



Toxicological Summary for: Ethyl Ether

CAS: 60-29-7

Synonyms: Anesthesia Ether, Diethyl Ether, Diethyl Oxide, Ethane, 1,1'-Oxybis-Ether, Ether, Ethyl, Ethoxyane, Ethyl Oxide, 3-Oxapentane, 1,1'-Oxybisethane, Solvent Ether

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

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

Subchronic Non-Cancer Risk Assessment Advice (nRAA_{Subchronic}) = 1000 µg/L

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

$$= \frac{(0.42 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.070 \text{ L/kg-d})^{**}}$$

$$= 1200 \text{ rounded to } \mathbf{1000 \text{ µg/L}}$$

*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/Concentration:	(500 x 0.25)/300 = 0.42 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	determined by MDH in 2015
Point of Departure (POD):	500 mg/kg-d (NOAEL, as cited by EPA IRIS 1993 and EPA NCEA 2009)
Human Equivalent Dose (MDH, 2011):	500 x 0.25 = 125 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 (due to lack of data in other species, no oral 2-generation developmental or reproductive studies, and no oral studies evaluating behavior and endocrine effects)
Critical effect(s):	Decreased body weight; anesthesia, increased relative liver weight
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Nervous system

Chronic Non-Cancer Risk Assessment Advice (nRAA_{Chronic}) = 200 µg/L

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

$$= \frac{(0.042 \text{ mg/kg-d}) \times (0.2)^* \times (1000 \text{ µg/mg})}{(0.044 \text{ L/kg-d})^{**}}$$

$$= 191 \text{ rounded to } \mathbf{200 \text{ µg/L}}$$

*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/Concentration:	(500 x 0.25)/3000 = 0.042 mg/kg-d (Sprague Dawley Rat)
Source of toxicity value:	determined by MDH in 2015
Point of Departure (POD):	500 mg/kg-d (NOAEL, as cited by EPA IRIS 1993 and EPA NCEA 2009, subchronic duration)
Human Equivalent Dose (MDH, 2011):	500 x 0.25 = 125 mg/kg-
Total uncertainty factor (UF):	3000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (due to lack of data in other species, no oral 2-generation developmental or reproductive studies, and no oral studies evaluating behavior and endocrine effects), 10 for use of sub-chronic study
Critical effect(s):	Decreased body weight, anesthesia, increased relative liver weight
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system, Nervous system

Cancer Health Based Value (cRAA) = 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: Yes (high)

Summary of Guidance Value History:

A noncancer Chronic HRL of 100 ug/L was promulgated in 1993. Noncancer Subchronic and Chronic RAAs of 1000 and 200 ug/L were derived in 2010. The 2010 Chronic RAA was lower than the previous HRL as a result of: 1) a re-evaluation of the toxicity data; 2) updated MDH risk assessment methodology; and 3) rounding to one significant digit. In 2016, MDH evaluated the available toxicity data and recalculated the non-cancer RAAs using MDH's most recent assessment methodology, which resulted in no changes to any value.

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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes ¹	No ²	Yes ³	Yes ⁴	Yes ⁵

Comments on extent of testing or effects:

¹ Endocrine effects were only evaluated in inhalation studies. Mice exposed to ethyl ether at 1000 to 30,000 ppm experienced increases in plasma corticosterone and plasma adrenocorticotrophic hormone (ACTH) levels. The increases were only significant for corticosterone at 10,000 ppm and the statistical significance of the ACTH increases were not reported.

² Immunological effects were only evaluated in inhalation studies exposed to multiple anesthetic agents, which included ethyl ether. Effects included loss of complement activity, suppression of peripheral blood lymphocyte blastogenic response, an effect in B-cell response, and inhibition of the induction of splenic natural killer cell activity. However, it was unclear whether the effects were due to the general state of anesthesia or the chemical agents themselves.

³ Developmental effects were only evaluated in inhalation studies. Decreased health growth and increased frequency of skeletal variation were seen in offspring born to female mice exposed to ethyl ether by inhalation on gestation days 9 through 12. There was a significant increase in the number Purkinje cells of the cerebellum in offspring of female rats exposed 2 times during gestation days 17 through 21. Offspring exposed early in organogenesis (the period where organs and organ systems are forming during embryonic development) experienced hydronephrosis and increased resorptions occurred while mice exposed later in organogenesis experienced increased skeletal abnormalities. Rats exposed to ethyl ether early and later in organogenesis experienced decreased body weight and decreased long bone length.

⁴ Reproductive effects were only evaluated in inhalation studies. Male rats exposed as newborn infants to ethyl ether at anesthetic levels experienced decreased fertility as adults. Among 110 female anesthesiologists, 18 out of 31 pregnancies resulted in spontaneous abortions and those that had abnormal pregnancies were exposed for 25 hours/week or more and those with normal pregnancies were exposed for less than 15 hours/week. The effects observed in this study were not linked to ethyl ether exclusively because the anesthesiologists were exposed to unknown quantities of several different anesthetic agents.

⁵ Humans experienced anesthetic effects from inhalation of ethyl ether at concentrations ranging from ~20,000 ppm up to ~150,000 ppm. Workers exposed to ~1200 mg/m³ (exposure levels not directly measured) reported dizziness, headaches, mood instability, fatigue, sleep disturbances, difficulty concentrating, sexual dysfunction, and peripheral neuropathy. Anesthetic effects were seen in rats exposed to 3500 mg/kg-day by oral gavage and an increase in response rates were

observed in mice that inhaled ethyl ether at 1000 to 10,000 ppm with an extinguishment of response at all doses in animals exposed for 30 minutes.

Resources Consulted During Review:

ATSDR (Agency for Toxic Substances and Disease Registry). Minimal Risk

Levels. <http://www.atsdr.cdc.gov/mrls.html> and Toxicological Profiles -
<http://www.atsdr.cdc.gov/toxpro2.html>

California Environmental Protection Agency, OEHHA Toxicity Criteria Database.
<http://www.oehha.ca.gov/risk/ChemicalDB/index.asp> and
<http://www.oehha.ca.gov/risk/pdf/cancerpotalpha81005.pdf>

California Water Resources Control Board
http://www.waterboards.ca.gov/water_issues/programs/water_quality_goals/

Environmental Protection Agency (EPA). 1986. Rat oral subchronic study with ethyl ether. Prepared by American Biogenics Corporation for the Office of Solid Waste, Washington, DC. (as cited by IRIS 1993 & NCEA 2009)

EPA Health Effects Assessment Summary Tables (HEAST). July 1997.

EPA Integrated Risk Information System (IRIS) 1993. Ethyl Ether (CASRN 60-29-7)
<http://www.epa.gov/ncea/iris/subst/0423.htm>

EPA National Center for Environmental Assessment (NCEA). 2009 Provisional peer reviewed toxicity values for ethyl ether (diethyl ether) (CASRN 60-29-7). Superfund Health Risk Technical Support Center, NCEA, U.S. EPA.

EPA Office of Drinking Water <http://www.epa.gov/waterscience/criteria/drinking/dwstandards.pdf>

EPA Office of Pesticide Programs <http://www.epa.gov/pesticides/reregistration/status.htm>

EPA Toxicity and Exposure Assessment for Children's Health (TEACH)
<http://www.epa.gov/teach/>

EPA Voluntary Children's Chemical Evaluation Program (VCCEP)
<http://www.epa.gov/oppt/vccep/pubs/chemmain.htm>

European Union Pesticides Database
http://ec.europa.eu/food/plant/protection/evaluation/database_act_subs_en.htm

Health Canada Existing Substances - Priority Substances Assessment Program and Screening Assessment Reports: <http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php#existsub>

International Agency for Research on Cancer (IARC). Agents Reviewed by the IARC
<http://monographs.iarc.fr/ENG/Classification/index.php>

International Programme on Chemical Safety <http://www.who.int/ipcs/assessment/en/>

International Toxicity Estimates for Risk (ITER) http://iter.ctcnet.net/publicurl/pub_search_list.cfm

National Toxicology Program <http://ntp-server.niehs.nih.gov/>

NIOSH. 1993. NEG and NIOSH basis for an occupational health standard: Ethyl Ether. U.S. Department of Health and Human Services, Public Health Service, CDC. Link to abstract: <http://md1.csa.com/partners/viewrecord.php?requester=gs&collection=TRD&recid=20070431102306CE&q=&uid=1079016&setcookie=yes>

Oak Ridge National Laboratory. Screening Levels for Chemical Contaminants. <http://epa-prgs.ornl.gov/chemicals/download.shtml>

Syracuse Research PhysProp Database. <http://www.syrres.com/esc/physdemo.htm>

TOXNET search <http://toxnet.nlm.nih.gov/>

U.S. Geological Survey <http://infotrek.er.usgs.gov/traverse/f?p=HBSL:HOME:0>

Wisconsin Department of Health Services. 2009. Scientific support document for Cycle 9 revisions of NR 140.10, Groundwater enforcement standard and preventive action limit recommendations (includes Ethyl Ether). Division of Public Health, Wisconsin Department of Health Services.

WHO Recommended Classification of Pesticides by Hazard. 2004. http://www.who.int/ipcs/publications/pesticides_hazard_rev_3.pdf

World Health Organization:

http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/index.html (search Chapter 8 Chemical Aspects and Chapter 12 Chemical Fact Sheets for chemical name)