

Provisional Peer-Reviewed Toxicity Values for

1,1-Dichloropropene
(CASRN 563-58-6)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Dan D. Petersen, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

National Center for Environmental Assessment, Cincinnati, OH

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Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α 2u-g	alpha 2u-globulin	MN	micronuclei
ACGIH	American Conference of Governmental Industrial Hygienists	MNPCE	micronucleated polychromatic 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 Assessment
atm	atmosphere	NCI	National Cancer Institute
ATSDR	Agency for Toxic Substances and 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 number	POD _{ADJ}	duration-adjusted POD
CBI	covalent binding index	QSAR	quantitative structure-activity relationship
CHO	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
FEV ₁	forced expiratory volume of 1 second	SGOT	glutamic oxaloacetic transaminase, also known as AST
GD	gestation day	SGPT	glutamic pyruvic transaminase, also known as ALT
GDH	glutamate dehydrogenase	SSD	systemic scleroderma
GGT	γ -glutamyl transferase	TCA	trichloroacetic acid
GSH	glutathione	TCE	trichloroethylene
GST	glutathione-S-transferase	TWA	time-weighted average
Hb/g-A	animal blood-gas partition coefficient	UF	uncertainty factor
Hb/g-H	human blood-gas partition coefficient	UF _A	interspecies uncertainty factor
HEC	human equivalent concentration	UF _H	intraspecies uncertainty factor
HED	human equivalent dose	UF _S	subchronic-to-chronic uncertainty factor
i.p.	intraperitoneal	UF _D	database uncertainty factor
IRIS	Integrated Risk Information System	U.S.	United States of America
IVF	in vitro fertilization	WBC	white blood cell
LC ₅₀	median lethal concentration		
LD ₅₀	median lethal dose		
LOAEL	lowest-observed-adverse-effect level		

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,1-DICHLOROPROPENE (CASRN 563-58-6)

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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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

1,1-Dichloropropene (1,1-DCPe) (CASRN 563-58-6) is an industrial chemical found at some Superfund sites. No repeat-dose studies are available in the scientific literature on which to base a hazard identification or a dose-response evaluation for the derivation of toxicity values. The related compound 1,3-dichloropropene is used as a pesticide, while the other four dichloropropenes have no reported uses and are present in lower concentrations ([ATSDR, 2008](#)). 1,1-DCPe is on the Tox 21 list [10,000 chemicals, [U.S. EPA \(2015b\)](#)] currently undergoing in vitro toxicity testing. The molecular formula of 1,1-DCPe is C₃H₄Cl₂ (see Figure 1). A list of physicochemical properties is provided in Table 1.

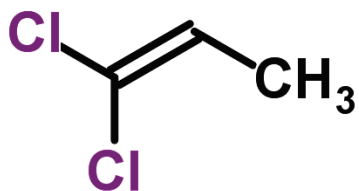


Figure 1. 1,1-Dichloropropene Structure

Table 1. Physicochemical Properties of 1,1-Dichloropropene (CASRN 563-58-6)^a	
Property (unit)	Value
Boiling point (°C)	76.5
Melting point (°C)	ND
Density (g/cm ³ at 20°C)	ND
Vapor pressure (mmHg at 20°C)	90.8
pH (unitless)	ND
Solubility in water (mg/L at 25°C)	749
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	110.97

^a[ChemIDplus \(2015\)](#).

ND = no data.

Table 2 provides a summary of available toxicity values for 1,1-DCPe (CASRN 563-58-6) from U.S. EPA and other regulatory agencies or organizations.

Table 2. Summary of Available Toxicity Values for 1,1-Dichloropropene (CASRN 563-58-6)

Source/Parameter ^{a,b}	Value (applicability)	Reference
Noncancer		
ACGIH	NV	ACGIH (2015)
ATSDR	NV	ATSDR (2015)
Cal/EPA	NV	Cal/EPA (2015b) ; Cal/EPA (2014)
NIOSH	NV	NIOSH (2015)
OSHA	NV	OSHA (2011) ; OSHA (2006)
IRIS	NV	U.S. EPA (2015a)
DWSHA	NV	U.S. EPA (2012)
HEAST	NV	U.S. EPA (2011)
CARA HEEP	NV	U.S. EPA (1994)
WHO	NV	WHO (2015)
Cancer		
IRIS	NV	U.S. EPA (2015a)
HEAST/WOE	NV	U.S. EPA (2011)
IARC	NV	IARC (2015)
NTP	NV	NTP (2014)
Cal/EPA	NV	Cal/EPA (2015a) ; Cal/EPA (2011)

^aSources: 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 Systems; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.

^bParameters: WOE = cancer weight of evidence ([U.S. EPA, 1986](#)).

NV = not available.

Literature searches were conducted on sources published from 1900 through April 2015 for studies relevant to the derivation of provisional toxicity values for 1,1-DCPe (CASRN 563-58-6). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET

(Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for toxicity values: 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 1,1-DCPe (CASRN 563-58-6) primarily focuses on its biodegradation, biotransformation by soil organisms, and use in the development of analytical methods. 1,1-DCPe is a contaminant in some drinking water sources. Because of this and the fact that no toxicological data were available for this compound, which is structurally similar to the rodent carcinogen 1,3-dichloropropene (1,3-DCPe), 1,1-DCPe was placed on the EPA's Contaminant Candidate List. No information is available on repeated-dose oral or inhalation exposure of humans or animals to 1,1-DCPe. A genetic toxicology study was conducted in several *Salmonella* strains ([Granville et al., 2005](#)). The study evaluated mutagenicity using the *Salmonella* assay, the deoxyribonucleic acid (DNA) damage (comet assay), and the apoptotic (caspase assay) activities in human lymphoblastoid cells. In *Salmonella*, 1,1-DCPe was not mutagenic in strains TA98, TA100, TA1535, or TA104 ±S9 mix. However, it was clearly mutagenic in strain RSJ100, which expresses the rat GSTT1-1 gene. 1,1-DCPe did not induce DNA damage in GSTT1-1-deficient human lymphoblastoid cells, and it induced apoptosis in these cells only at 5 mM. Consistent with its mutagenesis in RSJ100, 1,1-DCPe reacted with glutathione (GSH) in vitro, suggesting an addition-elimination mechanism to account for the detected GSH conjugate. 1,1-DCPe was approximately 5,000 times more mutagenic than 1,1-dichloroethylene (1,1-DCE). Neither 1,1-DCE nor 1,3-DCPe showed enhanced mutagenicity in strain RSJ100, indicating a lack of activation of these congeners by GSTT1-1. Thus, 1,1-DCPe appears to be a base-substitution mutagen, requiring activation by GSTT1-1, and possibly involving the production of a reactive episulfonium ion. This bioactivation mechanism of 1,1-DCPe is thus different from that of its congeners 1,1-DCE and 1,3-DCPe. 1,1-DCPe also has caused genotoxicity in fish ([Winn et al., 2006](#)). It is being tested as part of Tox 21, and is in the NTP 1408 compound library. However, following EPA guidance, the available mechanistic studies do not provide endpoints that are currently usable for identifying a point of departure (POD).

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 1,1-dichloropropene via the oral route were identified. Thus, no oral reference doses (RfDs) 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 p-RfCs

No subchronic-duration, chronic-duration, developmental toxicity, reproductive toxicity, or carcinogenicity studies on 1,1-dichloropropene via the inhalation route were identified. Thus, no inhalation reference doses (RfCs) 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 ChemIDplus database ([ChemIDplus, 2015](#)) at similarity levels >70%. Both ChemIDplus (which uses 3D QSAR models) and DSSTox (which uses 2D QSAR models) identified an overlapping list of analogs (see Table 3).

Table 3. Structural Analogues for 1,1-Dichloropropene		
Chemical Name	Structural Similarity	Information Source
1-Bromo-1-chloropropene	90%	ChemIDplus (2015)
1,1-Dibromopropene	88%	
1,1-Dichlorobutene	87%	
Trichloroethylene	80%	
1,1,2-Trichloropropene	77%	
1,2-Dichloro-1-flouroethylene	76%	
2-Bromo-1,1-dichloroethylene	75%	
1,1-Dichloroethylene	74%	
1-Chloropropene	80%	
1,1-DCE	70%	
Dimethylvinyl chloride	67%	
Tetrachloroethylene	64%	
Trichloroethylene	64%	
1,3-Dichloropropene	62%	

While there was in vivo repeat-dose information on some of these closely related compounds, including 1,1-DCE, 1,3-DCPe, tetrachloroethylene, and trichloroethylene, there was no data on the parent compound 1,1-DCPe to match health effects. The structurally closely related chemicals' toxicity profiles also showed no consistent pattern of target organ toxicity, as shown in Table 4. Due to a lack of matching repeat-dose toxicity information for any of the potential structural surrogates, derivation of risk values (e.g., RfD, RfC, and oral cancer slope factor [OSF]) based on the computational toxicological surrogate approach [Wang et al. \(2012\)](#) is not feasible for 1-DCPe.

Table 4: The Target Organs and RfD of Potential Surrogates		
Potential Surrogate Chemical	Target Organ	RfD
Trichloroethylene	Immune system	5×10^{-4} mg/kg-d
Tetrachloroethylene	Nervous system	6×10^{-3} mg/kg-d
1,1-DCE	Liver	5×10^{-2} mg/kg-d
1,3-DCPe	Nasal respiratory epithelium chronic irritant	3×10^{-2} mg/kg-d

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