Minnesota Department of Health

Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: November 2015

Toxicological Summary for: Acrylamide

CAS**: 79-06-1**

Synonyms: Acrylamide monomer, 2-Propenamide, Propenamide, Vinyl Amide, Acrylic Amide

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 7 µg/L

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

$$= \frac{\text{(0.010 mg/kg/d) x (0.2*) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 6.9 rounded to **7 µg/L**

*MDH utilizes the EPA Exposure Decision Tree (EPA, 2000) to select appropriate RSCs. Due to evidence of acrylamide in breast milk (Sorgel, 2002) and baby food (FDA, 2006), along with evidence that dietary exposures for some people exceed 50% of the short-term RfD, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration:	0.010 mg/kg-d (Long-Evans Rats)
Source of toxicity value:	MDH, 2014 (same as ATSDR, 2012)
Point of Departure (POD):	1.33 mg/kg-d ($BMDL_{10}$, Sublet, 1989)
Human Equivalent Dose (MDH, 2011):	0.31 mg/kg-d (PBPK basis, ATSDR, 2012)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Reproductive toxicity in male rodents causing germ cell damage that results in fetal resorptions and implantation loss
Co-critical effect(s):	Neurotoxicity such as loss of hindlimb use and altered head tilt; Male-mediated reproductive toxicity resulting in impaired mating and decreased number and vitality of fetuses, increased resorptions/implantation losses; Developmental toxicity including neurobehavioral effects in young animals, decreased pup body weight, and increased resorptions/implantation losses
Additivity endpoint(s):	Developmental, Male Reproductive system, Nervous system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0070 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 18 rounded to 20 µg/L

Reference Dose/Concentration	0.0070 mg/kg-d (F344 rats)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	1 mg/kg-d (NOAEL, Burek, 1980)
Human Equivalent Dose (MDH, 2011):	1 x 0.21 = 0.21 mg/kg-d
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability
Critical effect(s):	Peripheral nerve degeneration
Co-critical effect(s):	Neurological effects (decreased ability to learn, nerve damage/degeneration, altered head tilting), reproductive toxicity causing implantation losses and direct damage to male germ cells, developmental effects (decreased pup body weights, implantation loss), decreased adult body weight gain
Additivity endpoint(s):	Developmental, Male Reproductive system, Nervous system

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 7 µg/L. Additivity endpoints: Developmental, Male reproductive system, Nervous system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 7 µg/L

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

$$= \frac{\text{(0.0037 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 17 rounded to 20 µg/L

Reference Dose/Concentration:	0.0037 mg/kg-d (F344 rats)
Source of toxicity value:	MDH, 2014
Point of Departure (POD):	0.44 mg/kg-d ($BMDL_{05}$, ATSDR, 2012)
Human Equivalent Dose (MDH, 2011):	0.11 mg/kg-d (PBPK basis, ATSDR, 2012)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics) and 10 for intraspecies variability

Critical effect(s):	Nerve degeneration
Co-critical effect(s):	Nerve degeneration
Additivity endpoint(s):	Nervous system

The Chronic nHRL must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 7 µg/L. Additivity endpoints: Developmental, Male reproductive system, Nervous system

Cancer Health Risk Limit (cHRL) = 0.2 µg/L

$$\frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.5 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.5 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.5 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 0.205 rounded to **0.2 µg/L**

Cancer classification:	Likely to be carcinogenic to humans (USEPA, 2010)
Slope factor:	0.5 (F344 rats, Johnson, 1986)
Source of slope factor:	USEPA, 2010
Tumor site(s):	Tunica vaginalis mesotheliomas in testes and male thyroid tumors

Volatile: No (Nonvolatile)

Summary of Guidance Value History:
No previous MDH guidance. The Health-Based Values (HBVs) were adopted into rule as HRLs in November 2015.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

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] Endocrine effects have been seen only at very high doses. Decreased testosterone and serum prolactin level and alterations in thyroid hormone levels in have been reported in laboratory animals at doses 2,000 times higher than the current short-term reference dose. Alterations in the adrenal gland have also been reported in a chronic drinking water study in rats at doses over 1,000 times higher than the chronic reference dose.

[2] Immunotoxicity of acrylamide has been directly tested in two recent short-term studies. For acrylamide exposure to compromise immune system function, a very high dose of approximately 1,000 times higher than the current short-term reference dose was needed. At 100 times the current short-term reference dose, subtle changes in lymphocyte populations in the serum were detected. Immunotoxicity has also been indirectly tested during the chronic 2-year cancer studies, and no secondary observations have been noted on immune function in these three high quality long-term studies.

[3] Developmental effects include increased resorptions/implantation losses, reduced pup body weight, altered behavior activities and decreased learning ability, and changes in the brains of young rodents. Neurotoxicity is among the more sensitive developmental effects and has been reported at doses 100-500 times greater than the short-term reference dose.

[4] The short-term reference dose is based on reproductive toxicity in males (increased pre- and post-implantation losses, decreased live pups per litter, increased resorptions, decreased sperm count, abnormal sperm and decreased breeding success). Two-fold higher doses cause reproductive effects in females (body weight gain decreases and loss of hind limb use during gestation).

[5] Neurotoxicity, in the form of nerve degeneration and damage, is the critical effect for subchronic and chronic water guidance. Two to three-fold higher doses also caused other types of neurotoxicity in rodents such as altered hind limb use, head tilting, and difficulty learning. Developmental neurotoxicity has also been shown to occur at doses 100-500 times greater than the short-term reference dose (discussed above).

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