Toxicological Summary for: Cadmium
CAS: 7440-43-9
Synonyms: None

Acute Non-Cancer Health Risk Limits (nHRLAcute) = 5 µg/L

\[
\text{Acute Non-Cancer Health Risk Limits (nHRLAcute)} = \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Acute intake rate, L/kg-d})} = \frac{(0.0077 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \text{ µg/mg})}{(0.289 \text{ L/kg-d})} = 5.3 \text{ rounded to 5 µg/L}
\]

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-drinking water sources of dietary exposure to infants and children, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration: 0.0077 mg/kg-d (Sprague Dawley rats)
Source of toxicity value: MDH, 2014
Point of Departure (POD): 1 mg/kg-d (NOAEL, Sutou, Yamamoto et al. 1980a and Sutou, Yamamoto et al. 1980b)
Human Equivalent Dose (MDH, 2011): 1.0 x 0.23 = 0.23 mg/kg-day
Total uncertainty factor: 30
Uncertainty factor allocation 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s): Decreased fetal body weight and body length, increased fetal skeletal malformations
Co-critical effect(s): Decreased fetal body weight and body length, increased fetal skeletal malformations
Additivity endpoint(s): Developmental

Short-term Non-Cancer Health Risk Limit (nHRLShort-term) = 1 µg/L

\[
\text{Short-term Non-Cancer Health Risk Limit (nHRLShort-term)} = \frac{(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Short-term intake rate, L/kg-d})} = \frac{(0.0016 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \text{ µg/mg})}{(0.289 \text{ L/kg-d})} = 1.1 \text{ rounded to 1 µg/L}
\]

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-drinking water sources of dietary exposure to infants and children, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.
Reference Dose/Concentration: 0.0016 mg/kg-d (Wistar rats)
Source of toxicity value: MDH 2014
Point of Departure (POD): 0.71 mg/kg-d (LOAEL, Ali, Murthy et al. 1986)
Human Equivalent Dose (MDH, 2011): 0.71 x 0.22 = 0.16 mg/kg-day
Total uncertainty factor: 100
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for extrapolation from a LOAEL to a NOAEL (the neurological effects observed at the LOAEL were subtle, a factor of 3 is expected to be sufficiently protective)

Critical effect(s): Alteration in the development of cliff avoidance behavior and spontaneous locomotor activity in offspring exposed during the developmental period
Co-critical effect(s): Decreased plasma essential ions, decreased glomerular filtration rate
Additivity endpoint(s): Developmental; Nervous system; Renal (kidney) system

Subchronic Non-Cancer Health Risk Limit (nHRL\text{Subchronic}) = 1 \mu g/L

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(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
Subchronic intake rate, L/kg-d

\[
= (0.00044 \text{ mg/kg/d}) \times (0.2) \times (1000 \mu g/mg)
\]
(0.077 L/kg-d)

\[
= 1.1 \text{ rounded to } 1 \mu g/L
\]

Reference Dose/Concentration: 0.00044 mg/kg-d (Wistar rats)
Source of toxicity value: MDH, 2014
Point of Departure (POD): 0.2 mg/kg-d (LOAEL, Brzoska, Majewska et al. 2005a and Brzoska and Maniuszko-Jakoniuk 2005a)
Human Equivalent Dose (MDH, 2011): 0.2 x 0.22 = 0.044 mg/kg-day
Total uncertainty factor: 100
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for extrapolation from a LOAEL to a NOAEL (the bone effects observed at the LOAEL were subtle, a factor of 3 is expected to be sufficiently protective)

Critical effect(s): Decreased femoral bone resistance to fracture, increased fragility of the femoral bone, increased markers for bone resorption, and decreased markers for bone formation in rapidly growing young animals
Additivity endpoint(s): Developmental; Skeletal

Chronic Non-Cancer Health Risk Limit (nHRL\text{Chronic}) = 0.5 \mu g/L

\[
(\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})
\]
(Chronic intake rate, L/kg-d)
\[
= \frac{(0.00011 \text{ mg/kg/d}) \times (0.2) \times (1000 \mu g/mg)}{0.043 \text{L/kg-d}}
= 0.51 \text{ rounded to } 0.5 \mu g/L
\]

Reference Dose/Concentration: 0.00011 mg/kg-d (human)
Source of toxicity value: ATSDR, 2012
Point of Departure (POD): 0.00033 mg/kg-d (UCDL₁₀*, ATSDR 2012)
Human Equivalent Dose (MDH, 2011): Not applicable - human study used
Total uncertainty factor: 3
Uncertainty factor allocation: 3 for intraspecies variability to account for sensitive subpopulations
Critical effect(s): Low molecular weight proteinuria
Co-critical effect(s): Increased risk for osteoporosis
Additivity endpoint(s): Renal (kidney) system; Skeletal

*UCDL₁₀ is the 95% lower confidence limit on the estimated internal cadmium dose (urinary cadmium expressed as µg/g creatinine) corresponding to the probability of 10% excess risk of low molecular weight proteinuria.

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: B1; probable human carcinogen (U.S. EPA 1994) through the inhalation route
Slope factor: Not available. There are no positive studies of orally ingested cadmium suitable for quantitation.
Source of slope factor: N/A
Tumor site(s): N/A

Volatile: No

Summary of Guidance Value History:
The 2015 acute health Risk Limit (HRL) for cadmium (5 µg/L) is slightly higher than the 1993 HRL of 4 µg/L. The reasons it is higher are: 1) use of more recent toxicity information; and 2) rounding to one significant digit. The 2015 chronic HRL for cadmium (0.5 µg/L) is eight times lower than the 1993 HRL of 4 µg/L. The subchronic and short-term noncancer HRLs are 4 times lower. The reasons that the 2015 HRLs for the short-term, subchronic, and chronic durations are lower than the 1993 HRL are: 1) use of more recent toxicity information; 2) use of more recent intake rates that account for higher exposures during early life; and 3) rounding to one significant digit. Health-Based Values (HBVs) developed in 2014 were adopted into rule as HRLs in 2015.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

<table>
<thead>
<tr>
<th>Tested?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effects?</td>
<td>Yes¹</td>
<td>Yes²</td>
<td>Yes³</td>
<td>Yes⁴</td>
<td>Yes⁵</td>
</tr>
</tbody>
</table>

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.
Comments on extent of testing or effects:

1 In female animals treated with cadmium at levels at least 400 times the subchronic RfD, decreases of estradiol, FSH, LH, and progesterone were observed.

2 Immune effects have been observed in some studies, but not in others. In mice exposed to cadmium at doses more than 100 times the short-term RfD immunosuppression has been noted, but the mechanism is unclear. In a second study, mice exposed to cadmium 125 times higher than the short-term RfD showed enhanced T-lymphocyte-independent responses and suppressed T-lymphocyte-dependent responses. These responses may be due to a compensatory mechanism that is part of humoral immunity. Although one study showed that cadmium at doses 250 times higher than the short term RfD increased mortality from an infectious agent, a second study with a dose 2,000 times the short term RfD failed to show altered resistance to an infectious agent. A primate study showed that cadmium stimulated cell-mediated immunity at a dose of more than 2,000 times the short term RfD.

3 Developmental effects form the basis for the acute, short-term, and subchronic RfDs. While neurological effects in animals exposed in utero forms the basis of the short-term RfD, adverse skeletal effects in rapidly growing animals forms the basis of the acute and subchronic RfDs. Multiple studies reported reduced fetal body weight and size as well as an increase in skeletal malformations in pups exposed in utero to cadmium at levels at least 30 times higher than the acute RfD. Other developmental effects such as fetal resorptions and delayed ossification were noted from 300 to over 5000 times the acute RfD.

4 Epidemiology studies have been conducted examining the effect of cadmium on male and female reproductive toxicity. The results have been inconsistent. Although two studies showed a relationship between male sex hormone levels and cadmium, others did not. The relationship between sperm quality and serum cadmium levels is also not clear. While one study reported a decrease in sperm quality with increased blood cadmium level, two others did not. Data on reproductive toxicity in women is limited. Among infertile women, no association between cadmium body burden and the risk of endometriosis was observed. Elevated urine cadmium levels have been associated with an increased time to pregnancy. A number of animal studies have also demonstrated reproductive effects, but at very high dose levels greater than 3,000 times the acute RfD.

5 Neurotoxicity following in utero exposure is the basis of the short-term RfD. In some animal studies, effects have been reported at doses 50 times the chronic RfD. Other studies have reported neurological effects in rats exposed to cadmium at doses thousands of times higher than the short-term RfD. The effects have included impacts on grooming, learning, movement, rearing, behavior, hearing, and vision.

References:


ATSDR (2012). "Toxicological Profile for Cadmium."


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