Microcystin-LR – Drinking Water Guidance in Minnesota

Inland HAB Discussion Group
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Source: MPCA
Minnesota Concerns

- “Land of 10,000 Lakes” – many lakeshore residential properties, agricultural lands

- Ambient/Recreational Water Quality – Swimming, boating, fishing, livestock, pets

- Drinking Water Quality
  - Surface source-waters
  - Groundwater under the influence of surface waters

MC = microcystin
MC-LR in Minnesota – Occurrence

- Interagency Work Group formed, 2004

- MPCA/USGS Surveys, 2006
  - Up to 12 MN eutrophic lakes

- EPA National Lake Assessment Project, 2007
  - MPCA, DNR, MDA
  - 50 MN lakes, mid- to late summer, multiple “ecoregions” – not just eutrophic lakes

MC-LR = Microcystin-LR
MPCA = MN Pollution Control Agency; DNR = MN Department of Natural Resources; MDA = MN Dept. of Agriculture
MC-LR in Minnesota
– Public Consultations

- MDH Site Consultation, July 2011 – Little Rock Lake
  - MCs detected @ 38,000 μg/L and > 80,000 μg/L in lake in 2007
  - Near-shore shallow residential wells sampled in Aug-Sept 2011
    - all non-detect during mild algal bloom, but wells considered vulnerable

- MDH Consultations – Budd Lake, Fairmont MN
  - Budd Lake = drinking water source for city
  - Citizen concerns raised, summer 2012
MDH Guidance Development
– Selection of Microcystin-LR

- Drinking Water Contaminants of Emerging Concern (CEC) program
  - MN Clean Water, Land and Legacy constitutional amendment, Nov. 2008
  - Nominations (Public, State Agencies, MDH Staff, etc.)
  - MDH screening and ranking for priority

- MC-LR Nominated to MDH’s CEC program by MPCA in April 2011
  - MDH- ranked as high priority based on toxicity and exposure factors
MDH Guidance — MC-LR

- Health-Based Value (HBV) = 0.04 μg/L
  - for short-term, subchronic and chronic durations
  - insufficient data for acute guidance

- Guidance posted on MDH website
  - Sept. 2012
Critical Studies Selected

- **Short-term** – Heinze, 1999; 28-day drinking water study in rats, serum liver enzymes, ↑ rel liver wt, liver lesions
- **Subchronic** – Fawell et al., 1999; 13-wk gavage study in mice, serum liver enzymes, ↑ rel liver wt
- **Chronic** – Fawell et al., 1999; 13-wk gavage study in mice, serum liver enzymes, ↑ rel liver wt, degenerative liver lesions, Kupffer cell activation in liver

**POD** (Dose causing no harm to animals)

- **Short-term** – 6.4 μg/kg-d
- **Subchronic & Chronic** - 58 μg/kg-d
Drinking Water Guidance Values: MDH & WHO Comparison

Short-term and Subchronic:
MDH (0.04 ug/L)
WHO (n/a)

Chronic:
MDH (0.04 ug/L) 25 x lower!
WHO (1 ug/L)
# Microcystin-LR - Chronic Duration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO</th>
<th>MDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Basis</td>
<td>Fawell et al. 1999, 13-week gavage study in mice</td>
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</tr>
<tr>
<td>Health Endpoints</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>Animal Dose Level causing no harm (POD)</td>
<td>0.04 mg/kg-d (NOAEL)</td>
<td>0.058 mg/kg-d (EPA BMDL$_{1SD}$)</td>
</tr>
<tr>
<td>Human Equivalent Dose (HED)</td>
<td>n/a</td>
<td>0.0081 mg/kg-d (per EPA 2011 guidance)</td>
</tr>
<tr>
<td>Uncertainty Factors</td>
<td>1000 (10 interspecies, 10 intraspecies, 10 database uncertainty)</td>
<td>1000 (3 interspecies, 10 intraspecies, 10 database uncertainty, 3 subchronic to chronic)</td>
</tr>
<tr>
<td>Human Dose Level expected to cause no harm (RfD)</td>
<td>0.00004 mg/kg-d</td>
<td>0.0000081 mg/kg-d</td>
</tr>
<tr>
<td>Drinking water allocation factor (RSC)</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Drinking water intake rates</td>
<td>0.0333</td>
<td>0.043</td>
</tr>
<tr>
<td>Drinking water guidance value (HBV)</td>
<td>1 ug/L</td>
<td>0.2 ug/L (calculated)</td>
</tr>
</tbody>
</table>

\[
\text{HBV} = \frac{\text{RfD} \times \text{RSC} \times 1000}{\text{Intake Rate}}
\]

5 x lower than WHO

0.04 ug/L (set to short-term)
**Microcystin-LR Short-term Duration (1 to 30 days)**

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<tr>
<td>Study Basis</td>
<td>n/a</td>
<td>Heinze 1999, 28-day drinking water study in rats</td>
</tr>
<tr>
<td>Health Endpoints</td>
<td>n/a</td>
<td>Liver</td>
</tr>
<tr>
<td>Animal Dose Level causing no harm (POD)</td>
<td>n/a</td>
<td>0.0064 mg/kg-d (EPA BMDL&lt;sub&gt;10&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Human Equivalent Dose (HED)</td>
<td>n/a</td>
<td>0.0015 mg/kg-d</td>
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<tr>
<td>Uncertainty Factors</td>
<td>n/a</td>
<td>100 (3 interspecies, 10 intraspecies, 3 database uncertainty)</td>
</tr>
<tr>
<td>Human Dose Level expected to cause no harm (RfD)</td>
<td>n/a</td>
<td>0.000015 mg/kg-d</td>
</tr>
<tr>
<td>Drinking water allocation factor (RSC)</td>
<td>n/a</td>
<td>0.8</td>
</tr>
<tr>
<td>Drinking water intake rates (infant intake rate)</td>
<td>n/a</td>
<td>0.289 L/kg bw-day</td>
</tr>
<tr>
<td>Drinking water guidance value (HBV)</td>
<td>n/a</td>
<td>0.04 ug/L</td>
</tr>
</tbody>
</table>

\[
HBV = \frac{[RfD \times RSC \times 1000]}{\text{Intake Rate}}
\]

6-7 x higher than chronic intake rate
Age-Adjusted Drinking Water Intake Rates

- 2004 EPA Estimated Water Ingestion in the U.S.
- 2006 Draft/2008 Final EPA Child-Specific Exposure Factors Handbook
Microcystin-LR - Cancer

- IARC Group 2B carcinogen (possibly carcinogenic to humans) - Liver, colon
  - Tumor promoter -
    - “Strong” evidence for tumor promotion
    - Threshold dose is likely
  - Epidemiology drinking water studies –
    - Reports of associations w/ cancer at microcystin levels ranging from 0.1 to 2 ug/L
    - Reference populations (control groups) reported to have exposures up to 0.04 ug/L [note that this is also the same as MDH HBV]

- The MDH non-cancer HBV is considered protective for potential carcinogenicity.
Toxicology issues: Further study needed?

- Male Reproductive Effects?? (Chen et al. 2011)
  - Sperm, hormones, testes – may be more sensitive than liver?
  - Mouse study, drinking water, “potential” HBV 4x lower
  - Addressed in database uncertainty factor
  - MDH RfDs considered protective (i.e., 6-11 times lower than the LOAEL\textsubscript{HED} from repro study)

- Other microcystin congeners, MC-LF and MC-LW, may have greater toxicity than MC-LR
Monitoring Challenges

- HBV of 0.04 μg/L is below LOD (0.15 μg/L)
  - ELISA is limited in accuracy, sensitivity and specificity
  - Congener-specific methods exist – LC/MS/MS

- Sampling – seasonal, diurnal, hourly variations

- Assumes MC-LR is most toxic and abundant variant – but may not be in all cases?
Questions?

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Source: MPCA
Useful links -

MDH – Microcystin-LR in Drinking Water

MDH – Little Rock Lake
http://www.health.state.mn.us/divs/eh/hazardous/sites/benton/littlerocklake/index.html

MPCA – Blue-green Algae and Harmful Algal Blooms

MPCA – National Lakes Assessment Project report:
Extra details, if questions…. Male repro

Chen et al. 2011

- Limitations and Uncertainties:
  - Mechanistic uncertainties – toxicokinetics, blood-testes barrier
  - Methodology uncertainties – no historical control data, low sperm motility in controls, sample handling and measurement

- MDH Conclusions on Repro Tox:
  - Uncertainties prevented use of Chen et al. study as a critical study
  - Repro uncertainty addressed in database uncertainty factor
  - MDH RfDs are 6-11 times lower than the LOAEL_{HED} from Chen study (i.e., considered protective)
  - Further research is needed to replicate and support findings
Extra details, if questions….
Other microcystin congeners

- Human Hepatocytes and HEK293 cells (Fischer et al. 2010):
  - MC-LW & LF - 7 to 70x greater cytotoxicity than MC-LR
  - Due to greater OATP receptor uptake into cells

- CHO cells (Huang et al. 2009) — cytotox LF > LW > LR

- HeLa cells (Monks et al. 2007) — cytotox: LR>LF>LW; but growth inhibition (IC$_{50}$ OATPs): LW>LF>LR

- Fischer et al. 2010 - Concluded that risk of human microcystin toxicity may be underestimated in algal blooms where MC-LW and MC-LF are predominant.