

Provisional Peer-Reviewed Toxicity Values for

Propylene Glycol Monoethyl Ether

(Alpha Isomer [CASRN 52125-53-8] and Beta Isomer [CASRN 1569-02-4])

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TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS	i
BACKGROUND	1
DISCLAIMERS	1
QUESTIONS REGARDING PPRTVs	1
INTRODUCTION	2
REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)	5
DERIVATION OF PROVISIONAL VALUES	6
CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR	7
MODE-OF-ACTION (MOA) DISCUSSION	
APPENDIX A. PHYSICOCHEMICAL PROPERTIES OF PUTATIVE STRUCTURAL	
ANALOGS TO PROPYLENE GLYCOL MONOETHYL ETHER ISOMERS	8
APPENDIX B. REFERENCES	9

COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin	MN	micronuclei
ACGIH	American Conference of Governmental	MNPCE	micronucleated polychromatic
	Industrial Hygienists		erythrocyte
AIC	Akaike's information criterion	MOA	mode-of-action
ALD	approximate lethal dosage	MTD	maximum tolerated dose
ALT	alanine aminotransferase	NAG	N-acetyl-β-D-glucosaminidase
AST	aspartate aminotransferase	NCEA	National Center for Environmental
atm	atmosphere	110211	Assessment
ATSDR	Agency for Toxic Substances and	NCI	National Cancer Institute
modit	Disease Registry	NOAEL	no-observed-adverse-effect level
BMD	benchmark dose	NTP	National Toxicology Program
BMDL	benchmark dose lower confidence limit	NZW	New Zealand White (rabbit breed)
BMDS	Benchmark Dose Software	OCT	ornithine carbamoyl transferase
BMR	benchmark response	ORD	Office of Research and Development
BUN	blood urea nitrogen	PBPK	physiologically based pharmacokinetic
BW	body weight	PCNA	proliferating cell nuclear antigen
CA	chromosomal aberration	PND	postnatal day
CAS	Chemical Abstracts Service	POD	point of departure
CASRN	Chemical Abstracts Service Registry	POD _[ADJ]	duration-adjusted POD
CHISTER	Number	QSAR	quantitative structure-activity
CBI	covalent binding index	QB/IIC	relationship
СНО	Chinese hamster ovary (cell line cells)	RBC	red blood cell
CL	confidence limit	RDS	replicative DNA synthesis
CNS	central nervous system	RfC	inhalation reference concentration
CPN	chronic progressive nephropathy	RfD	oral reference dose
CYP450	cytochrome P450	RGDR	regional gas dose ratio
DAF	dosimetric adjustment factor	RNA	ribonucleic acid
DEN	diethylnitrosamine	SAR	structure activity relationship
DMSO	dimethylsulfoxide	SCE	sister chromatid exchange
DNA	deoxyribonucleic acid	SD	standard deviation
EPA	Environmental Protection Agency	SDH	sorbitol dehydrogenase
FDA	Food and Drug Administration	SE	standard error
FEV1	forced expiratory volume of 1 second	SGOT	glutamic oxaloacetic transaminase, also
GD	gestation day		known as AST
GDH	glutamate dehydrogenase	SGPT	glutamic pyruvic transaminase, also
GGT	γ-glutamyl transferase		known as ALT
GSH	glutathione	SSD	systemic scleroderma
GST	glutathione-S-transferase	TCA	trichloroacetic acid
Hb/g-A	animal blood-gas partition coefficient	TCE	trichloroethylene
Hb/g-H	human blood-gas partition coefficient	TWA	time-weighted average
HEČ	human equivalent concentration	UF	uncertainty factor
HED	human equivalent dose	UF_A	interspecies uncertainty factor
i.p.	intraperitoneal	$\mathrm{UF_H}$	intraspecies uncertainty factor
IRIS	Integrated Risk Information System	UF_S	subchronic-to-chronic uncertainty factor
IVF	in vitro fertilization	UF_D	database uncertainty factor
LC_{50}	median lethal concentration	U.S.	United States of America
LD_{50}	median lethal dose	WBC	white blood cell
LOAEL	lowest-observed-adverse-effect level		

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR PROPYLENE GLYCOL MONOETHYL ETHER

(Alpha Isomer [CASRN 52125-53-8] and Beta Isomer [CASRN 1569-02-4])

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Propylene glycol monoethyl ether (alpha isomer [CASRN 52125-53-8] and beta isomer [CASRN 1569-02-4]) is a clear colorless liquid used to make lacquers, paints, leather finishes, wood stains, furniture polishes, inks, polyglycol ethers, and cleaning products. It is also used as an antifreeze, solvent, adhesive additive, as well as in agrochemical formulations and nail care products (ChemIDplus, 2014). The molecular formula of both propylene glycol monoethyl ether isomers is $C_5H_{12}O_2$ (see Figure 1). A list of physicochemical properties of the propylene glycol monoethyl ether isomers is provided in Table 1.

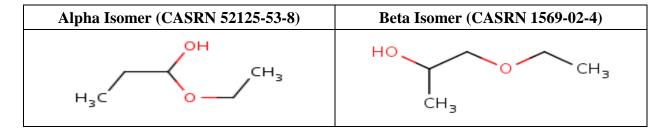


Figure 1. Chemical Structures of Propylene Glycol Monoethyl Ether Isomers

	Value		
Property (unit)	Alpha Isomer (CASRN 52125-53-8)	Beta Isomer (CASRN 1569-02-4)	
Boiling point (°C)	ND	131	
Melting point (°C)	ND	ND	
Density (g/cm³ at 20°C)	ND	ND	
pH (unitless)	ND	ND	
Relative vapor density (air = 1)	ND	ND	
Vapor pressure (mm Hg at 25°C)	2.42	3.86	
Solubility in water (mg/L at 25°C)	3.66×10^{5}	3.66×10^{5}	
LogP (octanol-water)	NV	NV	
Molecular weight (g/mol)	104.15	104.15	
Henry's law constant (atm-m³/mol)	7.38×10^{-8}	7.38×10^{-8}	

^aChemIDplus (2014).

ND = no data; NV = no value.

Table 2 provides a summary of available toxicity values for propylene glycol monoethyl ether from the U.S. EPA and other regulatory agencies or organizations.

Table 2. Summary of Available Toxicity Values for Propylene Glycol Monoethyl Ether Isomers (Alpha Isomer [CASRN 52125-53-8]^a and Beta Isomer [CASRN 1569-02-4]^b)

Source/Parameter ^{c,d}	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	NV ^{a,b}	NA	ACGIH (2013)	NA
ATSDR	NV ^{a,b}	NA	ATSDR (2013)	NA
Cal/EPA	NV ^{a,b}	NA	<u>Cal/EPA (2014a)</u>	9-9-2014 ^d
NIOSH	NV ^{a,b}	NA	NIOSH (2010)	NA
OSHA	$NV^{a,b}$	NA	OSHA (2011, 2006)	NA
IRIS	NV ^{a,b}	NA	U.S. EPA	9-9-2014
Drinking water	$NV^{a,b}$	NA	<u>U.S. EPA (2012)</u>	NA
HEAST	NV ^a	NA	<u>U.S. EPA (2011)</u>	NA
	^b Chronic RfD = 7 × 10 ⁻¹ mg/kg-day ^b Subchronic RfD = 7 × 10 ⁰ mg/kg-day	The critical effect is decreased weight gain in rats for both the chronic and subchronic RfDs (Smyth and Carpenter, 1948).	U.S. EPA (2011)	
HEA	NV ^a	NA	U.S. EPA (1984)	NA
	^b AIS = 476 mg/kg-day ^b AIC = 47.6 mg/kg-day	Based on the incidence of reduced growth and kidney changes in rats (Smyth and Carpenter, 1948).	U.S. EPA (1984)	
CARA HEEP	NV ^{a,b}	NA	U.S. EPA (1994)	NA
WHO	NV ^{a,b}	NA	WHO	9-9-2014
Cancer				'
IRIS	$NV^{a,b}$	NA	U.S. EPA	9-9-2014
HEAST/WOE	NV ^{a,b}	NA	U.S. EPA (2011)	NA
IARC	NV ^{a,b}	NA	<u>IARC (2013)</u>	NA
NTP	NV ^{a,b}	NA	NTP (2011)	NA

Table 2. Summary of Available Toxicity Values for Propylene Glycol Monoethyl Ether Isomers (Alpha Isomer [CASRN 52125-53-8]^a and Beta Isomer [CASRN 1569-02-4]^b)

Source/Parameter ^{c,d}	Value (Applicability)	Notes	Reference	Date Accessed
Cal/EPA	$NV^{a,b}$	NA	Cal/EPA (2014b, 2009)	NA

^aAlpha isomer of propylene glycol monoethyl ether

AIC = acceptable intake chronic; AIS = acceptable intake subchronic; IDLH = immediately dangerous to life or health; NA = not applicable; NSRL = no significant risk level; NV = not available; PEL = permissible exposure level; REL = recommended exposure level; RfD = oral reference dose TLV = threshold limit value; TWA = time weighted average; WOE = cancer weight of evidence.

^bBeta isomer of propylene glycol monoethyl ether

cources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; HEA = Health Effects Assessment; HEAST = Health Effects Assessment; Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.

^dThe Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://oehha.ca.gov/tcdb/index.asp) was also reviewed and found to contain no information on propylene glycol monoethyl ether.

Literature searches were conducted on sources published from 1900 through August 2014 for studies relevant to the derivation of provisional toxicity values for propylene glycol monoethyl ether (alpha isomer [CASRN 52125-53-8] and beta isomer [CASRN 1569-02-4]). The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

The available data on both isomers of propylene glycol monoethyl ether primarily focus on their physicochemical properties. No repeated-dose toxicity studies via the oral or inhalation route of exposure are available in humans or laboratory animals for the alpha isomer of propylene glycol monoethyl ether. For the beta isomer of propylene glycol monoethyl ether, the only relevant study that warrants any consideration for derivation of provisional references doses (p-RfDs) is an oral range-finding study by Smyth and Carpenter (1948). In this study, propylene glycol monoethyl ether was administered in the drinking water to groups of Sherman rats (5/sex/dose) at doses of 0 (control), 160, 680, or 2,140 mg/kg-day for 30 days. Body weight, appetite, and morbidity were measured, and microscopic analysis of the adrenals, upper intestine, kidney, liver, and spleen were performed (although the time at which these measurements were conducted was not reported, it was assumed to have been at study termination). Appetite was judged on the basis of water consumption (in mL). Reduced appetite and reduced growth at 2,140 mg/kg-day were reported by the study authors (sex of rats affected was not specified). Although propylene glycol monoethyl ether-induced "kidney changes" were mentioned in the U.S. EPA (1984) Health Effects Assessment (HEA), no such changes were mentioned in the original Smyth and Carpenter (1948) study report. No details regarding the examination or observation of other toxicological endpoints were provided in the study.

Oral toxicity values have been previously derived using the <u>Smyth and Carpenter (1948)</u> range-finding study (<u>U.S. EPA, 2011</u>, <u>1984</u>; see Table 2). However, the HEA (<u>U.S. EPA, 1984</u>) document reported that the <u>Smyth and Carpenter (1948)</u> study is only marginally adequate for risk assessment purposes, as this study utilized a relatively small number of animals, and hematology, serum biochemistry, urinalysis, organ weights, and detailed histopathology were not reported. Thus, the <u>Smyth and Carpenter (1948)</u> study does not comprehensively evaluate sufficient toxicological endpoints, and is not considered adequate for use in the derivation of any p-RfD values by current standards.

No toxicity information is available regarding inhalation exposure of humans or animals to the beta isomer of propylene glycol monoethyl ether.

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF ORAL REFERENCE DOSES Feasibility of Deriving Subchronic and Chronic p-RfDs

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on the alpha isomer of propylene glycol monoethyl ether via the oral route were identified. For the beta isomer of propylene glycol monoethyl ether, only a 30-day oral range-finding study (Smyth and Carpenter, 1948) in Sherman rats is available. However, as stated above, this study is not considered adequate for use in the derivation of any p-RfD values by current standards. Thus, an attempt was made to use a computational toxicological surrogate approach to identify surrogate chemicals for both isomers of propylene glycol monoethyl ether (see Wang et al., 2012 for details on this established methodology). For the alpha isomer of propylene glycol monoethyl ether, no suitable analogs with >50% structural similarity and possessing repeated-dose toxicity values were identified using the ChemIDplus database. For the beta isomer of propylene glycol monoethyl ether, two putative structural analogs (1-methoxy-2-hydroxypropane [or propylene glycol monomethyl ether; CASRN 107-98-2] and propylene glycol [CASRN 57-55-6]) with >50% structural similarity and possessing repeateddose toxicity values were identified using the ChemIDplus database. Although subchronic and chronic p-RfDs are available in a PPRTV assessment of propylene glycol (U.S. EPA, 2008), these p-RfDs are based on hematological endpoints observed in male Wistar rats following 5 weeks of oral administration in drinking water (Vaille et al., 1971). Thus, when compared to the beta isomer of propylene glycol monoethyl ether, it cannot be determined whether the 1-methoxy-2-hydroxypropane and propylene glycol structural analogs share similar target organs of toxicity or toxicity endpoints following oral exposure. Additionally, due to the general lack of information on the physicochemical properties of the alpha and beta isomers of propylene glycol monoethyl ether (see Table 1), it is difficult to analyze for comparability with those of the two putative structural analogs (see Appendix A; note known differences in solubility and vapor pressure). Finally, no metabolism information is available for either of the propylene glycol monoethyl ether isomers. Taken together, a computational toxicological surrogate approach based on the established Wang et al. (2012) methodology is not feasible for either isomer of propylene glycol monoethyl ether; therefore, no p-RfDs are derived in this PPRTV assessment.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS Feasibility of Deriving Subchronic and Chronic Provisional Reference Concentrations (p-RfCs)

Although a chronic inhalation reference concentration (RfC) is available on IRIS for the 1-methoxy-2-hydroxypropane structural analog to the beta isomer of propylene glycol monoethyl ether (<u>U.S. EPA, 1995</u>), no short-term-duration, subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on either the alpha or beta isomers of propylene glycol monoethyl ether via the inhalation route were available for comparative toxicity analysis. Thus, application of a computational toxicological surrogate approach in the derivation of p-RfCs is precluded in this PPRTV assessment.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Limitations in the available data preclude development of a WOE descriptor for both isomers of propylene glycol monoethyl ether.

MODE-OF-ACTION (MOA) DISCUSSION

Limitations in the available data preclude determination of a MOA discussion for both isomers of propylene glycol monoethyl ether.

APPENDIX A. PHYSICOCHEMICAL PROPERTIES OF PUTATIVE STRUCTURAL ANALOGS TO PROPYLENE GLYCOL MONOETHYL ETHER ISOMERS

Physicochemical Properties of Putative Structural Analogs to Propylene Glycol Monoethyl Ether Isomers^a

	Value		
Property (unit)	1-Methoxy-2-Hydroxypropane (CASRN 107-98-2)	Propylene Glycol (CASRN 57-55-6)	
Boiling point (°C)	119	187.6	
Melting point (°C)	-1.42×10^2	-6.00×10^{1}	
Density (g/cm ³ at 20°C)	ND	ND	
pH (unitless)	ND	ND	
Relative vapor density (air = 1)	ND	ND	
Vapor pressure (mm Hg at 25°C)	12.5	0.129	
Solubility in water (mg/L at 25°C)	1.00×10^6	1.00×10^6	
LogP (octanol-water)	-0.490	-0.92	
Molecular weight (g/mol)	90.12	76.09	
Henry's law constant (atm-m ³ /mol)	9.20×10^{-7}	1.29×10^{-8}	

^aChemIDplus (2014).

ND = no data.

APPENDIX B. REFERENCES

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