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Provisional Peer-Reviewed Toxicity Values for

1-Chlorooctadecane
(CASRN 3386-33-2)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1-CHLOROOCTADECANE (CASRN 3386-33-2)

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

1-Chlorooctadecane (CASRN 3386-33-2) is a high production volume chemical used as a solvent and an intermediate in the manufacture of surfactant, pharmaceuticals, and other organic compounds. The molecular formula of 1-chlorooctadecane is $CH_3(CH_2)_{17}Cl$ (see Figure 1). A list of physicochemical properties is provided in Table 1.

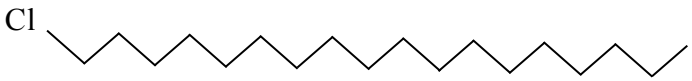

Figure 1. 1-Chlorooctadecane (CASRN 3386-33-2) Structure

Table 1. Physicochemical Properties of 1-Chlorooctadecane (CASRN 3386-33-2)[a]

Property (Unit)	Value
Boiling point (°C)	348
Melting point (°C)	28.6
Density (g/cm^3 at 20°C)	ND
Vapor pressure (mm Hg at 25°C)	1.71×10^{-5}
pH (unitless)	ND
Solubility in water (mg/L at 25°C)	1.25×10^{-4}
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	288.943

[a]ChemIDplus (2013).

ND = no data.

Table 2 provides a summary of available toxicity values for 1-chlorooctadecane from EPA and other regulatory agencies or organizations.

Table 2. Summary of Available Toxicity Values for 1-Chlorooctadecane (CASRN 3386-33-2)

Source/Parameter[a,b]	Value (Applicability)	Reference
Noncancer		
ACGIH	NA	ACGIH (2013)
ATSDR	NA	ATSDR (2013)
Cal/EPA	NA	(Cal/EPA);Cal/EPA (2014)[c]
NIOSH	NA	NIOSH (2010)
OSHA	NA	OSHA (2011); OSHA (2006)
IRIS	NA	(U.S. EPA)
DWSHA	NA	U.S. EPA (2012a)
HEAST	NA	U.S. EPA (2011)
CARA HEEP	NA	U.S. EPA (1994)
WHO	NA	(WHO)
Cancer		
IRIS	NA	(U.S. EPA)
HEAST/WOE	NA	U.S. EPA (2011)
IARC	NA	(IARC)
NTP	NA	NTP (2014)
Cal/EPA	NA	(Cal/EPA); Cal/EPA (2015a); Cal/EPA (2011)

[a]Sources: 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; DWSHA = Drinking Water Standards and Health Advisories; 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.

[b]Parameters: Cancer weight of evidence (WOE) (U.S. EPA, 1986).

[c]The 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 1-chlorooctadecane.

NA = not available.

Literature searches were conducted on sources published from 1900 through February 2015 for studies relevant to the derivation of provisional toxicity values for 1-chlorooctadecane (CASRN 3386-33-2). 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 1-chlorooctadecane primarily focuses on its biodegradation, biotransformation by marine creatures, incorporation into the fatty acids of microorganisms, and usage in the development of analytical methods. No usable information is available regarding repeated-dose oral or inhalation exposure of humans or animals to 1-chlorooctadecane.

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 1-chlorooctadecane via the oral route were identified. Thus, no oral reference doses could be derived. However, as noted below, a computational toxicological surrogate approach was attempted.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Feasibility of Deriving Subchronic and Chronic Provisional Reference Concentrations (p-RfCs)

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 1-chlorooctadecane via the inhalation route were identified. Thus, no inhalation reference doses could be derived. However, as noted below, a computational toxicological surrogate approach was attempted.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Limitations in the available data preclude development of a weight-of-evidence (WOE) descriptor.

MODE-OF-ACTION (MOA) DISCUSSION

Limitations in the available data preclude determination of a mode-of-action (MOA) discussion.

ALTERNATIVE METHODS

The surrogate approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for surrogate analysis are presented in Wang et al. (2012). Three types of potential surrogates (structural, metabolic, and toxicity) are identified to facilitate the final surrogate chemical selection. The surrogate approach may or may not be route-specific or applicable to multiple routes of exposure. All information was considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable surrogate both toxicologically and chemically.

An initial surrogate search focused on the identification of structurally similar chemicals with toxicity values from the Integrated Risk Information System (IRIS), PPRTV, and Health Effects Assessment Summary Tables (HEAST) databases to take advantage of the well-characterized chemical-class information. This was accomplished by searching the US EPA's DSSTox database (DSSTox, 2012) at similarity levels >60%, and the National Library of Medicine's ChemID*plus* database (ChemIDplus, 2013) at similarity levels >80%. There were 20 compounds identified in DSSTox and 76 compounds identified in ChemID*plus*, for a total of 69 unique compounds. The larger number of compounds identified in ChemID*plus* largely reflects its inclusion of other halogen substituted (fluorinated or brominated) compounds. However, there was no in vivo repeated-dose information on any of these related compounds. Due to a lack of repeat-dose toxicity information for any of the potential structural surrogates, derivation of risk values (e.g., RfD, RfC, and oral cancer slope factor) based on the computational toxicological surrogate approach (Wang et al., 2012) is not feasible for 1-chlorooctadecane.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2013). 2013 TLVs and BEIs. Based on documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). (2013). Minimal risk levels (MRLs) for hazardous substances. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR). Retrieved from http://www.atsdr.cdc.gov/mrls/index.asp

Cal/EPA (California Environmental Protection Agency). (2011). Hot spots unit risk and cancer potency values. Appendix A. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://www.oehha.ca.gov/air/hot_spots/2009/AppendixA.pdf

Cal/EPA (California Environmental Protection Agency). (2014). All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 2014. Sacramento, CA: Office of Health Hazard Assessment. http://www.oehha.ca.gov/air/allrels.html

Cal/EPA (California Environmental Protection Agency). (2015a). Chemicals known to the state to cause cancer or reproductive toxicity, May 11, 2015. Proposition 65 list. Sacramento, CA: Office of Environmental Health Hazzard Assessment. http://oehha.ca.gov/prop65/prop65_list/Newlist.html

Cal/EPA (California Environmental Protection Agency). (2015b). OEHHA toxicity criteria database [Database]. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from http://www.oehha.ca.gov/tcdb/

ChemIDplus. (2013). 1-Chloroctadecane. Bethesda, MD: Department of Health and Human Services, National Library of Medicine. Retrieved from http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp

DSSTox (Distributed Structure-Searchable Toxicity). (2012). DSSTox database network. Washington, DC: U.S. Environmental Protection Agency, National Center for Computational Toxicology. Retrieved from http://www.epa.gov/ncct/dsstox/

IARC (International Agency for Research on Cancer). (2015). IARC Monographs on the evaluation of carcinogenic risk to humans. Available online at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

NIOSH (National Institute for Occupational Safety and Health). (2010). NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Atlanta, GA: Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). (2014). Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html

OSHA (Occupational Safety & Health Administration). (2006). Table Z-1 limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. (OSHA standard 1910.1000). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

OSHA (Occupational Safety & Health Administration). (2011). Air contaminants: occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286

U.S. EPA (U.S. Environmental Protection Agency). (1986). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/R-00/004). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://epa.gov/raf/publications/pdfs/CA%20GUIDELINES_1986.PDF

U.S. EPA (U.S. Environmental Protection Agency). (1994). Chemical assessments and related activities (CARA) [EPA Report]. (600/R-94/904; OHEA-I-127). Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt

U.S. EPA (U.S. Environmental Protection Agency). (2011). Health effects assessment summary tables (HEAST). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. http://epa-heast.ornl.gov/

U.S. EPA (U.S. Environmental Protection Agency). (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: Office of Water. http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Integrated risk information system (IRIS). Washington, DC: U.S. Environmental Protection Agency, IRIS. Retrieved from http://www.epa.gov/iris/index.html

Wang, NC; Zhao, QJ; Wesselkamper, SC; Lambert, JC; Petersen, D; Hess-Wilson, JK. (2012). Application of computational toxicological approaches in human health risk assessment. I. A tiered surrogate approach. Regul Toxicol Pharmacol 63: 10-19. http://dx.doi.org/10.1016/j.yrtph.2012.02.006

WHO (World Health Organization). (2012). Online catalog for the Environmental Health Criteria Series. Available online at http://www.who.int/ipcs/publications/ehc/en/