CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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MEMORANDUM

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FROM: Lauren Zeise, Ph.D.
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Lauren Zeise (May 3, 2021 16:14 PDT)

DATE: May 3, 2021

SUBJECT: RECOMMENDATION FOR INTERIM NOTIFICATION LEVELS FOR SAXITOXINS, MICROCYSTINS AND CYLINDROSPERMOPSIN

In response to a request by the State Water Resources Control Board (SWRCB), the Office of Environmental Health Hazard Assessment (OEHHA) is recommending health-based interim notification levels (NLs) for saxitoxins, microcystins and cylindrospermopsin in drinking water as shown in the table below. These chemicals are toxins produced by cyanobacteria (also known as blue-green algae) in surface waters of California. The values are based on OEHHA's review of health-based advisory levels currently available from national and international health agencies and the peer-reviewed scientific studies they considered. OEHHA is recommending that these NLs be used on an interim basis while it completes its review of the sizeable database of recent toxicity studies on these cyanotoxins and derives final recommendations.

Recommended interim notification levels for three cyanotoxins

Chemical	Notification level recommendation (µg/L)[1]	Duration	Health effect	Peer-reviewed study
Saxitoxins	0.6	1 day	Neurotoxicity	EFSA, 2009
Microcystins	0.03	up to 3 months	Decline in sperm number	Chen et al., 2011
Cylindrospermopsin	0.3	up to 3 months	Liver damage	Chernoff et al., 2018

[1] One microgram per liter (µg/L) is equal to one part per billion (ppb).

SAXITOXINS

Saxitoxins (STX) are biotoxins produced by marine dinoflagellates or fresh water cyanobacteria. Saxitoxins interfere with voltage-gated sodium channels in nerve cells (WHO, 2020a; EFSA, 2009). The effects of saxitoxins include:

- neurological effects: neurotoxicity is the main adverse effect of saxitoxin exposure in animals and humans (saxitoxins are known to cause numbness and tingling in the mouth or extremities, muscular weakness and paralysis, respiratory failure and death[1]);
- genotoxicity and carcinogenicity: very limited information is available regarding the genotoxicity and carcinogenicity of saxitoxins.

Data on other effects of saxitoxins are sparse. There are over 50 saxitoxin analogues. The toxicity of saxitoxin analogues are often expressed as saxitoxin equivalents (STXeq).

The European Food Safety Authority (EFSA, 2009) developed an acute reference dose of 0.5 µg STXeq/kg for saxitoxins. The reference dose from EFSA (2009) was based on an acute lowest-observed-adverse-effect level (LOAEL) of 1.5 µg STXeq/kg identified from an analysis of reported human case studies. In combination, there are more than 500 individuals in these studies and most effects observed were neurotoxic in nature. Because no adverse effects were observed at this dose level in many individual studies, EFSA (2009) believed the LOAEL of 1.5 µg STXeq/kg was very close to the no-observed-adverse-effect level (NOAEL), and therefore applied a factor of 3 for the extrapolation from LOAEL to NOAEL. EFSA (2009) did not apply any factor to cover sensitive individuals (EFSA, 2009).

The acute reference dose developed by EFSA (2009) was adopted by the World Health Organization (WHO, 2020a), the Washington State Department of Health (2011), Ohio Environmental Protection Agency (2016), and Oregon Health Authority (2015) in developing their drinking water or fresh water recreational guideline values for saxitoxins.

Arnich and Thiebault (2018) studied 143 individuals from 13 human studies. Dose-response modeling was conducted and the dose associated with symptoms in 10% of the exposed people was estimated to be 0.37 µg STXeq/kg. OEHHA's review of the modeling suggested the dose calculated in Arnich and Thebault (2018) was likely the result of the use of a non-representative comparison group in the modeling and therefore did not select it as the POD for developing a health-protective concentration. It is worth noting that the lowest LOAEL of 1.8 µg STXeq/kg observed from the studies

[1] This is also referred to as paralytic shellfish poisoning (PSP) although both drinking water and consumption of contaminated shellfish are exposure pathways.

in Arnich and Thebault (2018) supports the LOAEL of 1.5 µg STXeq/kg identified from EFSA (2009).

To derive a health-protective concentration for STX, OEHHA first calculated an acceptable daily dose (ADD, in µg/kg-day), which is the estimated maximum dose of a chemical that can be consumed by humans, including sensitive individuals, without toxic effects. It can be calculated using the equation below:

$$ADD = POD \div UF_{combined} \qquad \text{(Equation 1)}$$

where:

POD = point of departure, µg STXeq/kg or µg/kg-day;
$UF_{combined}$ = combined uncertainty factor, unitless.

OEHHA adopted the point of departure (POD) of 1.5 µg STXeq/kg from EFSA (2009) and applied a combined uncertainty factor ($UF_{combined}$) of 10. It includes a UF of $\sqrt{10}$ for extrapolating from LOAEL to NOAEL and a UF of $\sqrt{10}$ to account for sensitive individuals. Using Equation 1 and the parameters discussed, OEHHA calculated an ADD of 0.15 STXeq/kg.

The health-protective concentration (C, in µg/L) for saxitoxins in drinking water can be calculated by using the equation below:

$$C = (ADD \times RSC) \div DWI \qquad \text{(Equation 2)}$$

where:

ADD = acceptable daily dose, µg STXeq/kg or µg/kg-day
RSC = relative source contribution, unitless;
DWI = drinking water intake rate, L/kg-day.

The relative source contribution (RSC) represents the fraction of exposure to a chemical attributed to tap water, as part of the total exposure from all sources (including food and air). The daily water intake rate (DWI) is adjusted for body weight and is age specific. For this determination, OEHHA identified infants as the sensitive population because infants may be particularly sensitive to neurotoxicity and they have a higher drinking water intake rate adjusted for body weight than adults. OEHHA applied the DWI of 0.237 L/kg-day (OEHHA, 2012b) for infants 0 to 6 months of age and used an RSC of 1 because tap water is considered the only source of exposure for the reconstituted formula-fed infant. Using Equation 2 and the parameters described, OEHHA calculated a health-protective concentration of 0.6 µg/L, equivalent to 0.6 parts per billion (ppb), for STX.

Comparison of the health-protective concentration for saxitoxins and drinking water advisory levels from other health agencies

Agency (year)	Critical Study	Health Effect	ADD or Equivalent (µg/kg-day)	Drinking Water Level (µg/L)
OEHHA (2021)	EFSA, 2009	Neurotoxicity	0.15	0.6
WHO (2020a)	EFSA, 2009	Neurotoxicity	0.5	3
FAO (2004)	FAO, 2004	Neurotoxicity	0.7	--

Because the POD, adopted from EFSA (2009), is based on case reports of human poisoning through consumption of contaminated shellfish, OEHHA recommends a duration of one day for the health-protective concentration of 0.6 µg/L for STX.

MICROCYSTINS

Microcystins (MC) are biotoxins produced by fresh water and marine cyanobacteria. MC causes inhibition of protein phosphatases, leading to alterations in the cytoskeleton, oxidative stress, and apoptosis. Several subchronic and chronic animal studies in the scientific literature describe effects associated with oral exposure to the most common MC, MC-LR:

- liver effects: enlargement of liver, chronic inflammation, necrosis of hepatocytes (Ito et al., 1997, Fawell et al., 1999, He et al., 2017);
- lung effects: thickening of the alveolar septum, disruption of cell junctions, alveolar collapse and lung cell apoptosis (Li et al., 2016; Wang et al., 2016);
- serum profile changes: increase in transaminases, decrease in the level of total proteins (Fawell et al., 1999; He et al., 2017);
- effects on the nervous system: cognitive impairment, histological lesions, oxidative injury, inflammation in memory-related brain regions (Li et al., 2012; Li et al., 2014, Li et al., 2015);
- reproductive and developmental effects: decreased sperm number and motility, abnormal sperm morphology, histological lesions in the testes, testicular atrophy, change in serum hormone concentrations, negative impacts in the ovaries (Chen et al., 2011; Chen et al., 2016, Chen et al., 2017; Wu et al., 2015; Zhang et al., 2017);
- carcinogenicity: the International Agency for Research on Cancer (IARC, 2010) classified microcystin–LR as “possibly carcinogenic to humans” based on studies showing the promotion of preneoplastic lesions in rats.

These toxicity studies have been reviewed by federal and international governments for the purpose of deriving drinking water health advisory (HA) levels or standards for these compounds.

In 2012, OEHHA developed a reference dose (ADD-equivalent) of 0.0064 µg/kg-day for MC based on liver lesions reported by Heinze (1999) and calculated recommended limits for exposure while recreating in natural waters. In 2015, the US Environmental Protection Agency (US EPA) developed a 10-day drinking water HA level of 0.3 ppb for MC for infants through preschool-aged children, based on liver lesions (US EPA, 2015a,b).

The most recent comprehensive reviews that resulted in a water advisory level or standard for MC were published by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, 2019a) and WHO (2020b).

WHO (2020b) chose a liver toxicity endpoint while ANSES (2019a) used the more sensitive reproductive toxicity endpoints to derive a subchronic toxicity reference value (TRV) for MC-LR. MC has been reported to cause liver toxicity in humans (Vidal et al., 2017, Giannuzzi et al., 2011, Carmichael et al., 2001, Jochimsen et al., 1998) but reproductive endpoints are more sensitive. In 2019, ANSES chose Chen et al. (2011) as the critical study to develop a POD and a subchronic TRV protective against reproductive toxicity endpoints.

The effects of reduced sperm number and quality reported by Chen et al. (2011) are supported by several other reproductive toxicity studies at similar dose levels (Chen et al., 2016; Chen et al., 2017; Wu et al. 2015; Zhang et al. 2017). OEHHA reviewed the documents and process used by ANSES to choose their critical study and key effects and found both to be rigorous and sufficient for establishing a health-protective concentration for MC (using MC-LR as a surrogate). Therefore, OEHHA also selected Chen et al. (2011) as the critical study for development of a health-protective concentration for MC.

Chen et al. (2011) exposed 10 male mice/exposure group to 0, 1, 3.2, or 10 µg/L MC-LR in drinking water for 3 months and 6 months. Using default biological values[2] (US EPA, 1988), OEHHA calculated doses of 0, 0.25, 0.79, or 2.5 µg/kg-day and identified a NOAEL of 0.25 µg/kg-day based on decreased sperm count, decreased sperm motility, and increased sperm abnormality.

OEHHA determined the POD by fitting dose-response models to the data using US EPA's Benchmark Dose Software (BMDS version 3.2[3]). BMDS uses mathematical models to determine the dose (benchmark dose or BMD) that corresponds to a pre-determined level of response (benchmark response or BMR). For continuous data such

[2] Subchronic mouse body weight of 0.0316 kg and drinking rate of 0.0078 L/day
[3] Available at: https://www.epa.gov/bmds/benchmark-dose-software-bmds-version-3

as sperm counts, a BMR of 1 standard deviation (SD) from the control mean is typically used when there are no data to indicate what level of response is biologically significant.

OEHHA modeled the data for decreased sperm count at 3 and 6 months, reported by Chen et al. (2011), using a BMR of 1 SD from the control mean. To account for uncertainty in the data, the model also calculates the 95% lower confidence limit of the BMD, known as the BMDL (L stands for lower confidence limit). The models with the best fit[4] produced BMDLs of 0.1510 µg/kg-day and 0.2112 µg/kg-day for the 3- and 6-month exposure groups, respectively. The geometric mean of $BMDL_{1SD}$ values for 3 and 6 months, 0.1786 µg/kg-day, is used as the POD for sperm decline.

OEHHA calculated an ADD of 0.001786 µg/kg-day by using Equation 1 with the POD of 0.1786 µg/kg-day and a $UF_{combined}$ of 100. The combined UF comprised 10 for extrapolating from rodents to humans and 10 to account for variability between humans (OEHHA's default intraspecies UF of 30 was lowered to 10 because this endpoint is not relevant to pre-pubescent children, thus they do not need to be included in variability considerations). No uncertainty factor was applied for database deficiencies, because several studies support the critical study and the endpoint is sensitive.

A health-protective concentration of 0.03 µg/L was calculated for MC by using Equation 2 with the ADD of 0.001786 µg/kg-day, RSC of 1, and a lifetime weighted average DWI of 0.053 L/kg-day (OEHHA, 2012b). An RSC of 1 was used because food and air are not expected to contribute to MC exposure. Because the POD was based on sperm effects observed at 3 and 6 months, OEHHA recommends a duration of three months for the health-protective concentration of 0.03 µg/L, equivalent to 0.03 ppb, for MC.

[4] The models with the best fit (visual fit, lowest Akaike information criterion (AIC), and significant p-values for goodness of fit) were Exponential 4 for the 3-month data and Exponential 3 for the 6-month data.

Comparison of the health-protective concentration for microcystins and drinking water advisory levels from other health agencies

Agency (year)	Critical Study	Health Effect	ADD or Equivalent (µg/kg-day)	Drinking Water Level (µg/L)
OEHHA (2021)	Chen et al., 2011	Decline in sperm number	0.0018	0.03 (up to three months)
OEHHA (2012a)	Heinze, 1999	Liver lesions	0.0064[a]	--
ANSES (2019)	Chen et al., 2011	Decline in sperm number, motility and increase in abnormal sperm	0.001	--
USEPA (2015a,b)	Heinze, 1999	Liver lesions	0.05	0.3 (infants,[b] 10 days) 1.6 (children[c]/adults, 10 days)
WHO (2020b)	Fawell et al., 1999	Liver damage	0.04	1 (lifetime [d])

[a] The difference between the OEHHA (2012a) and USEPA (2015a,b) ADD-equivalent values is mainly due to OEHHA using a larger UF and a benchmark dose approach. The difference between OEHHA (2012a) and OEHHA (2021) is mainly due to using a more sensitive endpoint.

[b] Includes young children of pre-school age.

[c] Includes children above pre-school age.

[d] Lifetime level can be exceeded for about two weeks by up to 12 ug/L before treatment is implemented.

CYLINDROSPERMOPSIN

Cylindrospermopsin (CYN) can be present in surface waters during and after cyanobacterial blooms. Several subchronic and chronic animal studies describe effects associated with oral exposure to CYN (Humpage and Falconer, 2002; Sukenik et al., 2006; Chernoff et al., 2018):

- kidney effects: enlarged kidney, histological alteration, alteration of proximal tubules;
- liver effects: enlarged liver, substantial necrosis, inflammation, morphological and histological changes;
- biochemical effects: increased liver enzyme levels in the serum, decreased cholesterol and triglyceride levels;
- genotoxicity, and a potential for tumor initiation (ANSES, 2019b).

These toxicity studies have been reviewed by national and international health agencies for the purpose of deriving drinking water HA levels or standards for these compounds.

In 2012, OEHHA developed a reference dose (ADD-equivalent) of 0.033 µg/kg-day for CYN based on increased relative kidney weight reported by Humpage and Falconer (2002, 2003) and calculated recommended limits for exposure while recreating in natural waters. In 2015, US EPA developed a 10-day drinking water HA level of 0.7 µg/L for CYN for infants through preschool-aged children, based on an increase in relative kidney weight (US EPA 2015c,d).

The most recent comprehensive reviews that resulted in a water advisory level or standard for CYN were published by ANSES (2019b) and WHO (2020c).

WHO (2020c) chose the endpoint of increased relative kidney weight in mice with a NOAEL of 30 µg/kg-day (Humpage and Falconer, 2002, 2003), to calculate a drinking water advisory level of 0.7 µg/L. ANSES (2019b) pointed out several limitations in Humpage and Falconer (2002, 2003) and chose the endpoints of increased relative liver and kidney weights in male mice from Chernoff et al. (2018). ANSES determined that the LOAEL of 75 µg/kg-day from Chernoff et al. (2018) should be used as the POD for developing a subchronic TRV protective against impacts to the liver and kidney. An increase in absolute and/or relative liver and kidney weights has been reported by several studies (Humpage and Falconer, 2002, 2003; Reisner et al., 2004; Sukenik et al., 2006; Chernoff et al., 2018) and could be associated with increased biological parameters and histological changes that were also observed. Thus, the increases in the weight of these organs is degenerative rather than adaptive. OEHHA reviewed the documents and process used by ANSES to make their decision and found them to be rigorous and sufficient for establishing a health-protective concentration for CYN. Thus, OEHHA concurred with the ANSES determination and chose Chernoff et al. (2018) as the critical study.

Chernoff et al. (2018) exposed 18 to 20 mice (divided equally between males and females) per exposure group to 0, 75, 150, or 300 µg/kg-day CYN via gavage for 90 days. The LOAEL of 75 µg/kg-day is based on increased relative liver and kidney weights in male mice, correlated with biochemical (e.g., increase in serum levels of transaminases and alkaline phosphatases) and histological effects (e.g., inflammation and hepatic necrosis). Because a 10% increase in relative liver weight is generally accepted as biologically significant, OEHHA modeled the Chernoff et al. (2018) data for increased relative liver weight with BMDS using a BMR of 10% relative deviation. The best fitting model[5] produced a $BMDL_{10}$ of 17.39 µg/kg-day, which was selected as the POD.

OEHHA calculated an ADD of 0.0174 µg/kg-day by using Equation 1 with a POD of 17.39 µg/kg-day and a $UF_{combined}$ of 1,000, which includes a UF of 10 for extrapolating

[5] The model with the best fit (visual fit, lowest Akaike information criterion (AIC), and significant p-values for tests 1-4) for relative liver weight male mice was the Hill model, run with non-constant variance.

from rodents to humans, a UF of 30 to account for variability between humans, and a UF of √10 for database deficiencies.

A health-protective concentration of 0.3 µg/L was calculated by using Equation 2 with a lifetime weighted average DWI of 0.053 L/kg-day (OEHHA, 2012b) and an RSC of 1. An RSC of 1 was applied because food and air are not expected to contribute to CYN exposure. Because the POD was derived from a 90-day toxicity study, OEHHA recommends a duration of up to three months for the health-protective concentration of 0.3 µg/L, equivalent to 0.3 ppb, for CYN.

Comparison of the health-protective concentration for cylindrospermopsin and drinking water advisory levels from other health agencies

Agency (year)	Critical Study	Health Effect	ADD or equivalent (µg/kg-day)	Drinking Water Level (µg/L)
OEHHA (2021)	Chernoff et al., 2018	Increased relative liver weight	0.017	0.3 (up to three months)
OEHHA 2012	Humpage and Falconer, 2002, 2003	Increased relative kidney weight	0.033[a]	--
ANSES (2019b)	Chernoff et al., 2018	Increased relative liver and kidney weights	0.14	--
USEPA (2015c,d)	Humpage and Falconer, 2002, 2003	Increased relative kidney weight	0.1	0.7 (infants,[b] 10 days) 3 (children[c]/adults, 10 days)
WHO (2020c)	Humpage and Falconer, 2002, 2003	Increased relative kidney weight	0.03	0.7 (lifetime[d])

[a] The difference between the OEHHA (2012) ADD-equivalent and that of US EPA (2015c,d) is mainly due to OEHHA using a larger UF and a benchmark dose approach.

[b] Includes young children of pre-school age.

[c] Includes children above pre-school age.

[d] Lifetime level can be exceeded for about two weeks by up to 3 ug/L before treatment is implemented.

RECOMMENDATION

Based on an initial review of the currently available health-based advisory levels and regulatory standards for STX, MC and CYN, OEHHA recommends that SWRCB adopt the health-protective concentrations of 0.6 µg/L for STX, 0.03 µg/L for MC and 0.3 µg/L for CYN, based on the studies and endpoints chosen by WHO (2020a) and ANSES (2019a,b), as interim NLs while OEHHA completes a review of the substantial database

of recent studies on cyanotoxins and derives final recommended drinking water NLs for these chemicals.

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