

Toxicological Summary for: n-Hexane

CAS: 110-54-3

Synonyms: hexane

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

Short-term Non-Cancer Risk Assessment Advice (RAA_{Short-term}) = 100 µg/L

$$\begin{aligned} & \frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Short-term Intake Rate, L/kg-d})} \\ &= \frac{(0.19 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.290 \text{ L/kg-d})^{**}} \\ &= 131 \text{ rounded to } \mathbf{100 \text{ µg/L}} \end{aligned}$$

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

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/1000 = 0.19 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al. 1981)
Dose Adjustment Factor (DAF):	0.24, body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 10 for database limitations, including the lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

Subchronic Non-Cancer Risk Assessment Advice ($RAA_{\text{Subchronic}}$) = $RAA_{\text{Short-term}}$ = 100 $\mu\text{g/L}$

$$\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Subchronic Intake Rate, L/kg-d})}$$
$$= \frac{(0.063 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ } \mu\text{g/mg})}{(0.074 \text{ L/kg-d})^{**}}$$
$$= 170 \text{ rounded to } 200 \text{ } \mu\text{g/L}$$

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

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 188/3000 = 0.063 mg/kg-d (male Wistar rat)
Source of toxicity value:	Determined by MDH in 2021
Point of Departure (POD):	785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al., 1981)
Dose Adjustment Factor (DAF):	0.24 Body weight scaling, default (US EPA 2011 and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 3 for extrapolation from a short-term duration study; 10 for database limitations, including lack of multigenerational and neurodevelopmental studies
Critical effect(s):	Reduced motor nerve conduction velocity
Co-critical effect(s):	None
Additivity endpoint(s):	Nervous system

**The Subchronic RAA must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic RAA is set equal to the Short-term RAA of 100 $\mu\text{g/L}$.
Additivity endpoints: Nervous system**

Chronic Non-Cancer Risk Assessment Advice (RAA_{Chronic}) = 80 $\mu\text{g/L}$

$$\frac{(\text{Reference Dose, mg/kg-d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor})}{(\text{Chronic Intake Rate, L/kg-d})}$$
$$= \frac{(0.019 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ } \mu\text{g/mg})}{(0.045 \text{ L/kg-d})^{**}}$$
$$= 84.4 \text{ rounded to } 80 \text{ } \mu\text{g/L}$$

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

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration: HED/Total UF = 188/10000 = 0.019 mg/kg-d (male Wistar rat)

Source of toxicity value: Determined by MDH in 2021

Point of Departure (POD): 785 mg/kg-d (administered dose LOAEL, neurotoxicity study by Ono et al. 1981, short-term exposure)

Dose Adjustment Factor (DAF): 0.24 Body weight scaling, default (US EPA 2011 and MDH 2017)

Human Equivalent Dose (HED): POD x DAF = 785 mg/kg-d x 0.24 = 188 mg/kg-d

Total uncertainty factor (UF): 10000

Uncertainty factor allocation: 3 for toxicodynamic differences between species; 10 for intraspecies variation; 3 for use of a LOAEL; 10 for the use of a shorter duration study.; 10 for database limitations, including lack of multigenerational and neurodevelopmental studies

Critical effect(s): Reduced motor nerve conduction velocity

Co-critical effect(s): None

Additivity endpoint(s): Nervous system

Cancer Risk Assessment Advice (cRAA) = Not Applicable

Cancer classification: Not Classified—Inadequate information (EPA, 2005)

Slope factor (SF): Not Applicable

Source of cancer slope factor (SF): Not Applicable

Tumor site(s): Not Applicable

Volatile: Yes (high)

Summary of Guidance Value History:

A noncancer chronic HRL of 400 µg/L was promulgated in 1994. MDH derived short-term, subchronic and chronic noncancer RAAs in 2021 that are lower than the 1994 HRL as a result of: 1) using MDH’s most recent assessment methodology; and 2) incorporation of additional toxicological information.

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	Yes	Yes	Yes	Yes
Effects observed?	-	Yes ¹	Yes ²	Yes ³	Yes ⁴

Comments on extent of testing or effects:

1. In one rat study, animals had increased levels of white blood cells, lymphocytes, granulocytes, and eosinophils in the blood and inflammatory cells and macrophages in the lung following oral exposure to levels 380 times higher than the short-term RfD.
2. One developmental mouse study reported decreased fetal body weight at doses more than 5,400 times the short-term reference dose. Absence of multigenerational developmental and neurodevelopmental study data is addressed with the application of a database uncertainty factor.
3. Oral rat studies reported decreased prostate weight and increased seminal vesicle weight at doses more than 13,000 and 26,000 times higher than the short-term reference dose, respectively. No histopathological changes were noted; however, testicular sperm count was decreased following a single exposure to a dose over 26,000 times higher than the short-term reference dose. Additionally, in a subchronic neurotoxicity study in rats, testicular atrophy was observed following exposure to doses more than 3,700 times the short-term reference dose. The absence of a multigenerational reproductive study contributed to the application of a database uncertainty factor.
4. The reference dose for short-term, subchronic, and chronic durations is based on neurotoxicity (i.e., reduced motor nerve conduction velocity). Uncertainty regarding the effects of n-hexane on a developing organism's nervous system are addressed with the addition of a database uncertainty factor.

Resources Consulted During Review:

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