EPA Health Advisories for Cyanotoxins

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Stakeholder Meeting
Overview of Harmful Algal Blooms

• Algal blooms are present naturally in marine and freshwater ecosystems

• In freshwater, cyanobacteria or blue-green “algae”, are the most common; some produce highly potent toxins. These blooms are known as Harmful Algal Blooms (HABs)

• One species can make multiple toxins. Different species can produce the same toxins. Toxins are not always produced. This makes it difficult to know if a bloom is toxic just by looking at it

• Toxins can be within or outside of cells. If they are within cells, toxins are released into the water when the cell walls are broken. Some aquatic herbicides and drinking water treatment process cause cells to break

• HABs tend to occur in late summer and fall in temperate zones and potentially year-round in tropical and subtropical zones and are fed by excess nutrients
Causes of Nutrient Pollution

- Nitrogen and phosphorus support the growth of algae and aquatic plants, which provide food and habitat for fish, shellfish and smaller organisms that live in water.
- But when too much nitrogen and phosphorus enter the environment – usually from human activities – algae, including HABs, can grow excessively.
- Very recent work has suggested that high concentrations of nitrogen are linked to increased concentrations of microcystins.
What impacts are associated with HABs?

• The prevalence of HABs in freshwater is increasingly reported in the U.S. and worldwide

• Algal blooms can cause:
  • Hypoxia, leading to fish kills
  • Taste and odor problems in treated drinking water
  • Toxins at levels that may be of concern for human health
  • Loss of drinking water, recreational/fishing uses

• HABs have caused economic losses to the fishing and recreation industries while increasing costs for managing and treating potable water supplies

• Presence in finished drinking water
  • 2013-2014: detection of > 1 µg/L total microcystins in finished water in drinking systems on western Lake Erie
  • City of Toledo, OH (population ~500,000) issued a “do not drink” advisory
National Monitoring of Freshwater HABs

EPA’s National Lakes Assessment conducted the first-ever national study of algal toxins in lakes.

- Microcystins were found to be present in about one-third of lakes
- Microcystin concentration exceeded the WHO guideline for moderate or high risk of recreational exposure in 1% of lakes.
- Wetlands, Rivers and Streams surveys included microcystins and 2015 Coastal (marine and Great Lakes) survey will include several microcystins and other algal toxins

State monitoring efforts:

- Are expanding, with greater awareness of the toxic effects of HABs
- Tend to focus on priority waters used for recreational and drinking water
- Typically sample seasonally and when blooms are observed

EPA has placed 3 cyanotoxins on the Safe Drinking Water Act’s Contaminant Candidate List (CCL):

- CCl 1 and CCL 2: Cyanobacteria, other freshwater algae, and their associated toxins
- CCL 3 and Draft CCL4: Cyanotoxins (including microcystin-LR, cylindrospermopsin, and anatoxin-a)
Exposure and Health Effects of Cyanotoxins

• Potential routes of exposure:
  • Dermal contact
  • Inhalation of toxins in aerosols
  • Ingestion during recreational activities
  • Consumption in drinking water and food

• Health effects related to exposure to cyanotoxins in freshwater:
  • Liver and kidney toxicity
    • Microcystins and cylindrospermopsin
    • Symptoms of acute exposure: Vomiting, diarrhea, fever
  • Neurotoxic (affects the nervous system)
    • Anatoxin-a and Saxitoxin
    • Symptoms of acute exposure: paralysis, seizure
  • Dermatoxic (affects the skin)
    • Lipopolysaccharides and Lyngbyatoxin (and others)
    • Symptoms of acute exposure: Irritation to eyes, ears, throat, rashes, skin lesions
## International Cyanotoxin Drinking Water Guidelines

<table>
<thead>
<tr>
<th>Authority/Country/State</th>
<th>Microcystin Value (lifetime)</th>
<th>Cylindrospermopsin Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization (WHO), 1998*</td>
<td>1 μg/L MC-LR</td>
<td>-</td>
</tr>
<tr>
<td>Health Canada, 2002</td>
<td>1.5 μg/L MC-LR</td>
<td>-</td>
</tr>
<tr>
<td>Brazil, 2005</td>
<td>1 μg/L MC-LR</td>
<td>15 μg/L</td>
</tr>
<tr>
<td>Australia, 2009</td>
<td>1.3 μg/L MC-LR TE</td>
<td>1 μg/L</td>
</tr>
<tr>
<td>New Zealand, 2009</td>
<td>1 μg/L MC-LR TE</td>
<td>1 μg/L</td>
</tr>
<tr>
<td>Singapore, Poland, Norway, Netherlands, Korea, Japan, Italy, Germany, France, Finland, Denmark, Czech Republic, China</td>
<td>1 μg/L MC-LR</td>
<td>-</td>
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</tbody>
</table>

- WHO will re-evaluate their guideline based on EPA’s assessments
EPA Cyanotoxin Toxicity Assessment: Microcystins

• Most studied and widespread cyanobacterial toxin (microcystin-LR)
• More than 100 congeners exist
• The toxicological database is almost exclusively limited to data on the LR congener

Noncancer Effects
• Human data suggest that the liver is the target organ of toxicity
  • Acute recreational exposure to cyanobacterial blooms (including microcystin-producing genera) has been reported to lead to allergic reactions, including hay fever-like symptoms; adverse skin reactions; and gastrointestinal distress

  • Elevated liver enzymes have been measured in humans served by a public water supply contaminated with a bloom of *M. aeruginosa*

  • Intravenous exposure to microcystins caused an outbreak of illness in 116 patients at a renal hemodialysis clinic in Caruaru, Brazil in 1996; 52 patients died of acute liver failure

  • These data are limited by the potential co-exposure to other toxins and microorganisms and by the lack of quantitative information
EPA Cyanotoxin Toxicity Assessment: Microcystins

• Chronic studies in laboratory animals are limited (i.e., inadequate number of doses utilized and endpoints evaluated) and have not reported significant effects

• Acute and sub-chronic studies in laboratory animals have demonstrated toxicity in the liver, kidney, and testes

  Liver Effects- increased liver weight, hepatic hemorrhage, increased serum enzymes (ALP and LDH) (most sensitive)

  Kidney Effects- vascular, glomerular and tubular effects

  Reproductive Effects- lesions in the testes, and decreased sperm counts and motility. Also few studies have shown female hormonal changes (FSH, LH) and potential changes of estrous cycle, and ovulation

  Developmental Effects- Maternal mortality and reduced fetal body weight
Cancer

- Several human epidemiological studies have reported an association between consumption of drinking water containing cyanobacteria and microcystins and liver or colon cancer in certain areas of China
  - The use of a surface drinking water supply was used as a surrogate for exposure to microcystins. Individual exposure to microcystins was not estimated
  - It is not clear whether these studies adequately controlled for confounding factors

- No chronic cancer bioassays designed to evaluate dose-response for the tumorigenicity of microcystins following lifetime exposures are available

- Applying the EPA 2005 Guidelines for Carcinogen Risk Assessment, there is inadequate information to assess the carcinogenic potential of microcystins

- At the request of EPA, the NTP is developing a research program to address some of the knowledge gaps regarding microcystin toxicity. Additional research will be done by EPA’s Office of Research and Development.
### EPA Cyanotoxin Toxicity Assessment: Cylindrospermopsin

#### Noncancer Effects
- Human data on oral toxicity of cylindrospermopsin suggests liver and kidney as the target organs
  - Reports of a hepatoenteritis-like outbreak (mostly children) in Palm Island, Australia in 1979 were attributed to consumption of drinking water with a bloom of *C. raciborskii*, an algae that can produce cylindrospermopsin. Symptoms included fever, headache, vomiting, bloody diarrhea, hepatomegaly and kidney damage.
  - Data are limited by lack of quantitative information.
- Animal studies of oral exposure to cylindrospermopsin focused on hepatic and renal toxicity
  - No chronic studies were identified.
  - Acute, short-term, and subchronic studies demonstrate the liver and kidney as target organs.
    - **Kidney Effects**- increase in kidney weight, decrease in the urinary protein/creatinine ratio and red blood cell changes (most sensitive)
    - **Liver Effects**- Lipid infiltration in liver and increased liver weight (only in high doses)

#### Cancer
- Applying the 2005 EPA Guidelines for Carcinogen Risk Assessment, there is *inadequate information to assess the carcinogenic potential* of cylindrospermopsin
  - No human or chronic cancer bioassays in laboratory animals are available
EPA Health Advisories for Cyanotoxins

• 2012 - Joint effort with Health Canada
  • Update of the 2002 Health Canada DW Guideline for microcystins
  • Development of EPA Health Advisories (HAs) for Cyanotoxins
• 2013 - Literature Review and Health Effects Support Documents (HESD) for microcystins, cylindrospermopsin and anatoxin-a development
  • Comprehensive review of the health effects information
  • Provides the health effects basis for the development of HAs
• 2014/15 - External Peer Reviews HESDs for microcystins, cylindrospermopsin and anatoxin-a
  • Peer reviewers affirmed data are inadequate to develop an HA for anatoxin-a
  • Peer reviewers confirmed data are adequate to develop HAs for microcystins and cylindrospermopsin
• 2015 - Health Advisories for microcystins and cylindrospermopsin
EPA Health Advisories

- Informal non-regulatory guidance for unregulated drinking water contaminants to assist federal, state and local officials, and public water systems in protecting public health

- Includes:
  - Background, Sources and Occurrence, Environmental Fate, Toxicokinetics, Summary of Health Effects
  - Conceptual Model
  - Quantification of toxicological effects (Health Advisory values)
  - Effects characterization
  - Recommended analytical methods and treatment technologies

- Short term HA: one-day and ten-day
  - Based on exposure to an infant

- Chronic HA: lifetime
  - Based on adult exposure
Health Advisories Quantification

• The Ten-day HA:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL or BMDL}) \times \text{BW}}{\text{UF} \times \text{DWI}}$$

• Where:
  • NOAEL or LOAEL or BMDL= No- or Lowest-Observed-Adverse-Effect Level or Bench Mark Dose Level (in mg/kg bw/day) from a study of appropriate duration
  • BW = Body weight
  • UF = Uncertainty factor in accordance with EPA guidelines (intra-human variability, interspecies variability, use of a exposure duration less than the duration of concern, use of a LOAEL rather than a BMDL or NOAEL, deficiencies in the database)
  • DWI = Drinking Water Intake

• Represents:
  • Concentration in drinking water at or below which no adverse non-carcinogenic effects are expected for a ten-day exposure
Children’s Exposure to Cyanotoxins

• Bottle-fed infants consume large amounts of drinking water compared to their body weight

• Infants can be exposed when their formula is prepared with tap water containing cyanotoxins

• Exposure to children < 12 months is 5 times higher than for adults > 21 years old, on a body-weight basis

• At six years and older, exposure on a body-weight basis is similar to that of an adult.

• Infant-specific exposure factors are available from U.S. EPA’s Exposure Factors Handbook (2011)
EPA Drinking Water HAs for Microcystins

• **Stressor:** microcystin-LR, considered a surrogate for all microcystins
  • Data are most complete
  • LR is the same or more toxic than other congeners, based on available data

• **Exposure pathway:** oral ingestion of drinking water

• **Most sensitive endpoint:** liver toxicity expressed as increase in liver weight and an increase in liver enzymes in the blood

• **Exposed life stage and population:** infants and adults

• **Exposure duration:** 10-day value
  • Short term exposure is more consistent with expected exposure pattern
  • No lifetime or carcinogenic value derived
EPA Drinking Water HAs for Microcystins

- **10 day HA for bottle-fed infants**

\[
HA_{10\text{ day}} = \frac{50 \mu g/Kg/d}{1000 \times 0.15L/kg/d} = 0.3 \mu g/L
\]

<table>
<thead>
<tr>
<th>LOAEL</th>
<th>50 µg/kg/day</th>
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<tbody>
<tr>
<td>UF</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>intraspecies:10; interspecies: 10; LOAEL to NOAEL: (10^{0.5}); database: (10^{0.5})</td>
</tr>
<tr>
<td>BW/DW</td>
<td>0.15L/kg/day</td>
</tr>
</tbody>
</table>

- **10 day HA for adult**

\[
HA_{10\text{ day}} = \frac{(50 \mu g/Kg/d) \times (80Kg)}{1000 \times 2.5L/d} = 1.6 \mu g/L
\]

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<tr>
<th>LOAEL</th>
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<tr>
<td>BW</td>
<td>80 Kg</td>
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<td>1000</td>
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<td></td>
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</tr>
<tr>
<td>DW</td>
<td>2.5 L/d</td>
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</tbody>
</table>
EPA Microcystins Health Advisory by Age Group

- School-age children and adults: 1.6 µg/L
- Bottle fed infants up to school age children: 0.3 µg/L

Age Range:
- Birth to <3 months
- 3 to <6 months
- 6 to <12 months
- 1 to <2 years
- 2 to <3 years
- 3 to <6 years
- 6 to <11 years
- 11 to <16 years
- 16 to <18 years
- 18 to <21 years
- > 21 years
EPA Drinking Water HAs for Cylindrospermopsis

- Stressor: cylindrospermopsis
- Exposure pathway: oral ingestion of drinking water
- Most sensitive endpoint: kidney damage expressed by increased weight of kidney and decreased urinary protein
- Exposed life stage and population: children and adults
- Exposure duration: 10-day value
  - Short term exposure is more consistent with expected exposure pattern
  - No lifetime or carcinogenic value
EPA Drinking Water HAs for Cylindrospermopsin

- 10 day HA for bottle-fed infants

\[ \text{HA}_{10\text{day}} = \frac{30 \mu g/\text{Kg/d}}{300 \times 0.15\text{L/kg/d}} = 0.7 \mu g/L \]

- 10 day HA for adult

\[ \text{HA}_{10\text{day}} = \frac{(30 \mu g/\text{Kg/d}) \times (80\text{Kg})}{300 \times 2.5\text{L/d}} = 3 \mu g/L \]

- NOAEL = 30 \mu g/kg/day
- UF = 300
  (intraspecies: 10; interspecies: 10; database: \text{10}^{0.5})
- BW/DW = 0.15\text{L/kg/day}
- NOAEL = 30 \mu g/kg/day
- BW = 80 \text{Kg}
- UF = 300
  (intraspecies: 10; interspecies: 10; database: \text{10}^{0.5})
- DW = 2.5 \text{L}
EPA Cylindrospermopsin Health Advisory by Age Group

- School-age children and adults: 3 µg/L
- Bottle fed infants up to school age children: 0.7 µg/L

Age Range:
- birth to <3 months
- 3 to <6 months
- 6 to <12 months
- 1 to <2 years
- 2 to <3 years
- 3 to <6 years
- 6 to <11 years
- 11 to <16 years
- 16 to <18 years
- 18 to <21 years
- > 21 years
EPA Health Advisory Summary

10-Day Health Advisory Values:
- Microcystins and cylindrospermopsin
- Exposure Pathway: oral ingestion of drinking water

<table>
<thead>
<tr>
<th>chemical</th>
<th>10-day advisory</th>
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<tbody>
<tr>
<td></td>
<td>Bottle-fed infants and pre-school children</td>
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<tr>
<td>microcystins</td>
<td>0.3 µg/L</td>
</tr>
<tr>
<td>cylindrospermopsin</td>
<td>0.7 µg/L</td>
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</table>

For those systems who choose to do so, having these two values provides an opportunity to take actions to reduce exposure in finished drinking water by refining treatment processes to minimize public health risks.
Next Steps

• Publish before summer 2015
  • Health Effects Support Documents
    • microcystins
    • cylindrospermopsin
    • anatoxin-a
  • Health Advisories
    • microcystins
    • cylindrospermopsin

• 2016
  • Recreational criteria for cyanotoxins
Contact Information

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CyanoHABs website
http://water.epa.gov/scitech/swguidance/standards/criteria/nutrients/cyanohabs.cfm