



Toxicological Summary for: Anatoxin-a

CAS: 64285-06-9

Synonyms: Anatoxin A; (+)-Anatoxin-a; Anatoxin I; Very Fast Death Factor

The oral toxicity data set to support risk assessment of anatoxin-a is very limited. The available studies include one 5-day gavage study, one 28-day gavage study in mice, one developmental screening study in mice, and one 7-week drinking water study in rats. There are no chronic studies.

The exact cause for two deaths reported in the 28-day mouse study could not be determined; therefore, a treatment-related effect could not be ruled out. The deaths occurred within 2.5 hours of dose administration. Microscopic investigation of the tissues showed no evidence for gavage injury. The incidence of lethality (1/20) in the high dose group was the same as the mid-dose group, rather than increasing with dose, as is commonly expected for a treatment-related effect. However, a 2.5-fold higher dose in a 5-day study caused 25% mortality and a 5-fold higher dose resulted in 100% mortality. This indicates that (1) there is a very steep dose-response curve with a narrow margin between a potential no adverse effect level and lethality and/or (2) suitable biochemical or microscopic indicators of early non-lethal toxicity have not been identified and incorporated into the studies.

After a careful review of the available toxicological information, MDH decided the lowest dose tested in the 28-day study is a conservative and health-protective NOAEL for the short-term duration. MDH recommends the short-term non-cancer risk assessment advice (nRAA) presented below because the data are not adequate to confidently develop a health-based value (HBV). MDH is unable to recommend subchronic or chronic guidance (RAA or HBV) because (1) the only subchronic study evaluated algal extracts without reporting the extent or nature of impurities and did not measure the actual doses received by the animals and (2) there are no chronic studies.

Acute Non-Cancer Risk Assessment Advice (nRAA_{Acute}) = Not Derived (Insufficient Data)

Short-term Non-Cancer Risk Assessment Advice (nRAA_{Short-term}) = 0.1 µg/L

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

$$= \frac{(0.000047 \text{ mg/kg-d}) \times (0.8)^* \times (1000 \text{ µg/mg})}{(0.285 \text{ L/kg-d})^{**}}$$

$$= 0.13 \text{ rounded to } \mathbf{0.1 \text{ µg/L}}$$

*Relative Source Contribution: MDH 2008, Section IV.E.1. 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 anatoxin-a, 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 anatoxin-a.

**Intake Rate: MDH 2008, Section IV.E and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81.

Reference Dose/Concentration: (POD x DAF)/Total UF = 0.000047 mg/kg-d
(CrI:CD-1(ICR)BR mice)
Source of toxicity value: Determined by MDH in 2016
Point of Departure (POD): 0.098 mg/kg-d (NOAEL, Fawell et al. 1994, 1999)
Human Equivalent Dose (MDH, 2011): POD x DAF = 0.098 mg/kg-d x 0.14 = 0.014 mg/kg-d
Total uncertainty factor (UF): 300
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics),
10 for intraspecies variability, and 10 for database
uncertainty (lack of multigenerational reproductive
study, lack of relevant biochemical/biomarker data
for early non-lethal signs of anatoxin-a
neurotoxicity)
Critical effect(s): Death (the exact cause of death could not be
determined in the critical study, but it is well-
established that anatoxin-a causes death by
respiratory paralysis from nervous system toxicity)
Co-critical effect(s): None
Additivity endpoint(s): Nervous system

Subchronic Non-Cancer Risk Assessment Advice (nRAA_{Subchronic}) = Not Derived (Insufficient Data)

Chronic Non-Cancer Risk Assessment Advice (nRAA_{Chronic}) = Not Derived (Insufficient Data)

Cancer Health Based Value (cHBV) = Not Derived

Cancer classification: Not Classified
Slope factor (SF): Not Applicable
Source of cancer slope factor (SF): Not Applicable
Tumor site(s): Not Applicable

Volatile: No

Summary of Guidance Value History:

The Short-term nRAA for anatoxin-a is new. No previous MDH values exist for anatoxin-a. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process anatoxin-a will likely undergo re-evaluation in 2021.

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?	No	No	Yes	Yes	Yes
Effects observed?	-	-	Yes ¹	Yes ²	Yes ³

Comments on extent of testing or effects:

¹ In one oral developmental study of anatoxin-a in mice, the mean fetal body weight was marginally lower than controls at a human equivalent dose 7,000 times higher than the short-term RfD. There were no other significant effects noted. In one injection study, no significant postnatal neurotoxicity was reported, although slight neurobehavioral developmental effects (e.g., effects on righting reflex and hanging grip times) were reported in offspring of rats, at a dose over 250 times higher than the short-term RfD. Results from injection studies are not representative of drinking water exposure.

² There are no relevant oral reproductive studies for anatoxin-a. In one intraperitoneal injection study in mice, anatoxin-a caused changes in the testes of animals and decreased sperm counts. The injected dose reported to cause reduced sperm counts was about 150 times higher than the short-term oral RfD.

³ Respiratory paralysis from anatoxin-a neurotoxicity is a well-established cause of death in anatoxin-related poisonings. Death from nervous system toxicity occurred in a 5-day oral study in mice at a human equivalent dose more than 17,000 times higher than the short-term RfD. No overt nervous system clinical signs were reported in oral 28-day gavage study in mice (at HED over 7,000 times higher than short-term RfD) or in a 7-week drinking water study in rats (at HED over 2,500 times higher than short-term RfD). However, the cause of deaths in the 28-day mouse study could not be determined and the association with anatoxin-a treatment could not be ruled out. Since anatoxin causes death by respiratory paralysis related to nervous system mechanism, the nervous system was identified as a critical effect for the short-term RfD.

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