Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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Toxicological Summary for: Microcystin-LR

CAS**: 101043-37-2**

Synonyms: Microcystin LR; Microcystin; Microcystins; MC-LR; Microcystin toxin; Blue green algae toxin

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = Not Derived (Insufficient Data)

Due to limited information, no acute guidance value is derived. Based on the available information, the short-term HBV for microcystin-LR is also protective of acute effects.

Short-term Non-Cancer Health Based Value ($nHBV_{Short\text{-}term}$) = 0.1 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.000040 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 0.11 rounded to **0.1 µg/L**

*MDH utilizes the U.S. EPA Exposure Decision Tree (U. S. Environmental Protection Agency, 2000) to select appropriate Relative Source Contributions (RSCs), ranging from 0.2 to 0.8. An RSC greater than 0.8 may be warranted for situations where there are no other routes of exposure besides drinking water. In the case of microcystin, drinking water is likely to be the predominant source of exposure. However, without additional information a specific value cannot be determined at this time. Therefore, the recommended upper limit default of 0.8 was utilized. This approach, however, does not consider those who take algal dietary supplements that may be contaminated with microcystin.

Reference Dose/Concentration:	0.000040 mg/kg-d (male F1 inbred hybrid rats)
Source of toxicity value:	MDH, 2015
Point of Departure (POD):	0.05 mg/kg-d (LOAEL, Heinze 1999)
Human Equivalent Dose (MDH, 2011):	0.05 x 0.24 = 0.012 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for database uncertainty (lack of a multigenerational reproductive/developmental study), and 3 for use of LOAEL
Critical effect(s):	Slight to moderate liver necrosis with hemorrhage, increased serum liver enzymes (alkaline phosphatase and lactate dehydrogenase), increased absolute and relative liver weights
Co-critical effect(s):	None

Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = $nHBV_{Short-term}$ = 0.1 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.000023 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 0.24 rounded to 0.2 µg/L

*Refer to RSC explanation provided for the short-term non-cancer health-based value.

Reference Dose/Concentration:	0.000023 mg/kg-d (Crl:CD-1(ICR)BR mice)
Source of toxicity value:	MDH, 2015
Point of Departure (POD):	0.0485 mg/kg-d ($BMDL_{1SD}$, derived by MDH 2015 based on Fawell et al. 1999)
Human Equivalent Dose (MDH, 2011):	0.0485 x 0.14 = 0.0068 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (lack of a multigenerational reproductive/developmental study; lack of adequate neurotoxicity studies and uncertainties regarding gavage administration)
Critical effect(s):	Elevated male serum liver enzymes (ALT)
Co-critical effect(s):	Increased relative liver weight, increased serum liver enzymes (AST, ALP and LDH), histopathological degenerative liver lesions, activation of Kupffer cells in liver, chronic liver inflammation
Additivity endpoint(s):	Hepatic (liver) system

The Subchronic nHBV must be protective of the acute and short-term exposures that occur within the subchronic period and; therefore, the Subchronic nHBV is set equal to the Short-term nHBV of 0.1 µg/L. Additivity endpoints: Hepatic (liver) system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 0.1 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0000068 mg/kg-d) x (0.8*) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 0.13, rounded to **0.1 µg/L**

*Refer to RSC explanation provided for the short-term non-cancer health-based value.

Reference Dose/Concentration:	0.0000068 mg/kg-d (Crl:CD-1(ICR)BR mice)
Source of toxicity value:	MDH, 2015
Point of Departure (POD):	0.0485 mg/kg-d ($BMDL_{1SD}$, derived by MDH 2015 based on Fawell et al. 1999, subchronic study)
Human Equivalent Dose (MDH, 2011):	0.0485 x 0.14 = 0.0068 mg/kg-d
Total uncertainty factor:	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (lack of a multigenerational reproductive/developmental study; lack of adequate neurotoxicity studies and uncertainties regarding gavage administration), and 3 for extrapolation from subchronic to chronic duration
Critical effect(s):	Elevated male serum liver enzymes (ALT)
Co-critical effect(s):	Increased relative liver weight, increased serum liver enzymes (AST, ALP and LDH), histopathological degenerative liver lesions, activation of Kupffer cells in liver, chronic liver inflammation
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Based Value (cHBV) = Not Derived (Insufficient Data)

There are no adequate carcinogenicity studies of purified microcystin-LR in laboratory animals. According to the International Agency for Research on Cancer (IARC, 2010) there is strong evidence that microcystin-LR is a tumor promoter rather than a tumor initiator.

Both IARC (2010) and EPA (2015) concluded that the available human and animal studies are inadequate to assess the carcinogenicity of microcystin-LR. Therefore, a quantitative assessment for cancer is not possible at this time.

Cancer classification:	Classified as “Inadequate information to assess carcinogenic potential” (EPA 2015) IARC Group 2B (possibly carcinogenic to humans) (2010)
Slope factor:	No EPA slope factor exists
Source of slope factor:	not applicable
Tumor site(s):	Liver, colon

Volatile: No

Summary of Guidance Value History:
In 2012, an HBV of 0.04 µg/L was developed for short-term, subchronic, and chronic durations. In 2015, microcystin-LR was re-evaluated due to a new assessment by the USEPA. The USEPA evaluation used a different short-term POD than MDH used in 2012. The MDH HBVs for all durations were increased to 0.1 µg/L.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	Yes	No	Yes	Yes	Yes
Effects observed?	Yes[1]	[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1] One oral study reported decreased sperm motility, testosterone, FSH, and LH in male mice after 3 or 6 months of exposure in drinking water at human equivalent doses (HEDs) over 5 times higher than the subchronic RfD and 16 times higher than the chronic RfD. Results from this study, in part, formed the basis for incorporating a database uncertainty factor into the RfD calculation. Effects on male hormones (testosterone, LH, FSH), the hypothalamic-pituitary axis, and thyroid hormones (TH, freeT3, freeT4) have also been reported in *in vitro* and/or non-oral *in vivo* studies.

[2]No oral immunotoxicity studies on purified microcystin-LR have been conducted. Results from the short-term critical study include a significant increase in number of leukocytes due to lymphocytosis in rats exposed to microcystin-LR for 28 days in drinking water at a human equivalent dose 900 times higher than the short-term RfD.

[3]Developmental effects of purified microcystin-LR were reported at maternally toxic doses in a single gavage study in mice. Effects included decreased fetal body weight and delayed skeletal ossification at human equivalent doses (HED) over 6,500 times higher than the RfDs for all durations. Developmental neurobehavioral toxicity was reported in one oral study where rat offspring developed impaired learning and memory based on water maze swim tests. The neurobehavioral effects were reported at HED over 3 times higher than the short-term RfD or 5 times higher than the subchronic RfD.

[4] There are no oral multigenerational reproductive studies or oral reproductive studies which evaluated reproductive function and fertility with purified microcystin-LR. However, one study reported decreased sperm motility and testosterone in mice after 3 or 6 months of exposure in drinking water at human equivalent doses over 5 times higher than the subchronic RfD and 16 times higher than the chronic RfD. Results from this study, in part, formed the basis for incorporating a database uncertainty factor into the RfD calculation.

[5] There are no adequate oral studies to evaluate neurotoxicity, including developmental neurotoxicity. Effects on spatial learning and memory have been reported in two limited oral studies in which microcystin-LR was dissolved in methanol, a potential confounding agent for neurotoxicity. In one of these studies, rat offspring whose mothers were exposed for 8 weeks pre-mating (but not during gestation or lactation) developed impaired spatial learning and memory based on water maze swim test performance, significant increased serum cholinesterase, and signs of hippocampal astrocyte activation after exposure for 8 weeks to HED doses 13 times higher than the subchronic RfD. Neurological effects reported with acute lethal doses of microcystin-LR in mice, including hypoactivity and piloerection, occurred at doses over 1,750 times higher than the RfDs. Neurotoxicity was not reported as a clinical

sign or symptom in longer-term, repeat-dose oral studies in animals. Occasional reports of neurotoxic effects in humans, including headache, muscle weakness, visual disturbances, and vertigo, have occurred upon high exposure to cyanotoxin mixtures resulting from algal blooms; however, it is not known whether neurotoxic effects can be attributed to microcystin-LR or some other component of the complex mixtures.

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