listed in Figure 2 (cell counts) and Table 2 (toxins).

Cell count is required in addition to toxin testing to ensure there is minimal potential for further toxin release. This is because the presence of toxin is what causes illness, while the presence of toxigenic cyanobacteria represents the potential for toxin release. Be sure to choose a laboratory that can analyze for cyanotoxins produced by the cyanobacteria present (see Appendix B, Table B-1).

The accepted method for determining cell counts is Standard Methods Section 10200E and F (also called "SM10200"). We recommend contacting your lab for the most current cost of analyses and for preservation and shipping instructions for your sample.

If an advisory is issued based on Option 4 (toxin results above guideline values), OPHD will lift the advisory as soon as regular toxin testing indicates that total (intracellular and extracellular) toxin levels are below guideline values. In this case, even though the advisory has been lifted, OPHD advises continued toxin based monitoring every other week until the bloom is gone to ensure toxin levels remain below guideline values. If continued sampling shows an increase in toxins above guideline values, a second advisory would be issued.

Commercial laboratories use a variety of comparable methods currently available to analyze for cyanotoxins. When requesting toxin testing, ensure the lab uses a method detection level less than the guideline values in Table 2. Note: OPHD will not accept field-ready test kits for microcystin as a basis for lifting an advisory. However, these kits may be useful for monitoring the progress of a bloom throughout the season.

Analysis can be costly depending on the method and equipment used. Lab staff can provide you with the most current cost of toxin analyses prior to submitting a sample. In general, the ELISA method is least expensive for determining levels of microcystin, saxitoxin and cylindrospermopsin in the bloom. ELISA methods are not currently available for anatoxin-a. However, Abraxis has introduced a micro-titer plate format (96T) receptor-binding assay (RBA) kit for Anatoxin-a. The kit provides two protocols. The EZ protocol requires no sample preparation and has a range of 5 - 500 ppb. If a lower limit of detection is required, the enhanced sensitivity (ES) SPE sample concentration may be performed. This kit provides a real-time, economical, accurate and sensitive alternative for research and monitoring programs.

Note: All cyanobacteria produce lipopolysaccharides that can cause skin irritation, OPHD does not require testing for these endotoxins.

Public Notification Methods

Several concurrent notification methods are used by the OPHD in the issuing and lifting of public health advisories. The specific methods are as follows:

Email: An email alert is sent to the following groups:

- Health department staff in the county where the waterbody is located
- OPHD Partners including agency communications and water quality staff, waterbody managers, watershed council members, basin coordinators, etc.
- Stakeholders including interested citizens, resort owners, advocacy groups, public officials and others. Access to this list is open to all interested Oregonians

News Releases: OPHD issues statewide news releases which may be picked up and reported by broadcast and print media outlets across Oregon. These releases contain information about the nature and location of the advisory, possible health effects, recommended protective actions and where people can obtain more information. Statewide news releases are also issued when advisories are lifted.

GovDelivery listserv messages: A GovDelivery message is sent to notify members about a health advisory issue or lift immediately after the advisory news release is issued. Currently this listserv has over 3,500 members.

Program Website: The program maintains a website where advisory information (both issuing and lifting) is immediately posted, providing real-time access to advisory information. Resources for water samplers, prevention tips and general information about cyanoHABs can also be accessed. The website is available at ***www.healthoregon.org/hab***.

Hotline: A statewide toll-free telephone service (877-290-6767) provides updated advisory information to the public, which is particularly helpful for individuals without Internet access.

Program Contact Information

Email: habhealth@state.or.us
Phone: (971) 673-0440Toll Free: (877) 290-6767 and press 4
Website: ***www.healthoregon.org/hab***

Appendix A: Rationale for and history of standards to issue and lift recreational public health advisories for cyanoHABs

In 2004 and previous years, lakes were posted when harmful algae cell densities exceeded 15,000 cells/mL. In 2005, a decision was made to no longer use 15,000 cells/mL threshold as an absolute criterion for posting advisories at recreational access points.

The risk to recreational users at a cell density of 15,000 cells/mL is considered low and includes minor health symptoms such as skin irritation, which are thought to be related to lipopolysaccharide endotoxins found on cell walls. In a study by Pilotto et al, (Pilotto et al., 2004) acute skin irritant effects were tested over a range of cell densities (< 5000 cells/mL to > 200,000 cells/mL) after application of cyanobacterial extracts.

Genera tested included *Dolichospermum* (formerly known as *Anabaena*[1]), *Microcystis*, *Cylindrospermopsis* and *Nodularia*. Approximately 15% of the people reacted to the extracts with mild, self-limiting reactions. Furthermore, no dose-response relationship was established. The absence of a dose-response relationship, and therefore a threshold, makes it difficult to recommend quantitative guidance. Consequently, the focus of advisory postings is on the risk posed by cyanotoxins and the potential for more serious health effects such as nervous system or gastrointestinal disorders.

<u>Advisory guidelines for algae blooms dominated by *Microcystis* or *Planktothrix*:</u>

A focused risk assessment was conducted to characterize the risk associated with swimming in waters dominated by *Microcystis* or *Planktothrix* cyanobacteria. The equation and parameters are described below.

$$\text{Concentration of toxin } (\mu\text{g/L}) = \frac{\text{TDI} \times \text{BW}}{\text{IR}}$$

Where:

TDI (tolerable daily intake) = 0.05 µg/kg/day
BW (body weight) = 20 kg
IR (ingestion rate) = 0.1 L

The TDI was developed by the Oregon Public Health Division (OPHD) based on oral administration of microcystin-LR via drinking water in rats and effects on the liver (Heinze, 1999).

A body weight (BW) of 20 kg was used to represent a child. An ingestion rate (IR) was based on EPA guidance for incidental ingestion of surface waters, in which 0.05 L is accidentally ingested per one-hour event (Dang, 1996). For this guidance, it was assumed that a child might swim for up to two hours in a day.

Using the parameters described above, the equation results in 10 µg/L of microcystin toxin.

According to World Health Organization guidance, 10 µg/L would correspond to approximately 40,000 cells/mL if *Microcystis* were the dominant species (Chorus and Bartram, 1999). *Planktothrix* was included in the additional guidance, since it has the potential to contain higher endocellular microcystin compared with *Microcystis* (Codd et al., 2005).

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[1]Taxonomy for many types of cyanobacteria is currently being revised. This guidance reflects taxonomy as of 1/2015.

Advisory guidelines for algae blooms not dominated by *Microcystis* or *Planktothrix*:

At 100,000 cells/mL, the World Health Organization lists a moderate probability of adverse health effects, based in part on the ability of cyanotoxins to reach levels of concern. As the cell density increases, the potential for frequently occurring cyanobacteria to form scum may increase toxin production by 1000x in a few hours (Chorus and Bartram, 1999).

Rationale for using both cell counts and toxin testing results to lift public health advisories

Several northern California studies conducted between 2005 and 2009 have demonstrated that microcystin concentrations greater than the 10 µg/L advisory threshold can be present in rivers and reservoirs where cell counts are below advisory threshold values (Kann and Corum, 2009).

Other research (Manganelli et al., 2010) also suggests that cell count alone is not a good predictor of human health risk. In fact, the State of Washington's Department of Ecology uses only toxin testing data as a basis for public health advisories. The requirement of toxin and cell counts before lifting an advisory is consistent with the OPHD goal of public health protection.

Between August 21 and August 30, 2009, four dogs died of acute anatoxin poisoning shortly after drinking water from Elk Creek and the Umpqua River, near the confluence of these two streams at Elkton, Oregon.

Water samples collected from the area on September 1, 2009 had no detectable toxigenic cyanobacteria. However, other samples collected from the same areas on the same day revealed detectable levels of anatoxin-A (0.5 µg/L). Microcystin was measured at an average concentration of 15 µg/L (1.5 times above the advisory threshold of 10 µg/L). There was no visible bloom or scum reported in that area of the creek when these fatalities occurred.

This case demonstrates that lethal concentrations of cyanobacterial toxin can be present in the absence of detectable toxigenic cyanobacterial cells. This case and other research (Kann and Corum, 2009; Manganelli et al., 2010) demonstrate the importance of measuring both toxin and cell counts before an advisory is lifted.

Appendix B: Toxigenic cyanobacteria and related toxin information

A variety of species of cyanobacteria are capable of producing toxins that are harmful to people, pets and wildlife(Chorus and Bartram, 1999). The most common toxigenic genera observed during cyanoHABs in Oregon are *Microcystis* and *Dolichospermum.*

Microcystis can produce microcystin (liver toxin) and anatoxin-a (neurotoxin). *Dolichospermum*, in addition to producing microcystin and anatoxin-a, can also produce cylindrospermopsin (liver toxin) and saxitoxin (neurotoxin). A complete listing of toxigenic cyanobacteria considered when issuing health advisories in Oregon is presented in Table B-1.

Table B-1. Toxigenic cyanobacteria (data derived from evidence of toxin production (Chorus and Bartram, 1999; Carey et al., 2007; Funari and Testai, 2008; Voloshko et al., 2008))

	Hepatotoxin (liver toxins)			*Neurotoxins*	
	Microcystin	Nodularin	Cylindro-spermopsin	Anatoxin-a	Saxitoxin
Anabaenopsis	+				
Aphanizomenon(Except A. flos-aquae)			+	+	+
Arthrospira	+				
Cyanobium	+				
Cylindrospermopsis			+		+
Dolichospermum	+		+	+	+
Gloeotrichia	+				
Hapalosiphon	+				
Limnothrix	+				
Lyngba					+
Microcystis	+			+	
Nodularia		+			
Nostoc	+				
Oscillatoria	+			+	
Phormidium	+			+	
Planktothrix	+			+	+
Raphidiopsis			+	+	
Schizothrix					
Synechocystis	+				
Umezakia			+		

Note: Table B-1 is at the genus level. Not all species of a given genus produce all the toxins listed for that genus. Once the species involved in a specific bloom have been identified, OPHD recommends that waterbody mangers contact OPHD to determine exactly which toxins could be involved. Taxonomy for many types of cyanobacteria is currently being revised. This guidance reflects taxonomy as of 1/2015.

The primary cyanotoxins of concern in Oregon are microcystin and anatoxin because they have been the toxins most frequently tested and detected. However, cylindrospermopsin has been found above OPHD guideline values and saxitoxin has been detected in Oregon. OPHD requires testing for other cyanotoxins listed in Table B-1 to issue and lift advisories when genera reported that produce those toxins are present. Health advisories are not issued solely for algal production of lipopolysaccharides (LPS) as these compounds are produced by most algal species and exposure to LPS compounds typically produce mild, self-limiting rashes in people.

Microcystin

Background

Microcystins are the most commonly detected cyanotoxin in the world. Cyanobacteria known to produce microcystins include *Microcystis, Planktothrix, Oscillatoria, Nostoc, Dolichospermum, Anabaenopsis* and *Hapalosiphon*. Microcystins are cyclic heptapeptides with about 60 known structural variants (Rinehart et al., 1994). These variations have significant influence on the toxicity and physio-chemical properties of the toxin. The most studied variant is microcystin-LR.

The mechanism of toxicity of microcystins is the inhibition of protein phosphatases which can cause internal hemorrhaging of the liver. While the inhibition of protein phosphatases may be generally cytotoxic, the microcystins primarily target liver cells since they enter cells through a bile acid carrier most abundant on liver cells.

Exposure to microcystin has the potential to cause acute and chronic injury, depending on dose and duration of exposure. Sub-acute damage to the liver is likely to go unnoticed up to levels that are near severe acute damage (Chorus et al., 2000). Two aspects of chronic damage include progressive injury to the liver and tumor-promoting capacity. Microcystins alone have not been classified as carcinogenic. However, microcystins are considered to be tumor promoters based on studies in mice (Falconer and Buckley, 1989).

Most of the mammalian poisonings from the ingestion of microcystin have involved livestock. Symptoms reported from cattle that were exposed to *Microcystis aeruginosa* include generalized weakness, hyperthermia, anorexia, diarrhea, pale mucous membranes, mental derangement, muscle tremors, coma and death within a few days (Short and Edwards, 1990). Symptoms reported from British military recruits exposed to a bloom of *M. aeruginosa* during an exercise included abdominal pain, vomiting, diarrhea, sore throat, blistering of the mouth and pneumonia (Turner et al., 1990).

OPHD used a 28-day rat study (Heinze, 1999) as the critical study for determining a tolerable daily intake (TDI). In this study, researchers treated rats with purified microcystin LR in drinking water for 28 days then measured several endpoints. The Heinze study identified a lowest observable adverse effect level (LOAEL) of 50 µg/kg-day.

Provisional Tolerable Daily Intake

HABS used the LOAEL identified in the Heinze study (Heinze, 1999) described above (50 µg/kg-day) to derive a provisional TDI of 0.05 µg/kg-day as follows:

$$\mathrm{TDI} = \frac{\mathrm{LOAEL}}{\mathrm{UF}}$$

Where:

TDI = Tolerable Daily Intake (0.05 µg/kg-day)
LOAEL = Lowest Observable Adverse Effect Level (50 µg/kg-day)
UF = Uncertainty Factors (1,000 Total = 10 for LOAEL to NOAEL adjustment *

10 for interspecies variability * 10 for individual variability)

This TDI is intended for use with acute or short-term exposure scenarios and may not be protective for chronic or long-term exposures. This recommended TDI should be considered provisional and will be updated to conform to federal standards when they are issued or whenever additional toxicological information becomes available.

Additional support for this TDI: The TDI developed by WHO (0.04 µg/kg-day) based on the Fawell, study (Fawell et al., 1999a) is very similar to the provisional acute value (0.05 µg/kg-day) proposed here. OEHHA's selection (CalEPA, 2012) of the Heinze study (Heinze, 1999) also supports OPHD's decision to use the same study. A chronic (18 month) mouse toxicity study of microcystin LR in drinking water identified a NOAEL of 3 µg/kg-day (Ueno et al., 1999), similar to the 5 µg/kg-day NOAEL based on the Heinze study OPHD used to develop this provisional TDI.

<u>Summary</u>

Based on the TDI calculated above, the guideline value for microcystin in recreational water bodies is 10 µg/L.

Additional support for this recreational guideline value: OPHD's recreational water guideline (10 µg/L) is the same as the upper limit of "mild and/or low probability of adverse health effects" suggested by the WHO (Chorus and Bartram, 1999). Illinois also has a recreational guideline value of 10 µg/L (USEPA, 2014), slightly higher than the Washington State guideline of 6 µg/L (USEPA, 2014), which is also shared by Vermont and Virginia (USEPA, 2014).

Indiana and Kansas have tiered systems that use 4 µg/L as a threshold for recreational activities and 20 µg/L as a threshold for any water contact (USEPA, 2014). Ohio also has a tiered system using 6 and 20 µg/L as the guideline values (USEPA, 2014). Iowa, Nebraska, Oklahoma, and Texas use a 20 µg/L value (USEPA, 2014). Massachusetts and Rhode Island use 14 µg/L as a recreational guideline value for microcystin (USEPA, 2014). OPHD's value is 12.5 times greater than California's recreational value of 0.8 µg/L (USEPA, 2014). This difference is due to eliminating the uncertainty factor for database limitations from derivation of the TDI.

The primary limitation in the database relates to chronic toxicity. Because OPHD only intends to apply these guideline values in acute or short-term exposure scenarios, there is no extrapolation from acute to chronic toxicity. Therefore, OPHD considered the uncertainty factor for database limitations to be unnecessary.

Anatoxin-a

<u>Background</u>

OPHD reviewed available literature on the toxicology of anatoxin-a (Astrachan et al., 1980; Astrachan and Archer, 1981; Fawell and James, 1994; Chorus and Bartram, 1999; Fawell et al., 1999b; Duy et al., 2000; Rogers et al., 2005; Codd et al., 2005; Falconer and Humpage, 2005; van Apeldoorn et al., 2007; Burch, 2008; Pegram et al., 2008) as well as accepted and proposed threshold values used in other governmental jurisdictions (New Zealand Ministry of Health, 2002; USEPA, 2006; Washington Department of Health, 2008).

OPHD selected a study conducted by Fawell et al. (Fawell and James, 1994; Fawell et al., 1999b) as the critical study for derivation of a TDI. In this study, groups of 10 male and 10 female mice were orally treated with anatoxin-a every day for 28 days at 4 doses (0, 100, 500, and 2,500 μg/kg-day). The mice were observed for health effects over the course of the experiment and many health-related endpoints and physiological parameters were measured (Fawell and James, 1994; Fawell et al., 1999b).

Three animals died during the study. One of the deaths was not related to treatment but rather resulted from animals fighting in their cages. Two of the deaths, one at 500 μg/kg-day and one at 2,500 μg/kg-day, could have been related to treatment. None of the surviving animals had any observable adverse health effects. Therefore, OPHD selected 100 μg/kg-day as the no observable adverse effect level (NOAEL).

Provisional Tolerable Daily Intake

OPHD used the NOAEL identified in the Fawell et.al. study (Fawell and James, 1994; Fawell et al., 1999b) described above (100 μg/kg-day) to derive a provisional TDI of 0.1 μg/kg-day as follows:

$$\mathrm{TDI} = \frac{\mathrm{NOAEL}}{\mathrm{UF}}$$

Where:

TDI = Tolerable Daily Intake (0.1 μg/kg-day)
NOAEL = No Observable Adverse Effect Level (100 μg/kg-day)
UF = Uncertainty Factors (1,000 Total = 10 for interspecies variability * 10 for Individual variability * 10 for limitations in the database)

This TDI is intended only for use in acute or short-term exposure scenarios because the toxicity study upon which this TDI is based was short-term. Because most exposures in Oregon are acute or short-term, an acute or short-term TDI is the most useful.

OPHD applied a total uncertainty factor of 1,000. This number is a composite of 3 types of uncertainty about this TDI. First, the critical study was conducted in mice, which may have physiological differences in the way they absorb, distribute, metabolize and excrete anatoxin-a relative to humans. Mice may also be more or less sensitive to anatoxin-a toxicity than humans. Therefore, an uncertainty factor of 10 was applied to account for these potential interspecies differences in sensitivity to anatoxin-a.

Second, humans could have considerable individual variability in their sensitivity to anatoxin-a. For example, a child may be more sensitive than an adult or people with certain genetic traits may be more sensitive than the general population. Therefore, another uncertainty factor of 10 was applied to account for this individual variability. Finally, OPHD applied an additional uncertainty factor of 10 due to limitations in the database. Very few applicable studies have been conducted to identify dose-response relationships to anatoxin-a administered orally. Therefore, this uncertainty factor accounts for the possibility that additional studies in the future may reveal that anatoxin-a is more toxic than has been suggested in the currently available literature.

This recommended TDI should be considered provisional because of the paucity of toxicity data. OHA will update this TDI when more toxicity information becomes available.

Additional studies supporting this TDI: OPHD only identified two primary studies that employed oral administration of anatoxin-a: the Fawell, et.al. study selected as the critical study (Fawell and

James, 1994; Fawell et al., 1999b), and an older study conducted by Astrachan, et al. (Astrachan et al., 1980; Astrachan and Archer, 1981).

Independent reviews (Duy et al., 2000; Codd et al., 2005) of this Astrachan, et al. study have derived a TDI of 0.51 µg/kg-day, a value similar within a factor of 5 to the TDI selected (0.1 µg/kg-day). California's Environmental Protection Agency (CalEPA) has proposed an oral reference dose of 0.5 µg/kg-day (CalEPA, 2012), a value similar within a factor of 5 to the TDI selected here.

Other toxicity studies (Rogers et al., 2005) have been conducted using non-oral (mainly intraperitoneal injection) routes of exposure. Because human exposures to anatoxin-a in Oregon is expected to be primarily through ingestion, either in drinking water or accidental ingestion of surface water while recreating, OPHD only considered studies using the oral route of exposure.

Provisional Recreational Water Guideline Value

OPHD used the TDI of 0.1 µg/kg-day to derive a provisional recreational water guideline value of 20 µg/L:

$$\text{Guideline Value } = \frac{\text{TDI} \times \text{BW}}{\text{IR}}$$

Where:

Guideline Value = 20 µg/L
TDI = Tolerable Daily Intake (0.1 µg/kg-day)
BW = Body weight (20 kg)
IR = Ingestion rate (0.1 L/day)

OPHD used a body weight of 20 kg to represent a child. The ingestion rate (IR) was based on guidance from the Agency for Toxic Substances and Disease Registry (ATSDR) for incidental ingestion of surface waters, in which 0.05 L is accidentally ingested per one-hour event (ATSDR, 2005). For this guidance, it was assumed that a child might swim up to two hours in a single day.

This recreational water guideline value is based on a provisional TDI. Therefore, this guideline value should also be considered provisional and subject to change should the provisional TDI be updated to accommodate new scientific information.

Additional support for this recreational guideline value: CalEPA has also proposed a recreational water guideline value for swimmers derived using a higher TDI (2.5 µg/kg-day). However, the result (90 µg/L) (CalEPA, 2012) is similar, within a factor of 4.5 to the recreational water guideline value proposed for Oregon (20 µg/L). Washington State Department of Health adopted 1 µg/L as their guidance value for recreational water (USEPA, 2014). Ohio has a recreational guideline value of 80 µg/L with a no contact advisory at 300 µg/L (USEPA, 2014). Vermont has a guideline value of 10 µg/L for anatoxin-a (USEPA, 2014).

Summary

OPHD adopted health-based guideline values for anatoxin-A:

- Tolerable Daily Intake: 0.1 µg/kg-day
- Recreational Water Advisory Guideline Value: 20 µg/L

As noted above, very few studies have been done to quantify the oral dose-response to anatoxin-a. Therefore, these guideline values should be viewed as provisional and subject to revisions pending further research relevant to anatoxin-a toxicity.

Saxitoxins

Background

Saxitoxins (STXs) are a family of biological toxins associated with paralytic shellfish poisoning (PSP). This family includes saxitoxin (STX), neosaxitoxin (neoSTX), gonyautoxins, (GTX), C-toxins (C), 11-hydroxy-STX and decarbamoylsaxitoxins (dcSTXs)(van Apeldoorn et al., 2007). Because individual STXs vary in their toxicity, the European Food Safety Authority (EFSA) developed toxic equivalency factors (TEFs), based on toxicity in mice, so individual toxin concentrations can be considered relative to the toxicity of STX (EFSA, 2009). The proposed TEFs are: STX = 1, NeoSTX = 1, GTX1 = 1, GTX2 = 0.4, GTX3 = 0.6, GTX4 = 0.7, GTX5 = 0.1, GTX6 = 0.1, C2 = 0.1, C4 = 0.1, dc-STX = 1, dc-NeoSTX = 0.4, dc-GTX2 = 0.2, GTX3 = 0.4, and 11-hydroxy-STX = 0.3 (EFSA, 2009).

OPHD adopted these TEFs as the method for reporting STX-equivalents (STX-eq) results for public health analysis in Oregon. Most labs report total saxitoxins, which is also acceptable. Previously few waterbody managers tested for this cyanotoxin because it was considered an insignificant threat in the Northwest. However from 2009 to 2011, 4 of 30 Washington State lakes sampled tested positive for saxitoxin (Hardy and Farrer, 2011).

Given the documented presence of saxitoxin in Washington, it was important to determine whether this cyanotoxin was also present in Oregon. Since development of guideline values for saxitoxins in recreational waters by OPHD, this toxin has been detected in Oregon waters. OPHD asks water body managers to provide saxitoxin data when a waterbody contains taxa of cyanobacteria associated with this toxin.

EFSA established an acute RfD for STX-eq of 0.5 µg STX-eq/kg-day (EFSA, 2009). This acute RfD is based on available intoxication reports in humans across the European population. This acute RfD represents an estimated NOAEL.

Provisional Tolerable Daily Intake

OPHD used the RfD/NOAEL described above (0.5 µg/kg-day) to derive a provisional TDI of 0.05 µg/kg-day as follows:

$$\mathrm{TDI} = \frac{\mathrm{NOAEL}}{\mathrm{UF}}$$

Where:

TDI = Tolerable Daily Intake (0.05 µg/kg-day)
NOAEL = No Observable Adverse Effect Level (0.5 µg/kg-day)
UF = Uncertainty Factors (10 for limitations in the database).

This TDI is based on an acute toxicity study, so it is only applicable to acute or short-term exposure scenarios. OPHD applied a total uncertainty factor of 10 for database limitations[2]. This is the only study of its kind for saxitoxin and additional studies may find a lower RfD.

[2]OPHD did not originally apply the uncertainty factor for database limitations to the TDI for saxitoxins. Application of this uncertainty factor dropped OPHD's previous TDI and all guideline values based on that TDI (recreational water and drinking water guideline values) by a factor of 10. OPHD applied the database limitation uncertainty factor in this revision in keeping with the Ohio EPA, which first applied this uncertainty factor in 2014.

For humans, no uncertainty factor for interspecies variability was needed since the data were from human illnesses. OPHD also did not apply an uncertainty factor for individual variability since the EFSA study covered the general population which included sensitive individuals.

Provisional Recreational Water Guideline Value

Using this TDI (0.05 µg/kg-day), OPHD calculated a recreational water guideline value of 10 µg/L for SXT-eq:

$$\text{Guideline Value } = \frac{\text{TDI} \times \text{BW}}{\text{IR}}$$

Where:

Guideline Value = 10 µg STX-eq/L
TDI= Acute oral reference dose (0.05 µg STX-eq/kg-day)
BW = Body weight (20 kg)
IR = Ingestion rate (0.1 L/day)

OPHD used a body weight of 20 kg to represent a child. An ingestion rate (IR) was based on guidance from the Agency for Toxic Substances and Disease Registry (ATSDR) for incidental ingestion of surface waters, in which 0.05 L is accidentally ingested per one-hour event (ATSDR, 2005). For this guidance, it was assumed that a child might swim up to two hours in a single day.

OPHD applies this SXT-eq guideline value to total saxitoxin results. This provisional recreational water guideline value is based on EFSA's acute RfD. This value is subject to change should additional toxicological information become available in the future.

Additional studies supporting recreational water guideline value: Washington also used EFSA's acute RfD as the basis for their recreational water guidance value of 75 µg STX-eq/L [18]. The difference in values is because Oregon used 20 kg as the assumed body weight of a child while Washington used 15 kg and Washington did not apply the uncertainty factor for database limitations to the EFSA acute RfD. Ohio uses a tiered system of 0.8 µg/L for recreational contact and 3 µg/L to avoid all contact [6]. Ohio also used the EFSA acute RfD but they applied an additional uncertainty factor of 10 for individual variability (Ohio EPA, 2014) where OPHD did not since the EFSA study included the general population including sensitive groups (EFSA, 2009).

Summary

OPHD adopted a recreational water advisory guideline value of 10 µg STX-eq/L for saxitoxins. As noted above, this guideline value should be viewed as provisional and subject to revisions pending further research relevant to STX toxicity.

Cylindrospermopsin

Background

Previously, few waterbody managers tested for this cyanotoxin because it had been considered an insignificant threat in the Northwest. However, in 2011, a water body in Washington tested positive for cylindrospermopsin (Hardy and Farrer, 2011). Since 2011, cylindrospermopsin has been detected in Oregon above the recreational guideline value established by OPHD. Given the documented presence of cylindrospermopsin in Washington and Oregon, OPHD asks waterbody managers to provide cylindrospermopsin data when a waterbody contains taxa of cyanobacteria associated with this toxin.

Provisional Tolerable Daily Intake

To develop a TDI for cylindrospermopsin, OPHD used the same study by Humpage et. al., 2003 that the EPA selected as the critical study in development of their 10-day Health Advisory for cylindrospermopsin. This 11-week study used male Swiss albino mice in which groups of mice were dosed with 0, 30, 60, 120, or 240 µg/kg-day (10 mice per dose group) of purified cylindrospermopsin by daily gavage. Authors monitored food and water consumption and body weights throughout the study. At nine weeks, authors conducted clinical exams with a focus on physiological and behavioral signs of toxicity. Near the end of the study an extensive panel of parameters was measured in serum and urine along with hematological endpoints. No deaths were reported in the study. Upon necropsy, organs were weighed and all tissues were examined histologically. The most sensitive endpoint observed was kidney weight, which increased in a dose-dependent manner starting at 60 µg/kg-day. The EPA selected 60 µg/kg-day from this study as the LOAEL and 30 µg/kg-day as the NOAEL [23].

Consistent with EPA's Health Advisory methodology, OPHD applied a total uncertainty factor of 300 to the NOAEL of 30 µg/kg-day. The total UF of 300 was a composite of an UF of 10 for interspecies variability, 10 for individual variability, and 3[3] for database limitations. OPHD used the NOAEL of 30 µg/kg-day to derive a provisional TDI of 0.1 µg/kg-day as follows:

$$\mathrm{TDI} = \frac{\mathrm{NOAEL}}{\mathrm{UF}}$$

Where:

TDI = Tolerable Daily Intake (0.1 µg/kg-day)
NOAEL = No Observable Adverse Effect Level (30 µg/kg-day)
UF = Uncertainty Factors (300).

Provisional Recreational Water Guideline Value

To derive a recreational water guideline value, OPHD applied exposure factors to the TDI derived above (0.1 µg/kg-day) as follows:

$$\text{Guideline Value} = \frac{\mathrm{TDI} \times \mathrm{BW}}{\mathrm{IR}}$$

Where:

Guideline Value = 20 µg/L
TDI = Oral reference dose (0.1 µg/kg-day)
BW = Body weight (20 kg)
IR = Ingestion rate (0.1 L/day)

OPHD used a body weight of 20 kg to represent a child. An ingestion rate (IR) was based on guidance from the Agency for Toxic Substances and Disease Registry (ATSDR) for incidental ingestion of surface waters, in which 0.05 L is accidentally ingested per one-hour event (ATSDR, 2005). For this guidance, it was assumed that a child might swim up to two hours in a single day.

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[3] The previous assessment of cylindrospermopsin included a database limitation factor of 10. An uncertainty factor of 3 was used in the current 10-day Health Advisory issued by the EPA's Office of Water on June 17, 2015. To be consistent with EPA guidance, OPHD adopted this uncertainty factor which resulted in an increase in the TDI from the previous value by an approximate factor of 3.

This provisional recreational water guideline value is based on an acute/subchronic TDI. There is little information in the toxicological literature about chronic exposures and resultant health outcomes. Therefore, this value should be considered provisional and subject to change and should only be applied to acute, short-term or subchronic exposure scenarios pending further guidance from the EPA or other federal agencies.

Additional studies supporting recreational water guideline value: The provisional guideline value is similar to those proposed by other governmental bodies. CalEPA proposed a value of 4 µg/L (CalEPA, 2012). The Department of Health for Washington State has proposed a recreational guideline value of 4.5 µg/L (Washington Department of Health, 2011). Ohio has a recreational guideline value of 5 µg/L with a no-contact advisory level of 20 µg/L (USEPA, 2014). These values are similar (within a factor of 10) to the provisional recreational water guideline value developed for Oregon (20 µg/L).

Summary

OPHD adopted 20 µg/L as a health-based guideline values for cylindrospermopsin in recreational water. As noted above, these guideline values should be viewed as provisional and subject to revisions pending further research relevant to cylindrospermopsin toxicity.

Appendix C: Exposure pathways

The primary pathway for exposure to cyanotoxins is ingestion of water. Dermal effects are possible from the lipopolysaccharides found on cell surfaces, however cyanotoxins are not likely to cross the skin barrier and enter the bloodstream. Inhalation and aspiration of toxin is possible, especially through activities where the toxin is aerosolized, such as water skiing or splashing.

Ingestion of water can occur through both incidental and intentional ingestion. The risk of incidental ingestion is particularly high for children playing in near-shore areas where scum tends to accumulate. Exposure levels can be broadly defined as high, moderate and low based on recreational activity (Table C-1).

Table C-1. Level of recreational activity (modified from Queensland Health, 2001)

Level of Exposure	*Recreational Activity*
High	Swimming, diving, water skiing
Moderate	Canoeing, sailing, rowing
Low to none	Fishing, pleasure cruising, picnicking, hiking

Two possible scenarios for human intentional ingestion of recreational water should be considered. One is lake water used for drinking or cooking purposes by campers and hikers. Boiling, filtering or treating contaminated water with camping equipment will not make it potable. The second risk for exposure occurs when people draw in-home water directly from a lake or river. Private treatment systems have not proven effective in removing algae toxins. This exposure information is addressed in all advisory news releases, educational materials and signs.

Public Drinking Water Systems

Drinking water is another exposure pathway of concern for cyanotoxins. Occasionally, cyanoHABs occur in waters that are drinking water sources. OPHD has developed provisional acute toxicity values for cyanotoxins in drinking water (Table C-2). Drinking water containing toxins above the acute values in Table C-2 could cause immediate harm to public health. Although these are not enforceable Maximum Contaminant Levels (MCLs), OPHD recommends that public water systems use them as “Do Not Drink” thresholds.

For information regarding these guidelines, contact OPHD at 971-673-0400 or HAB.health@state.or.us. For more guidance specific to drinking water system operators, visit: http://public.health.oregon.gov/HealthyEnvironments/DrinkingWater/Operations/Treatment/Pages/algae.aspx.

Table C-2.Provisional acute or short-term drinking water cyanotoxin toxicity values (µg/L)

Drinking Water Guidance Value:	*Anatoxin-a*	*Cylindrospermopsin*	*Microcystin*	*Saxitoxin*
Adults	3	3	1.6	1.6*
Ages 5 years and younger	0.7	0.7	0.3	0.3

Note: Rounding conventions are consistent with EPA’s 10-day Health Advisories

*OPHD’s previous drinking water guidance value for saxitoxin was 3 µg/L and was based on guidance used in other countries and not a TDI. This new drinking water value is based on the TDI established in Appendix B.

Table C-3 lists the exposure factors used to calculate drinking water guideline values using the TDIs established in Appendix B. The equation used to calculate drinking water guidelines is identical to the equation used to calculate recreational guideline values in Appendix B.

Table C-3. Exposure factors used to calculate drinking water guideline values

Parameter	Adults	Children 5 and younger
Body Weight	80 kilograms	---
Intake Rate	2.5 liters	---
Body Weight-Normalized Intake Rate	---	0.15 liters/kilogram-body weight per day

Note: OPHD adopted EPA's exposure factors used in their derivation of 10-day Health Advisories for microcystin and cylindrospermopsin and applied them to the TDIs OPHD derived for anatoxin-a and saxitoxins as well.

Fish Consumption

At this time, there is insufficient information to determine the risk of consuming fish caught in waters with a cyanoHAB. Studies have shown that toxins mainly accumulate in the liver and viscera of fish, and microcystin has been detected in the fillet (Vasconcelos, 1999; de Magalhaes et al., 2001; Kann, 2008; Washington Department of Ecology, 2010; Kann et al., 2011). At a minimum, organs and skin should be removed and discarded prior to cooking fillets and caution should be taken with shellfish as cyanotoxins have been shown to accumulate in edible tissue (Vasconcelos, 1999).

Risk to Animals

Animals are extremely sensitive to cyanotoxins. Routes of exposure are ingestion when pets and wildlife drink water from a harmful algae-filled lake or pond, lick their fur after swimming or eat dried cells that accumulate along the shoreline. If toxins are present when animals drink the water, the animals can become very ill and possibly die.

Because dogs are cyanotoxin sensitive animals and there have been confirmed dog deaths due to cyanoHABs, OPHD has developed dog-specific guideline values for cyanotoxins in recreational water (Table C-4).

Table C-4. Dog-specific guideline values for cyanotoxins in recreational waters (µg/L)

Dog Guidance Value:	*Anatoxin-a*	*Cylindrospermopsin*	*Microcystin*	*Saxitoxin*
	0.4	0.4	0.2	0.02

Note: All dog-specific guideline values have been changed in this revision because California EPA's estimate of the amount of water an exercising dog consumes per kilogram body weight was updated in 2012 (from

0.168 to 0.255 L/kg-day). Current dog-specific guideline values are now consistent with the California EPA update. The dog-specific value for saxitoxins was further modified by application of an uncertainty factor to the dog-specific TDI for interspecies differences in sensitivity between humans (the species in the critical study) and dogs.

OPHD does not intend to use these dog-specific guidelines values as the basis for public health advisories. Rather, they are offered as a resource to veterinarians and veterinary associations to use as appropriate. OPHD will use these values and potential exposure scenarios in discussions with individual veterinarians or pet owners to educate them on the vulnerability of pets to cyanotoxin exposures. Contact OPHD for details about the origin of these dog-specific values.

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