Microcystin-LR – Drinking Water Guidance in Minnesota

Inland HAB Discussion Group

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Source: MPCA

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Minnesota Concerns

- "Land of 10,000 Lakes" – many lakeshore residential properties, agricultural lands
- Ambient/Recreational Water Quality – Swimming, boating, fishing, livestock, pets

Source: MPCA

- 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
  - Several dog deaths – algal blooms suspected; MPCA met with MDH, DNR, and the MN Vet. Med. Assoc.
- 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

Source: MPCA

- 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

MDH Guidance Development – MC-LR

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

Parameter	WHO	MDH
Study Basis	Fawell et al. 1999, 13-week gavage study in mice	Fawell et al. 1999, 13-week gavage study in mice
Health Endpoints	Liver	Liver
Animal Dose Level causing no harm (POD)	0.04 mg/kg-d (NOAEL)	0.058 mg/kg-d (EPA $BMDL_{1SD}$)
Human Equivalent Dose (HED)	n/a	0.0081 mg/kg-d (per EPA 2011 guidance)
Uncertainty Factors	1000 (10 interspecies, 10 intraspecies, 10 database uncertainty	1000 (3 interspecies, 10 intraspecies, 10 database uncertainty, 3 subchronic to chronic)
Human Dose Level expected to cause no harm (RfD)	0.00004 mg/kg-d	0.0000081 mg/kg-d ✓ **5 x lower than WHO**
Drinking water allocation factor (RSC)	0.8	0.8
Drinking water intake rates	0.0333	0.043 ✓
Drinking water guidance value (HBV)	1 ug/L	0.2 ug/L (calculated) **0.04 ug/L (set to short-term)** ✓

HBV = [RfD x RSC x 1000]/Intake Rate

Microcystin-LR Short-term Duration (1 to 30 days)

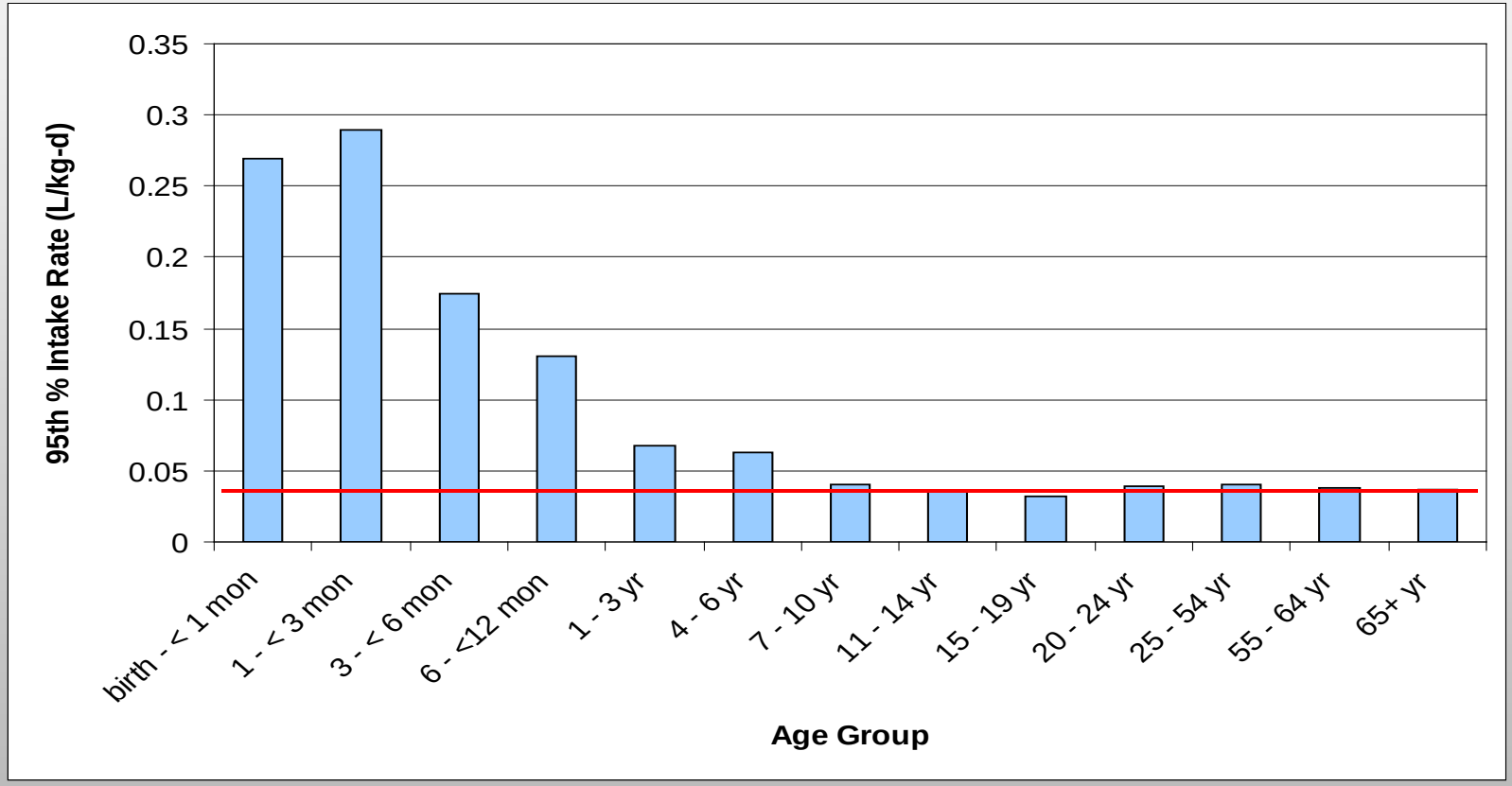
Parameter	WHO	MDH
Study Basis	n/a	Heinze 1999, 28-day drinking water study in rats ✓
Health Endpoints	n/a	Liver
Animal Dose Level causing no harm (POD)	n/a	0.0064 mg/kg-d (EPA $BMDL_{10}$)
Human Equivalent Dose (HED)	n/a	0.0015 mg/kg-d
Uncertainty Factors	n/a	100 (3 interspecies, 10 intraspecies, 3 database uncertainty)
Human Dose Level expected to cause no harm (RfD)	n/a	0.000015 mg/kg-d
Drinking water allocation factor (RSC)	n/a	0.8
Drinking water intake rates (infant intake rate)	n/a	0.289 L/kg bw-day ✓
Drinking water guidance value (HBV)	n/a	**0.04 ug/L** ✓

6-7 x higher than chronic intake rate

HBV = [RfD x RSC x 1000]/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 promotor -
  - "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 $LOAEL_{HED}$ 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?

Source: MPCA

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Useful links -

MDH – Microcystin-LR in Drinking Water

http://www.health.state.mn.us/divs/eh/risk/guidance/gw/mclrinfo.pdf

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

http://www.pca.state.mn.us/index.php/water/water-types-and-programs/surface-water/lakes/lake-water-quality/blue-green-algae-and-harmful-algal-blooms.html?menuid=&redirect=1&expandable=1

MPCA – National Lakes Assessment Project report:
http://www.pca.state.mn.us/index.php/view-document.html?gid=6231

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.