Adopted as Rule: August 2018

Toxicological Summary for: *S*-Ethyl-*N,N*-dipropylthiocarbamate

CAS: **759-94-4**
Synonyms: EPTC

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = 300 µg/L

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

$$= \frac{\text{(0.16 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 281 rounded to **300 µg/L**

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

Reference Dose:	HED/Total UF = 48/300 = 0.16 mg/kg-d (lpk:APfSD rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	200 mg/kg-d LOAEL (Brammer 1993 aci (U.S. Environmental Protection Agency 2011), MRIDs 43039701 and 43297401)
Dose Adjustment Factor (DAF):	0.16 Body weight scaling, default (US EPA 2011 and MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 200 mg/kg-d x 0.16 = 48 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 10 for extrapolation from a LOAEL to a NOAEL due to the severity of the effect (brain necrosis)
Critical effect(s):	Necrosis of the pyriform/entorhinal cortex and/or dentate gyrus of the brain
Co-critical effect(s):	Not Applicable
Additivity endpoint(s):	Nervous system

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 300 µg/L

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

$$= \frac{\text{(0.16 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 281 rounded to **300 µg/L**

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

Reference Dose:	HED/Total UF = 4.8/30 = 0.16 mg/kg-d (Wistar rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	21.9 mg/kg-d NOAEL (Lees 2004 aci (U.S. Environmental Protection Agency 2011), MRID 46319101)
Dose Adjustment Factor (DAF):	0.22 Body weight scaling, default (US EPA 2011 and MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 21.9 mg/kg-d x 0.22 = 4.8 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased pup weight at postnatal day 1, clinical signs of neurotoxicity in dams at parturition, increased whole litter losses
Co-critical effect(s):	Decreased pup body weight, decreased pup body weight gain
Additivity endpoint(s):	Developmental, Female Reproductive system, Nervous system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 90 µg/L

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

$$= \frac{\text{(0.033 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 94.3 rounded to **90 µg/L**

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

Reference Dose:	HED/Total UF = 1.0/30 = 0.033 mg/kg-d (Prague Dawley rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	5 mg/kg-d in females, 4 mg/kg-d in males NOAEL (Minor et al., 1982 aci (U.S. Environmental Protection Agency 2011), MRIDs 0012128 and 40420408, and Tisdel et al., 1986c aci (U.S. Environmental Protection Agency 2011), MRID 00161597)
Dose Adjustment Factor (DAF):	0.22 and 0.24 (female/male) Body weight scaling, default (US EPA 2011 and MDH 2011)
Human Equivalent Dose (HED):	[((5 mg/kg-d x 0.22)+(4 mg/kg-day x 0.24))/2] = 1.0 mg/kg-day
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability
Critical effect(s):	Myocardial degeneration
Co-critical effect(s):	Not Applicable
Additivity endpoint(s):	Cardiovascular system

Chronic Non-Cancer Health Risk Limit (nHRL:$_{Chronic}$) = 40 µg/L

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

$$= \frac{\text{(0.0083 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 37.7 rounded to **40 µg/L**

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

Reference Dose:	HED/Total UF = 2.5/300 = 0.0083 mg/kg-d (Crl;CD(SD)BR rats)
Source of toxicity value:	Determined by MDH in 2015
Point of Departure (POD):	9 LOAEL (Dickie 1987 aci (U.S. Environmental Protection Agency 2011), MRID 40215001)
Dose Adjustment Factor (DAF):	0.28 mg/kg-d Body weight scaling, default (US EPA 2011 and MDH 2011)
Human Equivalent Dose (HED):	POD x DAF = 9 mg/kg-d x 0.28 = 2.5 mg/kg-d
Total uncertainty factor (UF):	300

Uncertainty factor allocation:	3 for interspecies extrapolation (toxicodynamics); 10 for intraspecies variability; 10 for extrapolation from LOAEL to NOAEL because the effects were severe
Critical effect(s):	Cardiomyopathy
Co-critical effect(s):	Myocardial degeneration
Additivity endpoint(s):	Cardiovascular

Cancer Health Risk Limit (cHRL) = Not Applicable

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

Volatile: Yes (Moderate)

Summary of Guidance Value History:
The previous 93/94 nHRL for EPTC is 200 µg/L. It represents the chronic duration and is derived from an EPA IRIS reference dose (RfD). There is also an MDH rapid assessment derived in 2014 of 80 µg/L. The current values for EPTC are 300 µg/L for the acute and short term duration, 90 µg/L for the subchronic duration and 40 µg/L for the chronic duration. There were no previous acute, short term or subchronic values. The reasons that the 2015 HBV for the chronic duration was 5x lower than the 1993 HRL are: 1) use of additional, more recent toxicity information; 2) use of enhanced duration-specific intake rates; and 3) rounding to one significant digit. In 2016 MDH updated the intake rate values used to derive guidance values. The updated intake rates did not result in any change to the nHBV values derived in 2015. The 2016 guidance values were adopted into rule as HRLs in 2018.

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?	No	No	Yes[1]	Yes[2]	Yes[3]

Comments on extent of testing or effects:
[1] Decreased pup body weight forms the basis for the short term RfD. Increased embryotoxicity was observed at 130-fold the acute RfD, along with fetal malformation at over 800-fold higher than the short term RfD.
[2] Total litter loss forms part of the basis of the short term RfD.

[3] Neurotoxicity forms the basis for the acute RfD. Effects seen included necrosis of the brain in adults exposed to EPTC, while neurobehavioral testing such as learning and memory tests did not show a difference in EPTC treated animals over control animals. Clinical signs such as hunched posture, pinched in sides, and hair standing on end in pregnant animals near the time of birth form the basis of the short term RfD. Several studies reported reduced brain weights in adult animals at doses more than 750-fold the subchronic RfD. Another study reported significant decreases in brain weights and neuronal necrosis at doses more than 250-fold the subchronic RfD.

Resources Consulted During Review:

Australian Government Department of Health. (1995). "Acceptible Daily Intakes for Agriculture and Vetrinary Chemicals."

California Environmental Protection Agency - Department of Pesticide Regulation (1995). "EPTC (S-Ethyl-Dipropylthiocarbamate) Risk Characterization Document."

California State Water Resources Control Board (2011). "Compilation of Water Quality Goals."

Lees, D. (2004). "EPTC: Data Evaluation Record of a Developmental Neurotoxicity Study, MRID#46319101."

Minnesota Department of Health (MDH). (2008). Statement of Need and Reasonableness (SONAR), July 11, 2008. Support document relating to Health Risk Limits for Groundwater Rules. Retrieved from http://www.health.state.mn.us/divs/eh/risk/rules/water/hrlsonar08.pdf

Minnesota Department of Health (MDH). (2011). MDH Health Risk Assessment Methods to Incorporate Human Equivalent Dose Calculations into Derivation of Oral Reference Doses (May 2011, revised 2017) from http://www.health.state.mn.us/divs/eh/risk/guidance/hedrefguide.pdf

U.S. Environmental Protection Agency - Office of Pesticide Programs. "Human Health Benchmarks for Pesticides." from https://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home.

U.S. Environmental Protection Agency - Office of Research and Development. (1988). "Recommendations for and Documentation of Biological Values for Use in Risk Assessment." from http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. Environmental Protection Agency (EPA) - Office of Research and Development. (2011). Exposure Factors Handbook: 2011 Edition. Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

U.S. Environmental Protection Agency - Office of the Science Advisor. (2011). "Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose." from http://www.epa.gov/raf/publications/pdfs/recommended-use-of-bw34.pdf.

U.S. Environmental Protection Agency - Office of Water Contaminant Candidate List. from http://www.epa.gov/safewater/ccl/index.html

U.S. Environmental Protection Agency - Regional Screening Tables. "Mid-Atlantic Risk Assessment - Regional Screening Table." from http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/Generic_Tables/index.htm

U.S. Environmental Protection Agency. (1986). "S-Ethyl dipropylthiocarbamate (EPTC) (CASRN 759-94-4)." from http://www.epa.gov/iris/subst/0237.htm.

U.S. Environmental Protection Agency. (1999). "Reregistration Eligibility Decision for EPTC." from https://nepis.epa.gov/Exe/ZyPDF.cgi/20000SBW.PDF?Dockey=20000SBW.PDF

U.S. Environmental Protection Agency (2008a). "Regulatory Determinations Support Document for Selected Contaminants from the Second Drinking Water Contaminant Candidate List (CCL 2)."

U.S. Environmental Protection Agency (2008b). "Health Effects Support Document for S-Ethyl dipropylthiocarbamate (EPTC)."

U.S. Environmental Protection Agency (2011). "EPTC: Human Health Risk Assessment for Proposed Uses on Grass Grown for Seed."