United States
Environmental Protection
Agency

EPA/690/R-22/001F | September 2022 | FINAL

Provisional Peer-Reviewed Toxicity Values for

cis-1,2-Dichloroethylene (*cis*-1,2-DCE)
(CASRN 156-59-2)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

United States Environmental Protection Agency

EPA/690/R-22/001F
September 2022
https://www.epa.gov/pprtv

Provisional Peer-Reviewed Toxicity Values for

cis-1,2-Dichloroethylene (*cis*-1,2-DCE)
(CASRN 156-59-2)

Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Allison L. Phillips, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

CONTRIBUTORS

Lucina E. Lizarraga, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

Chelsea A. Weitekamp, PhD
Center for Public Health and Environmental Assessment, Research Triangle Park, NC

SCIENTIFIC TECHNICAL LEAD

Lucina E. Lizarraga, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Jeffry L. Dean II, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

Roman Mezencev, PhD
Center for Public Health and Environmental Assessment, Cincinnati, OH

PRIMARY EXTERNAL REVIEWERS

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

PPRTV PROGRAM MANAGEMENT

Teresa L. Shannon
Center for Public Health and Environmental Assessment, Cincinnati, OH

J. Phillip Kaiser, PhD, DABT
Center for Public Health and Environmental Assessment, Cincinnati, OH

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS v
BACKGROUND 1
QUALITY ASSURANCE 1
DISCLAIMERS 2
QUESTIONS REGARDING PPRTVs 2
1. INTRODUCTION 3
2. REVIEW OF POTENTIALLY RELEVANT DATA FOR DERIVATION OF NONCANCER AND CANCER INHALATION REFERENCE VALUES 8
2.1. OTHER DATA (SHORT TERM TESTS, OTHER EXAMINATIONS) 8
2.1.1. Supporting Animal Studies 16
2.1.2. Genotoxicity 18
2.1.3. Metabolism/Toxicokinetic Studies 19
3. DERIVATION OF PROVISIONAL VALUES 21
3.1. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS 21
3.2. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES 21
3.3. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR 21
3.4. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES 22
APPENDIX A. SCREENING NONCANCER PROVISIONAL VALUES 23
APPENDIX B. REFERENCES 70

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
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
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
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	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
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	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum 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_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *CIS*-1,2-DICHLOROETHYLENE (CASRN 156-59-2) [NONCANCER INHALATION VALUES]

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 U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

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.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA eComments Chemical Safety website at https://ecomments.epa.gov/chemicalsafety/.

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

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. 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 content of this PPRTV assessment should be directed to the U.S. EPA ORD CPHEA website at https://ecomments.epa.gov/pprtv.

1. INTRODUCTION

cis-1,2-Dichloroethylene (*cis*-1,2-DCE; CASRN 156-59-2) belongs to the class of compounds known as halogenated alkenes. *cis*-1,2-DCE is an isomer of dichloroethylene. Mixtures of *cis*-1,2-DCE with its isomer, *trans*-1,2-dichloroethylene (*trans*-1,2-DCE), have several commercial uses. 1,2-DCE mixtures are used in the production of other chlorinated compounds and for solvent vapor and surface cleaning (Dreher et al., 2014; Mertens, 2000; ATSDR, 1996). 1,2-DCEs are also used as foam blowing additives, as refrigerants, and in silicone etching (Dreher et al., 2014). Other reported uses of 1,2-DCEs include low temperature solvent extraction for organic materials such as waxes, resins, dyes, perfumes, lacquers, and thermoplastics and extraction of oil and fats from fish and meat (Dreher et al., 2014; Mertens, 2000). *cis*-1,2-DCE can be produced directly by chlorinating acetylene (Mertens, 2000). 1,2-DCEs are also produced as a byproduct of chlorinated compound production (Mertens, 2000). *cis*-1,2-DCE is listed on the U.S. EPA nonconfidential Toxic Substances Control Act (TSCA) inventory (U.S. EPA, 2021c) and is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2020).

The empirical formula for *cis*-1,2-DCE is $C_2H_2Cl_2$, and its structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of *cis*-1,2-DCE. *cis*-1,2-DCE is a clear, colorless liquid with a sharp, ether-like odor (NLM, 2021g; ATSDR, 1996). Given its high vapor pressure, *cis*-1,2-DCE is expected to exist solely as a vapor in the atmosphere. Its vapor pressure and moderate Henry's law constant indicate that it will likely volatilize from either dry or moist soil surfaces and from water surfaces. The high water solubility and low soil adsorption coefficient indicate that *cis*-1,2-DCE will have the potential to leach to groundwater or undergo runoff after a rain event.

Figure 1. *cis*-1,2-DCE (CASRN 156-59-2) Structure

Table 1. Physicochemical Properties of *cis*-1,2-DCE (CASRN 156-59-2)

Property (unit)	Value[a]
Molecular formula (unitless)	$C_2H_2Cl_2$
Molecular weight (g/mol)	96.94
Physical state	Liquid[b]
Physical properties	Clear, colorless, ether-like odor
Boiling point (°C)	54.4
Melting point (°C)	−64.9
Density (g/cm^3 at 20°C)	1.24 (predicted)
Vapor density (at boiling point and 760 mm Hg)	3.54 g/L[b]
Vapor pressure (mm Hg)	200[b]
Water solubility (mol/L)	0.0493
Log K_{ow}	1.86
pKa (unitless)	NA
Henry's law constant (atm-m^3/mole)	0.00673
Flash point (°C)	10.3 (predicted)
Auto flammability (°C)	460[b]
Viscosity (cp at 20°C)	0.456
Refractive index (at 25°C/D)	1.45 (predicted)
Dielectric constant	NA

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (*cis*-1,2-dichloroethylene, CASRN 156-59-2. https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID2024030. Accessed on May 12, 2021). All values are experimental averages unless otherwise specified.
[b]Data are from NLM (2021g).

cis-1,2-DCE = *cis*-1,2-dichloroethylene; NA = not applicable; U.S. EPA = U.S. Environmental Protection Agency.

A summary of available toxicity values for *cis*-1,2-DCE from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for *cis*-1,2-DCE (CASRN 156-59-2)

Source/Parameter[a,b]	Value (applicability)	Notes	Study Observing Critical Effect	Reference
Noncancer				
IRIS (RfC)	NV	Information reviewed but value not derived		U.S. EPA (2010)
IRIS (RfD)	0.002 mg/kg-d	Based on increased relative kidney weight in male rats	McCauley et al. (1995); McCauley et al. (1990)	
PPRTV (subchronic p-RfD)	0.02 mg/kg-d	Based on increased relative kidney weight in male rats	McCauley et al. (1995); McCauley et al. (1990)	U.S. EPA (2011c)
DWSHA (RfD)	0.002 mg/kg-d	NA		U.S. EPA (2018a)
HEAST (subchronic RfD)	NV	NA		U.S. EPA (2011b)
ATSDR (MRL, oral acute)	1 mg/kg-d	Based on decreased RBC counts and hematocrit levels in female rats exposed for 14 d	McCauley et al. (1990)	ATSDR (1996)
ATSDR (MRL, oral intermediate)	0.3 mg/kg-d	Based on decreased hematocrit levels in male rats and decreased hemoglobin levels in rats of both sexes exposed for 90 d	McCauley et al. (1990)	
CalEPA (ADD)	0.00125 mg/kg-d	Based on increased relative kidney weights in male rats exposed for 90 d	McCauley et al. (1995)	CalEPA (2018)
AEGL (AEGL-1)	10 min: 140 ppm 30 min: 140 ppm 60 min: 140 ppm 4 h: 140 ppm 8 h: 140 ppm	Based on ocular irritation in humans	Lehmann and Schmidt-Kehl (1936)	U.S. EPA (2018b, 2008)
AEGL (AEGL-2)	10 min: 500 ppm 30 min: 500 ppm 60 min: 500 ppm 4 h: 340 ppm 8 h: 230 ppm	Based on narcosis in rats (4 and 8 h) or anesthetic effects in humans (10, 30, and 60 min)	Hurtt et al. (1993)	
AEGL (AEGL-3)	10 min: 850 ppm 30 min: 850 ppm 60 min: 850 ppm 4 h: 620 ppm 8 h: 310 ppm	Based on a no-effect level for death in rats (4 and 8 h) or dizziness, intracranial pressure, and nausea in humans (10, 30, and 60 min)	Kelly (1999)	

Table 2. Summary of Available Toxicity Values for *cis*-1,2-DCE (CASRN 156-59-2)

Source/Parameter[a,b]	Value (applicability)	Notes	Study Observing Critical Effect	Reference
ACGIH (TLV-TWA)[c]	200 ppm	Based on CNS impairment and eye irritation	Lehmann and Schmidt-Kehl (1936)	ACGIH (2020)
OSHA (PEL)[c]	200 ppm (790 mg/m^3)	8-h TWA for general industry, construction, and shipyard employment		OSHA (2020a, 2020b, 2020c)
NIOSH (REL)[c]	200 ppm (790 mg/m^3)	TWA for up to a 10-h workday during a 40-h workweek		NIOSH (2019)
NIOSH (IDLH)[c]	1,000 ppm	Based on acute inhalation toxicity data in humans	von Oettingen (1955, 1937)	NIOSH (2019, 2014)
Cancer				
IRIS (WOE)	Inadequate information to assess carcinogenic potential	NA		U.S. EPA (2010)
DWSHA (WOE)	Inadequate information to assess carcinogenic potential	NA		U.S. EPA (2018a)
HEAST	NV	NA		U.S. EPA (2011b)
NTP	NV	NA		NTP (2016)
IARC	NV	NA		IARC (2021)
CalEPA	NV	NA		CalEPA (2021)
ACGIH[c]	NV	NA		ACGIH (2020)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; 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; PPRTV = Provisional Peer-Reviewed Toxicity Value.
[b]Parameters: ADD = acceptable daily dose; AEGL = acute exposure guideline level; IDLH = immediately dangerous to life or health concentrations; MRL = minimum risk level; PEL = permissible exposure level; p-RfD = provisional reference dose; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.
[c]Values are for 1,2-dichloroethylene (unspecified mixed isomer) and are not specific for 1,2-*cis*-DCE.
[d]McCauley et al. (1990) (unpublished report) was subsequently published as McCauley et al. (1995).

cis-1,2-DCE = *cis*-1,2-dichloroethylene; CNS = central nervous system; NA = not applicable; NV = not available; RBC = red blood cell.

Non-date-limited literature searches were conducted in October 2017 and updated most recently in July 2022 for studies relevant to the derivation of provisional toxicity values for *cis*-1,2-DCE (CASRN 156-59-2). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[1] (including TSCATS1), and Web of Science. The following additional resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), U.S. EPA TSCATS2/TSCATS8e, U.S. EPA High Production Volume (HPV), Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search update from July 2022.

2. REVIEW OF POTENTIALLY RELEVANT DATA FOR DERIVATION OF NONCANCER AND CANCER INHALATION REFERENCE VALUES

No short-term, subchronic, or chronic studies; developmental or reproductive toxicity studies; or carcinogenicity studies of *cis*-1,2-DCE in humans or animals conducted by inhalation exposure were identified.

2.1. OTHER DATA (SHORT TERM TESTS, OTHER EXAMINATIONS)

Data for *cis*-1,2-DCE are limited to a single acute inhalation study, oral studies, injection studies, and studies on 1,2-DCE mixtures containing both the *cis*- and *trans*-1,2-DCE isomers. The findings from relevant studies are briefly summarized in the text below. More detailed descriptions of the individual studies are provided in Table 3.

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]

Test	Materials and Methods	Results	Conclusions	References
Supporting studies in animals following inhalation exposure				
Acute (*cis* isomer)	Rats (5/sex/group; strain not specified) were exposed to *cis*-1,2-DCE vapor concentrations of 0, 12,100, 13,500, 15,700, or 23,200 ppm (equivalent to 0, 47,900, 53,400, 62,200, and 91,900 mg/m^3) for 4 h. Animals were observed for 14 d.	No deaths occurred at 47,900 mg/m^3. 4/10 rats died at 53,400 mg/m^3, and 10/10 animals died in the two highest dose groups. During exposure, animals were prostrate, with eyes open, and unresponsive to alerting stimulus. Animals that survived exhibited irregular respiration immediately after exposure and slight to severe weight loss for 1 d after exposure.	Rat LC_{50} (4 h) = 13,700 ppm (54,320 mg/m^3).	DuPont Haskell Lab (1999)
Supporting studies in animals following oral exposure				
Acute (*cis* and *trans* isomers)	Male Holtzman rats (3−4/group) were administered single oral doses of 0, 400, or 1,500 mg/kg *cis*-1,2-DCE or *trans*-1,2-DCE in corn oil via gavage. At 20 h after dosing, liver G6P, tyrosine transaminase and ALP activities, and plasma ALP and ALT activities were measured.	Results for *cis* isomer: ↑ liver ALP at ≥400 mg/kg; ↓ liver tyrosine transaminase and G6P at 1,500 mg/kg; ↓ plasma ALT at 1,500 mg/kg. Results for *trans* isomer: ↑ liver G6P at 400 mg/kg (only); ↓ liver tyrosine transaminase at 1,500 mg/kg.	Limited evidence of liver effects for *cis*-1,2-DCE at ≥400 mg/kg, unlike *trans*-1,2-DCE, at 1,500 mg/kg *cis*-1,2-DCE: ↑ liver ALP, ↓ plasma ALT suggesting that the *cis* isomer elicits a slightly greater biochemical response than the *trans* isomer at this dose.	Jenkins et al. (1972)
Acute (*cis* and *trans* isomers)	Male Sprague Dawley rats (6/dose) were administered single oral doses of 0, 26, or 51 mmol/kg *cis*-1,2-DCE (~2,500 or 5,000 mg/kg) by gavage in sesame seed oil. Levels of liver GSH and plasma ALT, AST, and SDH activity were measured after 24 h.	Results for *cis* isomer: ↑ liver GSH (19 and 28%) and ↑ serum SDH (57 and 56.5%) at 2,500 and 5,000 mg/kg, respectively; ↑ serum AST (56%) at 5,000 mg/kg; no change in serum ALT. Two animals in the 5,000 mg/kg group died. Results for *trans* isomers: No significant changes in enzyme levels. One treated animal died.	Limited evidence of liver effects for *cis*-1,2-DCE at ≥2,500 mg/kg, with no response from *trans*-1,2-DCE.	Mcmillan (1986), dissertation

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]

Test	Materials and Methods	Results	Conclusions	References
Short-term (*cis* isomer)	Sprague Dawley rats (10/sex/dose) were administered 0, 1.0, 3.0, 10.0, or 20.0 mmol/kg *cis*-1,2-DCE (~0, 97, 291, 970, and 1,940 mg/kg-d) by gavage for 14 d. Animals were monitored for mortality, clinical signs of toxicity, food and water intake, serum chemistry, hematology, organ weights, and histopathology.	The percent changes of select endpoints compared with controls in males and females at 97, 291, 970, and 1,940 mg/kg-d, respectively, are reported. Results shown are statistically significant except where noted as NS. **Females:** ↑ Absolute liver weight 21%, 24%, 35%, 44% ↑ Relative liver weight 15%, 18%, 29%, 39% ↑ Absolute kidney weight 11% (NS), 11% (NS), 20%, 16% ↑ Relative kidney weight 5% (NS), 5% (NS), 14%, 12% ↓ Hematocrit 8% (NS), 11%, 11%, 11% ↑ Cholesterol 15% (NS), 17% (NS), 25% (NS), 40% No significant changes in hemoglobin, RBC counts, or plasma AST levels. **Males:** ↑ Absolute liver weight 12% (NS), 19% (NS), 28%, 26% ↑ Relative liver weight 16%, 18%, 33%, 38% ↑ Absolute kidney weight 4% (NS), 16% (NS), 21% (NS), 5% (NS) ↑ Relative kidney weight 7% (NS), 15% (NS), 21% (NS), 15% (NS) ↓ Absolute spleen weight; (7%) in high-dose males. No significant changes in RBC parameters or plasma AST levels.	Limited evidence for an effect on liver (increased organ weights) in males and females at ≥97 mg/kg-d. Limited evidence for an effect on the kidney (increased organ weights) in females at ≥970 mg/kg-d. Hematological changes were small in magnitude, not clearly related to dose, and within the normal range of variation (U.S. EPA, 2010).	McCauley et al. (1995); McCauley et al. (1990)

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]

Test	Materials and Methods	Results	Conclusions	References
Subchronic (*cis* isomer)	Sprague Dawley rats (10/sex/dose) were administered 0, 0.33, 1, 3, or 9 mmol/kg-d *cis*-1,2-DCE (~0, 32, 97, 291, and 872 mg/kg-d) by gavage for 90 d. Animals were monitored for mortality, clinical signs of toxicity, food and water intake, serum chemistry, hematology, organ weights, and histopathology.	The percent changes of select endpoints in males and females at 32, 97, 291, and 872 mg/kg-d, respectively, are reported. Results shown are statistically significant except where noted as NS. **Females:** ↑ Absolute liver weight 3% (NS), 11% (NS), 15% (NS), 24% ↑ Relative liver weight 3% (NS), 14%, 19%, 30% ↑ Absolute kidney weight 3% (NS), 16% (NS), 17% (NS), 17% (NS) ↑ Relative kidney weight 3% (NS), 20% (NS), 23% (NS), 23% (NS) ↓ Hemoglobin 3% (NS), 5% (NS), 6%, 4% (NS) ↓ Hematocrit 4% (NS), 6% (NS), 10%, 8% ↓ RBC counts 3% (NS), 4% (NS), 8%, 6% (NS) ↑ Absolute (13%) and ↑ relative (17%) thymus weight in high-dose females. **Males:** ↑ Absolute liver weight 6% (NS), 13% (NS), 5% (NS), 15% (NS) ↑ Relative liver weight 11% (NS), 15%, 17%, 32% ↑ Absolute kidney weight 9% (NS), 17% (NS), 7% (NS), 14% (NS) ↑ Relative kidney weight 14%, 19%, 19%, 27% ↓ Hemoglobin 5% (NS), 3% (NS), 6%, 6%	LOAEL = 32 mg/kg-d based on increased relative kidney weights in male rats. Limited evidence for an effect on liver (increased organ weights) in males and females at ≥97 mg/kg-d. Hematological changes were small in magnitude, not clearly related to dose, within the normal range of variation (U.S. EPA, 2010), and possibly reflective of increased water intake observed in the treated rats.	McCauley et al. (1995); McCauley et al. (1990)

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]

Test	Materials and Methods	Results	Conclusions	References
		↓ Hematocrit 6% (NS), 6%, 9%, 9% No statistically significant changes in RBC counts.		
Supporting studies in animals via other routes				
Acute (i.p.) (*cis* and *trans* isomers)	Male Sprague Dawley rats (6/dose) were administered single i.p. doses of 0, 21, or 26 mmol/kg *cis*-1,2-DCE (~2,000 and 2,500 mg/kg) or 0, 20, or 25 mmol/kg *trans*-1,2-DCE (~1,900 and 2,300 mg/kg) in sesame seed oil. Levels of liver GSH and plasma ALT, AST, and SDH activities were measured after 24 h. In a separate time-course study performed with 2,500 mg/kg *trans*-1,2-DCE administered i.p., serum enzyme activities were measured at 2, 4, 8, 12, and 24 h postdosing. Liver histopathology was also characterized.	Results for *cis* isomer: Dose-related increases in AST and SDH, statistically significant at ≥2,000 mg/kg. No change in GSH. One animal died at the high dose. Results for *trans* isomer: Dose-related decrease in liver GSH, significant at 2,300 mg/kg. No significant changes in plasma ALT, AST, or SDH. Two animals died at the high dose. Results for *trans* isomer time-course: Plasma ALT, AST, and SDH peaked around 4 h postdosing, returning to near normal by 12 h. Histopathology indicated signs of necrosis. The extent was maximal at 4−8 h, decreasing to 24 h.	Evidence of liver effects (serum chemistry) for *cis*-1,2-DCE at ≥2,000 mg/kg 24 h postdosing. Evidence of liver effects (serum chemistry, necrosis) for *trans*-1,2-DCE at 2,500 mg/kg 4 h postdosing.	Mcmillan (1986), dissertation
Acute (i.p.) (*cis* and *trans* isomers)	Wistar rats (4/sex/group) were treated i.p. with 0 or 7.5 mmol/kg (730 mg/kg) of *cis*- or *trans*-1,2-DCE for 4 consecutive days. Animals were sacrificed 24 h after the last dose. Body-weight change was recorded, and liver, spleen, and thymus weights were measured.	Results for *cis* isomer: Statistically significant decreased body-weight gain (−9%) was observed in males but not females; no significant changes in relative liver, spleen, or thymus organ weights in either sex. Results for *trans* isomer: Statistically significant decreased body-weight gain (−4%) was observed in males but not females; no significant changes in relative liver, spleen, or thymus organ weights in either sex.	No effect on relative liver weight at 730 mg/kg 24 h after dosing on 4 consecutive days, even with significant decrease in body-weight gain.	Hanioka et al. (1998)

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]

Test	Materials and Methods	Results	Conclusions	References
Acute (i.p.) (*cis* and *trans* isomers)	Wistar rats (4−6/group) were given single i.p. doses of 0 or 500 mg/kg *cis*-1,2-DCE or *trans*-1,2-DCE in corn oil. Initial body weights were measured at the start of the treatment, and body, liver, and lung weights were measured 24 h postdosing.	*cis* isomer results: Statistically significant loss in body weight occurred in treated animals. An increase in relative liver weight (9.4%) was observed but did not reach statistical significance. No changes in relative lung weights were observed. *trans* isomer results: A decrease in body weight and an increase in relative liver weight (11%) were not statistically significant. No changes in relative lung weights were observed.	Marginal increase in relative liver weight at 500 mg/kg 24 h after a single dose of either *cis*- or *trans*-1,2-DCE, even with body weights reduced.	Nakahama et al. (2000)
Acute (i.p.) (*cis* and *trans* isomers)	Male Swiss mice (10/dose) were administered single i.p. doses of 0, 128, 1,280, or 2,560 mg/kg of *cis*-1,2-DCE or 0, 1,280, 2,560, or 5,120 mg/kg of *trans*-1,2-DCE in corn oil. Kidney function was assessed by measuring protein and glucose levels in urine. Histopathological examinations of proximal convoluted tubules were performed in groups of five mice at the mid dose.	4/10 (*cis* isomer) and 5/10 (*trans* isomer) animals died in the high-dose groups. Deaths occurred within 24 h and appeared to be due to narcosis. In the low-, mid-, and high-dose groups, 2/10, 2/10, and 3/6 (*cis* isomer) and 0/10, 1/10, and 3/5 (*trans* isomer) surviving animals, respectively, had increased urinary protein (≥100 mg% of protein, as indicated by a Combistix standard color chart). In controls, 32/60 had no protein, 23/60 had trace amounts of protein, 5/60 had 30 mg%, and 0/60 had 100 mg%. None of the treated mice or controls had elevated glucose. No swelling or necrosis of the proximal convoluted tubules was observed (0/5 mice) for either isomer at the mid dose.	The study authors considered these results to show limited evidence of nephrotoxicity for *cis*-1,2-DCE or *trans*-1,2-DCE.	Plaa and Larson (1965)

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting mixture studies				
Short-term (inhalation) (mixture [58% *cis*, 42% *trans* isomer])	Rats (10/sex) were exposed whole body to a 1,2-DCE vapor concentration of 1,000 ppm (~1,980 mg/m^3) for 7 h/d, 5 d/wk for 14 d. Untreated and air-only control groups were included. Endpoints included body weights, select organ weights, serum chemistry (BUN, ALP, ALT), and hematology.	↑ Relative kidney (males, 6.4%) and liver weights (both sexes <5%).	Limited evidence for an effect on the liver and kidney (increased organ weights) at 1,980 mg/m^3.	Dow Chemical (1994)
Subchronic (inhalation) (mixture [58% *cis,* 42% *trans* isomer])	Rats (24−35 at low dose; 12/sex at high dose) were exposed whole body to 1,2-DCE vapor concentrations of 500 or 1,000 ppm (~1,980 or 3,970 mg/m^3) for 7 h/d, 5 d/wk for 6 mo. Untreated and air-only control groups were included. Endpoints included body weights, select organ weights, serum chemistry (BUN, ALP, ALT), and hematology.	↑ Relative kidney weights in males (9 and 16%) at 1,980 and 3,960 mg/m^3. Relative kidney weights in females were increased by 18 and 9%, respectively, but were not statistically significant. ↑ Relative liver weights (19 and 23%, females only) at both exposure levels.	Limited evidence of liver and kidney effects (increased organ weights) at 1,980 mg/m^3.	Dow Chemical (1994)

Table 3. Supporting Animal Studies of *cis*-1,2-DCE[a]

Test	Materials and Methods	Results	Conclusions	References
Short-term (oral) (mixture [50:50])	Male Sprague Dawley rats (6/group) were administered 0 or 5 mmol/kg-d (equivalent to approximately 485 mg/kg-d) of a 50:50 mixture of *cis*- and *trans*-1,2-DCE by gavage in sesame seed oil for 14 d. Endpoints included body weights, food consumption, hematology, clinical chemistry, select organ weights, and histopathology; liver GSH analysis was performed.	↑ Relative kidney weights (13%). No significant changes in RBC or other hematology parameters. No clinical chemistry or histopathology findings.	Limited evidence of kidney effect (increased kidney weight).	Mcmillan (1986), dissertation
Subchronic (oral) (mixture [50:50])	Male Sprague Dawley rats (6/group) were administered 0 or 5 mmol/kg-d (equivalent to approximately 485 mg/kg-d) of a 50:50 mixture of *cis*- and *trans*-1,2-DCE by gavage in sesame seed oil for 30 d. Endpoints included body weights, food consumption, hematology, clinical chemistry, select organ weights, and histopathology; liver GSH analysis was performed.	↑ Relative liver weight (19%), ↑ relative lung weight (14%), ↓ RBC (6%), ↓ hemoglobin (5%), and ↓ hematocrit (5%). No effect on relative kidney weight. No biologically significant changes in serum chemistry. No histopathology was observed.	Limited evidence of effect on liver (increased organ weight).	Mcmillan (1986), dissertation

[a]Several studies conducted experiments on both *cis*- and *trans*-1,2-DCE isomers. When appropriate, results for both isomers are reported.

↑ = statistically significantly increased; ↓ = statistically significantly decreased; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood nitrogen urea; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; G6P = glucose-6-phosphate; GSH = glutathione; i.p. = intraperitoneal; LC_{50} = median lethal concentration; NS = not statistically significant; RBC = red blood cell; SDH = sorbitol dehydrogenase; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

2.1.1. Supporting Animal Studies

Inhalation Studies (Acute)

The only available inhalation study on *cis*-1,2-DCE is a lethality study reporting a 4-hour median lethal concentration (LC_{50}) in rats of 54,320 mg/m^3 (DuPont Haskell Lab, 1999).

Oral Studies (Acute)

Two studies, one detailed in a dissertation (Mcmillan, 1986), were located in which rats were administered single gavage doses (ranging from 400 to 5,000 mg/kg) of *cis*-1,2-DCE or *trans*-1,2-DCE and evaluated for serum markers of liver toxicity (e.g., serum alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and liver enzyme activities (e.g., glucose-6-phosphatase, tyrosine transaminase, and glutathione [GSH]) (Mcmillan, 1986; Jenkins et al., 1972). Both studies reported evidence of liver toxicity following dosing with *cis*-1,2-DCE, with a greater response in animals dosed with *cis*-1,2-DCE compared with the *trans* isomer.

Oral Studies (Short-Term and Subchronic Studies)

McCauley et al. (1990) and McCauley et al. (1995) conducted 14- and 90-day gavage studies in Sprague Dawley rats; these are the only short-term and subchronic oral studies available for *cis*-1,2-DCE. The unpublished report described in McCauley et al. (1990) was subsequently published as McCauley et al. (1995). Although errors in the documentation of doses and other minor inconsistencies were noted between the two documents, they were not considered to compromise the reliability of the findings and doses presented herein were confirmed by the study authors.[2]

In the short-term gavage study (McCauley et al., 1995; McCauley et al., 1990), Sprague Dawley rats (10/sex/dose) were administered *cis*-1,2-DCE in corn oil (at doses of 0, 97, 291, 970, or 1,940 mg/kg-day) for 14 days; doses as reported by U.S. EPA (2010). Several gavage-related deaths (2/10 males and 3/10 females) and clinical signs, including excessive clear secretions about the nose and/or mouth and agitation followed by lethargy and ataxia, were reported at the 1,940 mg/kg-day dose level. At the high dose, male body weights were significantly reduced by approximately 10%. Compared with controls, significant increases in water consumption were observed, particularly in the highest dose groups (20−35% higher), and water consumption per body weight was significantly increased for females in all treatment groups and for males at 1,940 mg/kg-day. The main observed effects included statistically significant, dose-related increases in relative liver weights in both sexes (males: 16−38%; females 15−39%) and increased absolute liver weights in females in all dose groups (by 21−44%) and in males at 970 and 1,940 mg/kg-day (by 28 and 26%, respectively). Relative and absolute kidney weights were statistically significantly increased in females at 970 and 1,940 mg/kg-day (by 14 and 12% and by 20 and 16%, respectively), but the increases were not dose-related. No statistically significant increases in kidney weights were observed in males, although increases were >10% in magnitude in several dose groups. In high-dose males, absolute spleen weights were statistically significantly decreased from control by approximately 7%. Supporting clinical chemistry changes were limited to significantly increased cholesterol levels

[2]Doses in the McCauley et al. (1995) study were incorrectly reported and converted from mmol/kg-day to mg/kg-day. In addition, the doses for the acute- and subchronic study as presented in the 1995 published paper were reversed (i.e., the doses listed for the 14-day study are for the 90-day study and vice-versa). The doses presented here reflect the correctly converted doses (confirmed by the study author) (U.S. EPA, 2010).

(by 25−40%) in both males and females in the highest dose groups. There were no statistically significant changes in plasma AST levels. Serum ALT and lactate dehydrogenase (LDH) levels were also measured, but the results were not reported in the study. Other serum chemistry changes (blood urea nitrogen [BUN], creatinine, phosphorus, calcium, and glucose) were generally small in magnitude, not dose-related, or not consistent between sexes. Hematocrit levels in females were statistically significantly decreased in the three highest dose groups, but the changes were small (11%) and did not increase with dose. No significant changes in hemoglobin or red blood cell (RBC) counts were observed; no other significant hematological changes (i.e., white blood cell [WBC] counts) were observed in females and no statistically significant hematological changes were observed in males. No gross or histopathological findings accompanying any organ-weight changes were observed.

In the 90-day study, groups of Sprague Dawley rats (10/sex/dose) were administered *cis*-1,2-DCE in corn oil via gavage at doses of 0, 32, 97, 291, or 872 mg/kg-day[3] for 90 days (McCauley et al., 1995; McCauley et al., 1990); doses as reported by U.S. EPA (2010). No compound-related deaths or clinical signs were observed, but an increase in water intake (as a percentage of body weight) occurred at the higher dose levels. Reductions in male body weights (10−11%) at 291 and 872 mg/kg-day did not reach statistical significance. Similar to the 14-day study, the liver and kidney were identified as main target organs. Relative liver weights were statistically significantly increased over controls in a dose-related manner in both sexes (by 3−32%), and absolute liver weights were significantly increased in high-dose females (by 24%). Absolute liver weights in males were not significantly different from controls. Relative kidney weights in males were significantly increased, compared with controls, in all dose groups (by 14−27%). Increased relative kidney weights in females and absolute kidney weight changes in both sexes were not statistically significant, but the magnitudes of change were >10% in most dose groups (see Table 3). In high-dose females, absolute and relative thymus weights were statistically significantly increased, compared with controls (by 13 and 17%, respectively). Statistically significant clinical chemistry changes were sporadic or not adverse. In females, hemoglobin and RBC levels were significantly decreased (by 6 and 8%, respectively) at 291 mg/kg-day (but not in the high-dose group), and reduced hematocrit levels (by 10 and 8%, respectively) were measured at 291 and 872 mg/kg-day. In males, significant decreases in hemoglobin occurred in the 291 and 872 mg/kg-day groups and hematocrit levels were decreased in the 97, 291, and 872 mg/kg-day groups. However, the changes were small (6−9% decreases) and not clearly related to dose (see Table 3). An analysis by U.S. EPA (2010) showed that the observed values were within the normal range of variation. These endpoints could have been affected by increased water intake observed in the higher dose groups. No treatment-related gross or histological lesions were observed. Increased relative kidney weight in male rats was selected as the critical effect for deriving the subchronic provisional reference dose (p-RfD) for *cis*-1,2-DCE in the PPRTV assessment and the chronic reference dose (RfD) in the *cis*-1,2-DCE IRIS assessment (see Table 2 and Table A-7) (U.S. EPA, 2011c, 2010).

[3]The administered doses in McCauley et al. (1995) were reported as 0, 0.33, 1, 3, and 9 mmol/kg-day that, when converted to mg/kg-day, are 0, 32, 97, 291, and 872 mg/kg-day, respectively. McCauley et al. (1995), however, reported the converted doses incorrectly as 0, 10, 32, 98, and 206 mg/kg-day. The doses presented here are the correctly calculated doses of doses of 0, 32, 97, 291, and 872 mg/kg-day, as reported in McCauley et al. (1990) (confirmed by the study author) (U.S. EPA, 2010).

Injection Studies

An acute injection study in rats reported in a dissertation (Mcmillan, 1986) showed dose-related increases in plasma AST and sorbitol dehydrogenase (SDH) activities 24 hours after single intraperitoneal (i.p.) injections of 0, ~2,000, and 2,500 mg/kg *cis*-1,2-DCE. Although a single i.p. dose of ~1,900 and 2,300 mg/kg *trans*-1,2-DCE did not show effects at 24 hours, time-course experiments performed with 2,500 mg/kg of the *trans* isomer as part of the same study did show the following effects: serum ALT, AST, and SDH activities peaked 4 hours postdosing, subsequently declining to near-normal levels; necrosis also was observed (maximal at 4−8 hours). Nakahama et al. (2000) found only marginal nonsignificant increases in relative liver weights (by 9.4−11%) in rats 24 hours after a single 500 mg/kg i.p. injection of either *cis*- or *trans*-1,2-DCE, even though body weights were reduced by both isomers. Similarly, there was no effect on relative liver weight in rats injected on 4 consecutive days with 730 mg/kg of either *cis*- or *trans*-1,2-DCE, despite significant decreases in body-weight gain with both isomers (Hanioka et al., 1998). Mice injected with 128−5,120 mg/kg of *cis*- or *trans*-1,2-DCE showed weak nephrotoxicity (increased urinary protein) in a study that also assessed urinary glucose levels and included histopathological examinations of proximal convoluted tubules (Plaa and Larson, 1965).

Mixture Studies

Several studies on 1,2-DCE mixtures containing both the *cis* and *trans* isomer are reviewed in U.S. EPA (2010). In many cases, the isomer compositions were not reported or were unknown, making the determination of the potential contribution of the *cis* isomer to the observed effects difficult. Select studies where compositions were reported are detailed in Table 3. In general, mixture studies (both inhalation and oral) identify the liver and kidney as primary target organs, which is consistent with observations from studies on the *cis*- and *trans*-1,2-DCE isomers alone. In an unpublished report, Dow Chemical (1994) performed a series of inhalation experiments using a 1,2-DCE mixture composed of 58% *cis*-1,2-DCE and 42% *trans*-1,2-DCE in rats (rabbits, guinea pigs, and beagle dogs were also tested, but group sizes were small and no statistical analysis was done) (U.S. EPA, 2010). This included a preliminary 14-day study, followed by a 6-month inhalation study in which rats were exposed to 1,2-DCE vapor concentrations of 0, 500, or 1,000 ppm (equivalent to ~1,980 or 3,970 mg/m^3). In the 6-month study, exposure concentration-related increases in relative kidney weights (by 9 and 16%) in males and relative liver weights (by 19 and 23%) in females at 1,980 and 3,970 mg/m^3, respectively, were statistically significant. In an oral mixture study described in a dissertation (Mcmillan, 1986), a statistically significant increase in relative kidney weights (by 13%) was reported in male Sprague Dawley rats administered 485 mg/kg-day 1,2-DCE (a 50:50 mixture of *cis*- and *trans*-1,2-DCE) via gavage for 14 days. In a follow-up 30-day study at the same dose, relative liver weights in the treatment group were significantly increased by 19%, compared with controls (Mcmillan, 1986).

2.1.2. Genotoxicity

The genotoxicity of *cis*-1,2-DCE has been evaluated in numerous in vitro studies and in a limited number of in vivo assays in both mammalian and nonmammalian systems summarized in U.S. EPA (2010). No new genotoxicity studies on *cis*-1,2-DCE were identified. Overall *cis*-1,2-DCE is generally negative for genotoxicity. *cis*-1,2-DCE was negative in six reverse mutation studies in *Salmonella typhimurium* and two studies for deoxyribonucleic acid (DNA) damage in *Escherichia coli*. Results from gene conversion, reverse mutation, or mitotic recombination studies in *Saccharomyces cerevisiae* were mixed. One study reported positive

results in *S. cerevisiae* D7 both with and without metabolic activation, but results were negative in three other studies (U.S. EPA, 2010). No chromosomal aberrations or evidence of sister chromatid exchange (SCE) were observed in Chinese hamster lung (CHL) cells, with or without activation, in two separate studies. Negative results were also reported for chromosomal aberrations (CAs) in one study in Chinese hamster ovary (CHO) cells, but results were inconclusive for SCE in this study. In vivo, *cis*-1,2-DCE was mutagenic in two of three available host-mediated assays in mice, produced CAs in one of two available mouse bone marrow assays, and was negative for SCE. Additional details can be found in the U.S. EPA (2010) IRIS toxicological review for *cis*-1,2-DCE.

2.1.3. Metabolism/Toxicokinetic Studies

Experimental data show inhaled *cis*-1,2-DCE to be well-absorbed through the lungs, a result consistent with the blood-air partition coefficients estimated in humans and rats for this chemical (9.2−9.8 and 21.6, respectively) (Gargas et al., 1989). Closed-chamber gas uptake studies in rats indicate an initial first phase of gas uptake to equilibrium that took approximately 2 hours and left approximately 50% of the gas remaining in the chamber (Filser and Bolt, 1979). Further uptake was dependent on the velocity of metabolism and showed a logarithmic (first-order) decline in chamber levels of *cis*-1,2-DCE when the initial exposure concentration was low (500 ppm). At a higher exposure concentration (1,000 ppm), equilibrium is followed by a phase showing a linear (zero-order) decline, suggesting saturation of metabolism at the higher concentrations. The equilibrium constant K_{eq} for *cis*-1,2-DCE is 20, approximately double that for the *trans* isomer (K_{eq} = 11.5), indicating that uptake of *cis*-1,2-DCE is ~2-fold higher, which is consistent with the rodent blood-gas partition coefficients of 21.6 and 9.58 for *cis*- and *trans*-1,2-DCE, respectively (Filser and Bolt, 1979; Bonse et al., 1975). No studies quantifying the rate or extent of *cis*-1,2-DCE uptake following oral or dermal exposure were located.

No studies were identified that investigated the tissue distribution of *cis*-1,2-DCE in the body. Tissue:air partition coefficients determined for rat tissues ex vivo were 15.3 for liver, 6.09 for muscle, and 227 for fat (Gargas et al., 1988), suggesting that *cis*-1,2-DCE in the blood will be distributed to the liver and will accumulate preferentially in fat.

Studies in vitro using liver microsomes indicate that metabolism of *cis*-1,2-DCE is initiated upon the binding of *cis*-1,2-DCE to the heme moiety of hepatic microsomal cytochrome P450s (CYP450s) (Costa and Ivanetich, 1984, 1982). Upon activation, presumably by CYP2E1 (in hepatic tissue), *cis*-1,2-DCE is metabolized to an unstable epoxide intermediate that rearranges to form 2,2-dichloracetaldehyde, which is enzymatically converted to 2,2-dichloroethanol and 2,2-dichloroacetic acid (DCA) by alcohol dehydrogenase (Nakajima, 1997; Costa and Ivanetich, 1984; Henschler and Bonse, 1979; Bonse et al., 1975). 2,2-Dichloroethanol appears to be the major metabolite, with smaller amounts of DCA formed (Costa and Ivanetich, 1984; Bonse et al., 1975). The rate of *cis*-1,2-DCE metabolite production appears to be faster and the total amount of metabolites produced is greater than for the *trans* isomer (by approximately 4−25 times) (Costa and Ivanetich, 1984). Although CYP2E1 is likely the primary CYP450 responsible for *cis*-1,2-DCE metabolism, other CYP450s could also be involved. For example, in vitro inhibition studies by Costa and Ivanetich (1984) indicated that cytochrome P448, which is induced by β-naphthoflavone, appeared to play a slight, but significant, role in the binding and metabolism of *cis*-1,2-DCE. Studies indicate that both *cis*- and *trans*-1,2-DCE (or their metabolites) can inhibit CYP450 enzymes via irreversible binding (i.e., suicide inactivation), with *trans*-1,2-DCE overall being the more potent inhibitor

(U.S. EPA, 2008; Nakahama et al., 2000; Hanioka et al., 1998; Lilly et al., 1998; Mathews et al., 1998; Barton et al., 1995; Clewell and Andersen, 1994; Costa and Ivanetich, 1984; Freundt and Macholz, 1978, 1972). The irreversible binding is anticipated to result in competitive inhibition of the metabolism of other CYP450 substrates in vitro. The zero-order turnover velocity (V_{max}) of *cis*-1,2-DCE was determined to be 2.4 mg/hour-kg (Filser and Bolt, 1979). The V_{max} was later determined to be 3.0 mg/hour-kg by Gargas et al. (1988) and to be 3.34 mg/hour-kg after compensating for enzyme inhibition and resynthesis (Gargas et al., 1990). Metabolic rates increased under conditions of fasting or chronic ethanol intake (Nakajima, 1997).

Data on the elimination of *cis*-1,2-DCE are limited. Biphasic elimination with an initial rapid elimination from blood followed by a second, only slightly slower, phase of elimination from highly perfused tissues was suggested from a single study in humans (Pleil and Lindstrom, 1997). Elimination rate constants based on concentrations in exhaled breath over time were estimated for two volunteers exposed in a 10-minute shower to *cis*-1,2-DCE from contaminated well water (exposure concentrations were 20.4−28.4 µg/L and 84−125 µg/m^3 measured in water and air, respectively). The elimination half-lives, corresponding to the two phases of elimination were 0.82 and 8.96 minutes, respectively, in the first volunteer, and 2.37 and 29.33 minutes, respectively, in the second volunteer (Pleil and Lindstrom, 1997). Elimination of the metabolite, DCA, has not been specifically evaluated in the context of exposure to *cis*-1,2-DCE but the downstream metabolism of DCA and subsequent elimination have been reviewed in the *Toxicological Review of Dichloroacetic Acid* (U.S. EPA, 2003). DCA is ultimately expected to be metabolized to produce glyoxylate that can be further processed to form oxalate, which is excreted in urine or reduced to form glycolic acid. DCA can also be broken down into carbon dioxide (Costa and Ivanetich, 1984, 1982). Trace amounts of 2,2-dichloroethanol are expected to be ultimately exhaled (U.S. EPA, 2010).

A physiologically based pharmacokinetic (PBPK) model is available for inhaled *cis*-1,2-DCE in rats, as described in U.S. EPA (2010), but does not include a compartment to account for oral exposure and has not been extended to humans. U.S. EPA (2010) concluded that "Since this PBPK model was not calibrated with human data, it cannot be scaled allometrically to humans, whose liver CYP2E1 activity, resynthesis rate, and sensitivity to inhibition differ from those in rats. Given the current state of knowledge, this PBPK model is not useful for estimating the human equivalent dose (HED) from the available animal data for *cis*- or *trans*-1,2-DCE." Because oral exposure is not accounted for, the model cannot be used for route-to-route extrapolation.

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No adequate studies were located regarding toxicity of *cis*-1,2-DCE to humans or animals via inhalation exposure. Chronic (U.S. EPA, 2010) and subchronic (U.S. EPA, 2011c) oral toxicity values based on renal effects in a subchronic rat study are available for *cis*-1,2-DCE; however, the available PBPK model for *cis*-1,2-DCE is not suitable for route-to-route extrapolation or estimation of HEDs. As a result of the limitations of the available inhalation toxicity data for *cis*-1,2-DCE, subchronic and chronic provisional reference concentrations (p-RfCs) were not derived directly. Instead, screening subchronic and chronic p-RfCs are derived in Appendix A using an alternative analogue approach. Based on the overall analogue approach presented in Appendix A, *trans*-1,2-DCE was selected as the most appropriate analogue for *cis*-1,2-DCE for deriving screening subchronic and chronic p-RfCs (see Table 4).

3.2. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 4 presents a summary of noncancer references values.

Table 4. Summary of Noncancer Risk Estimates for *cis*-1,2-DCE (CASRN 156-59-2)[a]

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HEC)	UF_C	Principal Study
Screening subchronic p-RfC (mg/m^3)	Rat/M	Decreased lymphocyte counts	4×10^{-1}	$BMCL_{1SD}$	109 (based on analogue POD)	300	Kelly (1998) as cited in U.S. EPA (2020)
Screening chronic p-RfC (mg/m^3)	Rat/M	Decreased lymphocyte counts	4×10^{-2}	$BMCL_{1SD}$	109 (based on analogue POD)	3,000	Kelly (1998) as cited in U.S. EPA (2020)

BMCL = benchmark concentration lower confidence limit; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; HEC = human equivalent concentration; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; SD = standard deviation; UF_C = composite uncertainty factor.

3.3. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Under the U.S. EPA Cancer Guidelines (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of *cis*-1,2-DCE by oral or inhalation exposure (see Table 5).

Table 5. Cancer WOE Descriptor for *cis*-1,2-DCE (CASRN 156-59-2)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to humans"	NS	NA	No human carcinogenicity data were identified to support this descriptor.
"Likely to be carcinogenic to humans"	NS	NA	No human or animal carcinogenicity data were identified to support this descriptor.
"Suggestive evidence of carcinogenic potential"	NS	NA	No human or animal carcinogenicity data were identified to support this descriptor.
"Inadequate information to assess carcinogenic potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any studies evaluating carcinogenicity of *cis*-1,2-DCE.**
"Not likely to be carcinogenic to humans"	NS	NA	No evidence of noncarcinogenicity was available.

cis-1,2-DCE = *cis*-1,2-dichloroethylene; NA = not applicable; NS = not selected; WOE = weight of evidence.

3.4. DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES

Table 6 presents a summary of cancer risk estimates. No human or animal studies of carcinogenicity are available for *cis*-1,2-DCE. Tests for genotoxicity were primarily negative. Thus, the database for *cis*-1,2-DCE provides inadequate information to assess carcinogenic potential.

Table 6. Summary of Cancer Risk Estimates for *cis*-1,2-DCE (CASRN 156-59-2)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

cis-1,2-DCE = *cis*-1,2-dichloroethylene; NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

APPENDIX A. SCREENING NONCANCER PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional inhalation toxicity values for *cis*-1,2-dichloroethylene (*cis*-1,2-DCE). However, some information is available for this chemical, which although insufficient to support deriving a provisional toxicity value under current guidelines, may be of use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH (METHODS)

The analogue 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 analogue analysis are presented in Wang et al. (2012). Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical selection. The analogue 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 analogue both toxicologically and chemically.

The analogue identification approach of Wang et al. (2012) was expanded to collect a more comprehensive set of candidate analogues for the compounds undergoing a U.S. Environmental Protection Agency (U.S. EPA) PPRTV screening-level assessment. As described below, this method includes application of a variety of tools and methods for identifying candidate analogues that are similar to the target chemical based on chemical structure and key features; metabolic relationships; or related toxic effects and mechanisms of action.

To identify structurally related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus (ChemIDplus, 2021), CompTox Chemicals Dashboard (U.S. EPA, 2019), and Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox (OECD, 2022). Additional analogues identified as ChemIDplus-related substances, parent, salts, and mixtures, and Comptox-related substances are considered. Comptox GenRA analogues are collected when available using the methods available on the publicly available GenRA Beta version, which may include Morgan fingerprints, Torsion fingerprints, ToxPrints and ToxCast, Tox21, and ToxRef data. For compounds that have very few analogues identified by structural similarity using a similarity threshold of 0.8 or 80%, substructure searches in the QSAR Toolbox may be performed, or similarity searches may be rerun using a reduced similarity threshold (e.g., 70 or 60%). The compiled list of candidate analogues is batch run through the CompTox Chemicals Dashboard where QSAR-ready simplified molecular-input line-entry system (SMILES) are

collected and toxicity data availability are determined (e.g., from the Agency for Toxic Substances and Disease Registry [ATSDR], Office of Environmental Health Hazard Assessment [OEHHA), California Environmental Protection Agency [CalEPA], U.S. EPA Integrated Risk Information System [IRIS], PPRTVs). The batch output information is then uploaded into the Chemical Assessment Clustering Engine (ChemACE) (U.S. EPA, 2011a), which clusters the chemicals based on chemical fragments and displays the toxicity data availability for each candidate. The ChemACE output is reviewed by an experienced chemist, who narrows the list of structural analogues based on known or expected structure-toxicity relationships, reactivity, and known or expected metabolic pathways.

Toxicokinetic studies identified from the literature searches performed for this PPRTV assessment were used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites were also identified from the two OECD QSAR Toolbox metabolism simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator). Targeted PubMed searches were conducted to identify metabolic precursors and other compounds that share any of the observed or predicted metabolites identified for the target chemical. Metabolic analogues are then added to the pool of candidate analogues and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTVs).

In vivo toxicity data for the target chemical (if available from the literature searches) are evaluated to determine whether specific or characteristic toxicity was observed (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation). In addition, in vitro mechanistic data identified from the literature searches or obtained from tools including GenRA, ToxCast/Tox21, and Comparative Toxicogenomics Database (CTD) (Davis et al., 2021) were evaluated for this purpose. Data from CompTox Chemicals Dashboard ToxCast/Tox21 are collected to determine bioactivity of the target chemical in in vitro assays that may indicate potential mechanism(s) of action. The GenRA option within the Dashboard also offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays. Using the ToxCast/Tox21 bioactivity data, nearest neighbors identified with similarity indices of ≥0.5 may be considered potential candidate analogues. The CTD (Davis et al., 2021) is searched to identify compounds with gene interactions similar to interactions induced by the target chemical; compounds with gene interactions similar to the target chemical (with a similarity index >0.5) may be considered potential candidate analogues. These compounds are then added to the pool of candidate analogues, and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTVs).

The tools used for the expanded analogue searches were selected because they are publicly available, which allows for transparency and reproducibility of the results, and because they are supported by U.S. and OECD agencies, updated regularly, and widely used. The application of a variety of different tools and methods to identify candidate analogues serves to minimize the limitations of any individual tool with respect to the pool of chemicals included, chemical fragments considered, and methods for assessing similarity. Further, the inclusion of techniques to identify analogues based on metabolism and toxicity or bioactivity expands the pool of candidates beyond those based exclusively on structural similarity.

ANALOGUE SEARCH PROCESS

The initial analogue search focused on the identification of chemicals structurally similar to *cis*-1,2-DCE using the U.S. EPA CompTox Chemicals Dashboard (Tanimoto method) [successor to the DSSTox, one of the tools discussed in Wang et al. (2012)], ChemID Plus (method not described) [also discussed in Wang et al. (2012)], and the more recently developed OECD Toolbox (Dice method). The GenRA module (Beta version) in the Dashboard was employed to identify structural analogues but was not functional for this compound (returned an error message due to insufficient data availability). Results of the search are presented in Table A-1. Eight unique structural analogues were identified, based on a similarity threshold criterion of 80%. One identified analogue (vinyl chloride-d3, CASRN 6745-35-3) was excluded because it is a deuterated compound (replacing a chemical's nondeuterated hydrogens (i.e., protium or hydrogen-1) with deuterium can alter the chemical's toxicokinetics) (Foster, 1984).

Table A-1. Candidate Structural Analogues Identified for *cis*-1,2-DCE

Tool (method)	Similarity Threshold	Number of Analogues Identified	Analogue (CASRN) Selected for Toxicity Value Searches[b]
Dashboard (Tanimoto)	80%	4[a]	• ***trans*-1,2-DCE (156-60-5)** • 1,2-DCE, mixed isomers (540-59-0) • **Vinyl chloride (75-01-4)**
OECD Toolbox (Dice)	80%	3	• ***trans*-1,2-DCE (156-60-5)** • 1,2-DCE, mixed isomers (540-59-0) • (1E,3Z)-1,4-Dichlorobuta-1,3-diene (3588-13-4)
ChemID Plus (method not described)	80%	5	• ***trans*-1,2-DCE (156-60-5)** • 1,2-DCE, mixed isomers (540-59-0) • (Z)-1-Chloro-2-fluoroethene (2268-31-7) • (E)-1-Chloro-2-fluoroethene (2268-32-8) • 1-Chloro-2-fluoroethene, mixed isomers (460-16-2)

[a]One of the four was not selected for toxicity value searches because it is a deuterated compound (see text).
[b]**Bold** shows compounds with inhalation toxicity values.

cis-1,2-DCE = *cis*-1,2-dichloroethylene; OECD = Organisation for Economic Cooperation and Development; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

The seven identified candidate structural analogues for *cis*-1,2-DCE were searched for inhalation toxicity values. Of these, inhalation toxicity values were located only for *trans*-1,2-dichloroethylene (*trans*-1,2-DCE; CASRN 156-60-5) and vinyl chloride (CASRN 75-01-4).

Metabolites, metabolic precursors, and compounds that share metabolites with *cis*-1,2-DCE were also considered for analogues. As discussed in Section 2.1.3 in the main document, the primary liver metabolites of *cis*-1,2-DCE (based on in vitro studies using rat liver microsomes) are dichloroacetaldehyde (CASRN 79-02-7), 2,2-dichloroethanol (CASRN 598-38-9), and 2,2-dichloroacetic acid (DCA; CASRN 79-43-6) (Bonse et al., 1975). No information on metabolism in vivo was located, nor were data on metabolism in tissues other

than the liver. As hepatic metabolites have been identified and could be relevant to inhalation exposure, they were considered candidate analogues. No inhalation toxicity values were identified, however, for dichloroacetaldehyde, 2,2-dichloroethanol, or DCA.

PubMed searches (searching "*cis*-1,2-dichloroethylene" or "156-59-2" and "metabolite") were conducted to identify metabolic precursors to *cis*-1,2-DCE. No metabolic precursors yielding *cis*-1,2-DCE in vivo or in vitro were identified by this method. PubMed was also searched to identify other compounds that are metabolized to dichloroacetaldehyde, 2,2-dichloroethanol, or DCA (searching the metabolite name or CASRN and "metabolite"). The search identified four other compounds reportedly metabolized to one of the three *cis*-1,2-DCE metabolites: 1,1-dichloroethylene (1,1-DCE; CASRN 75-35-4) (Simmonds et al., 2004); trichloroethylene (TCE; CASRN 79-01-6) (Johnson et al., 1998); and the organophosphate pesticides, trichlorphon and dichlorvos (Yamano and Morita, 1992). The organophosphate pesticides were not considered further as candidate analogues on the basis of unshared structural properties with the target chemical (i.e., *cis*-1,2-DCE is not an organophosphate.) In the toxicological review for *cis*- and *trans*-1,2-DCE, U.S. EPA (2010) reported that *trans*-1,2-DCE is metabolized to the same compounds as is *cis*-1,2-DCE; thus, it can be considered a potentially relevant analogue on this basis, in addition to the structural similarity described above. Review of the metabolism information in the U.S. EPA (2011d) toxicological review for TCE also showed that DCA, a known metabolite of *cis*-1,2-DCE, can also be formed during metabolism of three other compounds: tetrachloroethylene (Perc; CASRN 127-18-7); 1,1-dichloroethane (CASRN 75-34-3); and 1,1,1,2-tetrachloroethane (CASRN 630-20-6). Among the six nonorganophosphate compounds sharing metabolites with *cis*-1,2-DCE, four chemicals (i.e., *trans*-1,2-DCE, Perc, 1,1-DCE, and TCE) have subchronic and/or chronic inhalation toxicity values and were selected as candidate metabolic analogues. No inhalation toxicity values were identified for 1,1-dichloroethane or 1,1,1,2-tetrachloroethane. Table A-2 summarizes the candidate metabolic analogues for 1,2-DCE.

Table A-2. Candidate Metabolic Analogues of *cis*-1,2-DCE

Relationship to *cis*-1,2-DCE	Compound[a]	CASRN
Metabolic precursor	None identified	
Metabolite	Dichloroacetaldehyde	79-02-7
	Dichloroacetic acid	79-43-6
	2,2-Dichloroethanol	598-38-9
Shares common metabolite(s)	1,1-Dichloroethane	75-34-3
	1,1-Dichloroethylene	**75-35-4**
	***trans*-1,2-Dichloroethylene**	**156-60-5**
	Trichloroethylene	**79-01-6**
	1,1,1,2-Tetrachloroethane	630-20-6
	Tetrachloroethylene	**127-18-4**

[a]**Bold** shows compounds with inhalation toxicity values.

cis-1,2-DCE = *cis*-1,2-dichloroethylene.

In addition to structural and metabolic data, available toxicity and mechanistic data for *cis*-1,2-DCE were evaluated to identify candidate analogues. The GenRA option within the Dashboard offers an option to search for analogues on the basis of similarities in activity in in vitro assays in ToxCast/Tox21; however, for *cis*-1,2-DCE, the GenRA module returned an error message. *cis*-1,2-DCE was only active in one ToxCast/Tox21 assay (of 235) and was not active in any EDSP21 assays (n = 22) or PubChem assays (n = 421). The single assay in which this compound was active was TOX21_RT_HEK293_FLO_16hr_viability. The endpoint of this assay (cell viability in human embryonic kidney cells) cannot be used to infer specific mechanisms of toxicity. The CTD had no entry for *cis*-1,2-DCE.

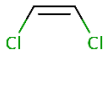
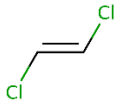
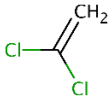
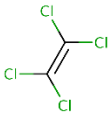
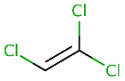
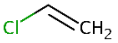
The toxicological data for *cis*-1,2-DCE, described in Section 2 of the main document, do not suggest any specific, characteristic toxicity that could be used to identify candidate analogues. Repeat-dose gavage studies identified the liver and kidneys as target organs (McCauley et al., 1995; McCauley et al., 1990). The target organs of the oral study might or might not be relevant to inhalation. The only inhalation study available, an unpublished acute lethality study (DuPont Haskell Lab, 1999), reported weight loss and clinical signs of central nervous system (CNS) depression (unresponsiveness, weakness, irregular respiration) at lethal concentrations but did not evaluate liver or kidney effects. None of the effects identified in the limited in vivo studies of *cis*-1,2-DCE suggested a characteristic or unique mechanism of toxicity that could be used to inform candidate analogue selection.

In summary, searches for structural, metabolic, and toxicity/mechanistic analogues for *cis*-1,2-DCE yielded a total of 15 unique analogues: 7 structural analogues (excluding 1 deuterated compound) and 9 metabolism-related analogues (excluding 2 organophosphates), 1 of which is also a structural analogue (*trans*-1,2-DCE). No analogues were identified on the basis of having similar mechanisms or modes-of-action (MOAs). Of the 15 identified candidates, 5 were found to have inhalation toxicity values: 1 structural analogue (vinyl chloride); 3 chemicals (1,1-DCE, Perc, and TCE) that share at least one common metabolite with the target compound; and *trans*-1,2-DCE, which is both a structural analogue and shares common metabolites with the target chemical.

Structural/Physicochemical Properties Similarity Comparisons

Table A-3 summarizes the physicochemical properties of the analogues. *cis*-1,2-DCE and the candidate analogues are members of the volatile organic compounds (VOC) chemical class. *cis*-1,2-DCE, *trans*-1,2-DCE, and 1,1-DCE share the same molecular weight. Melting and boiling points show that all of the compounds are liquids at room temperature except for vinyl chloride, which is a gas. Based on the Henry's law constants and vapor pressures, all of the compounds are expected to volatilize from water to air and from soil to air, respectively, and will exist mostly in the vapor (gas) phase in the atmosphere. *cis*-1,2-DCE and the candidate analogues are soluble in water. Vinyl chloride, with one chlorine atom, is the most water-soluble and has the lowest molecular weight and log K_{ow} value of the group. Perc, with four chlorine atoms, is the least water-soluble and has the highest molecular weight and log K_{ow} value. The target compound and all candidate analogues are expected to be bioavailable by the oral and inhalation routes (based on vapor pressure, water solubility, and log K_{ow} values). Overall, *trans*-1,2-DCE is the most similar candidate analogue to *cis*-1,2-DCE based on structural and physicochemical properties.

Table A-3. Physicochemical Properties of *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical	*cis*-1,2-DCE	*trans*-1,2-DCE	1,1-DCE	Perc	TCE	Vinyl Chloride
Role	Target	Analogue	Analogue	Analogue	Analogue	Analogue
Structure						
CASRN	156-59-2	156-60-5	75-35-4	127-18-4	79-01-6	75-01-4
DTXSID	2024030	7024031	8021438	2021319	0021383	8021434
Molecular weight (g/mol)	96.94	96.94	96.94	165.82	131.38	62.5
Melting point (°C)	−64.9	−59.7	−122	−11.6	−83.5	−155
Boiling point (°C)	54.4	52.0	32.5	121	87.0	−13.7
Vapor pressure (mm Hg)	200[b]	331[b]	600	18.5	69.0	2,980
Henry's law constant (atm-m^3/mole at 25°C)	0.00673	0.00673	0.0261	0.0177	0.00985	0.0278
Water solubility (mol/L)	0.0493	0.0484	0.0235	0.00178	0.0100	0.0923
Octanol-water partition coefficient (log K_{ow})	1.86	1.86	2.13	3.40	2.51	1.46[b]

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard: *cis*-1,2-dichloroethylene, CASRN 156-59-2; https://comptox.epa.gov/dashboard/chemical/properties/DTXSID2024030; accessed May 12, 2021; *trans*-1,2-dichloroethylene, CASRN 156-60-5; https://comptox.epa.gov/dashboard/chemical/properties/DTXSID7024031; accessed May 12, 2021; 1,1-dichloroethylene (1,1-DCE), CASRN 75-35-4; https://comptox.epa.gov/dashboard/chemical/properties/DTXSID8021438; accessed May 12, 2021; tetrachloroethylene (Perc), CASRN 127-18-4; https://comptox.epa.gov/dashboard/chemical/properties/DTXSID2021319; accessed May 12, 2021; trichloroethylene (TCE), CASRN 79-01-6; https://comptox.epa.gov/dashboard/chemical/properties/DTXSID0021383; accessed May 12, 2021; vinyl chloride, CASRN 75-01-4; https://comptox.epa.gov/dashboard/chemical/properties/DTXSID8021434; accessed May 12, 2021; all presented values are experimental averages unless otherwise specified.
[b]Compound-specific PubChem records (NLM, 2021g, h, i, j).

cis-1,2-DCE = *cis*-1,2-dichloroethylene; DCE = 1,1-dichloroethylene; DTXSID = DSSTox substance identifier; Perc = tetrachloroethylene; TCE = trichloroethylene; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; U.S. EPA = U.S. Environmental Protection Agency.

Structural alerts and toxicity predictions were identified using computational tools from the OECD QSAR Toolbox profilers, ToxAlerts, Toxtree, and *Patty's Toxicology, 6th Edition* (Bingham and Cohrssen, 2012). The model results for *cis*-1,2-DCE and its analogue compounds are shown in Figure A-1. Concerns for protein binding, hepatotoxicity, developmental or reproductive toxicity, and reactivity or metabolism of *cis*-1,2-DCE and its analogues were flagged when indicated by models within each predictive tool. Notably, *cis*-1,2-DCE and *trans*-1,2-DCE share the same structure activity relationship (SAR) predictions across all domains evaluated.

Structural Category	Analogues (CASRN)						Source
	cis-1,2-DCE (156-59-2)	*trans*-1,2-DCE (156-60-5)	1,1-DCE (75-35-4)	Perc (127-18-4)	TCE (79-01-6)	Vinyl Chloride (75-01-4)	
Protein Binding							
Protein binding (based on polarized alkenes with a halogen leaving group (SN_2) alert)—Organisation for Economic Cooperation and Development (OECD)							OECD quantitative structure-activity relationship (QSAR) Toolbox
Protein binding alerts identified (based on SN_2 alert)							Toxtree
Protein binding (based on vinyl type compounds with electron withdrawing groups (SN vinyl) alert)—OASIS							OECD QSAR Toolbox
Hepatotoxicity							
Hepatotoxicity (based on halogenated aliphatic compounds alert)—Hazard Evaluation Support System (HESS)							OECD QSAR Toolbox
Developmental/Reproductive Toxicity							
Developmental or reproductive toxicant (based on alkene structural alert)—Developmental and Reproductive Toxicity (DART) scheme							OECD QSAR Toolbox
Metabolism/Reactivity							
Cytochrome P450-mediated drug metabolism predicted (based on the presence of sp2 hybridized carbon atom alert)							ToxAlerts
Reactive, unstable, toxic (based on alkyl halides alert)							ToxAlerts
Reactive, unstable, toxic (based on haloethylenes alert)							ToxAlerts
Reactive, unstable, toxic (based on acyclic gem-dihalosubstituted carbon atom alert)							ToxAlerts
Reactive, unstable, toxic (based on polyhalogenated compounds [only chlorine, bromine, and iodine])							ToxAlerts
Other							
Unsaturated halogen hydrocarbons (general chemical class)							Bingham and Cohrssen (2012)

Model results or structural alerts indicating concern for toxicity
Model results or structural alert indicating no concern for toxicity
Models with results are presented in the heat map (models without results were omitted).

Figure A-1. Structural Alerts for *cis*-1,2-DCE and Candidate Analogues

cis-1,2-DCE and all candidate analogues, except for 1,1-DCE, met criteria indicating potential for protein binding by at least one model. The OECD QSAR Toolbox SN_2 and SN Vinyl at vinylic (sp2) carbon atom alerts are for protein binding through an SN_2 type mechanism with a halogen as a leaving group; however, these alerts have no chemicals reported in their training set to compare with *cis*-1,2-DCE and the candidate analogues.

The OECD QSAR Toolbox Hazard Evaluation Support System (HESS) model indicated a concern for hepatotoxicity for *cis*-1,2-DCE and all analogues. The structural alert applies to halogenated aliphatic compounds that do not contain a ring. The OECD QSAR Toolbox HESS model alert is based on data from 20 halogenated aliphatics, including the candidate analogue *trans*-1,2-DCE (CASRN 156-60-5). Chlorinated aliphatic compounds cause in vivo liver necrosis by multiple mechanistic pathways, including oxidative metabolism and reductive dehalogenation (Parkinson, 2001; O'Brien, 1988; Anders, 1985).

The OECD QSAR Toolbox Developmental and Reproductive Toxicity (DART) model indicated a concern for developmental and/or reproductive toxicity for *cis*-1,2-DCE and all analogues based on the structural alert for small (C1−4), halo- and multihalo-alkenes. The alert is derived from data on three chemicals: vinyl chloride (CASRN 75-01-4), hexachloro-1,3-butadiene (CASRN 87-68-3), and 2-chloro-1,3-butadiene (CASRN 126-99-8).

The ToxAlerts tool showed potential for reactivity and/or metabolism for *cis*-1,2-DCE and all analogues based on at least one of four reported structural alerts: the presence of an alkyl halide, haloethylene, acyclic gem-dihalosubstituted carbon atom, or polyhalogenated compound containing at least four halogen (chlorine, bromine, iodine) atoms. Supporting documentation for interpretation of these ToxAlerts is limited.

Toxicokinetic Similarity Comparisons

Table A-4 summarizes available toxicokinetic data for *cis*-1,2-DCE and the structurally similar compounds identified as potential analogues. *cis*-1,2-DCE and the candidate analogues are rapidly and readily absorbed via inhalation, with the rate and extent of absorption influenced by the concentration and duration of exposure, ventilation rates, cardiac output, body mass, physical activity, and blood-air partition coefficients. Available data indicate that the inhalation uptake of *cis*-1,2-DCE is ~2 times greater than that of the *trans* isomer (U.S. EPA, 2020, 2010; ATSDR, 1996).

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

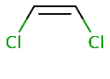
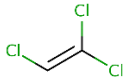
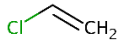
Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Structure						
Role	Target	Analogue	Analogue	Analogue	Analogue	Analogue
DTXSID	2024030	7024031	8021438	2021319	0021383	8021434
Absorption						
Rate and extent of inhalation absorption	**Humans:** ND **Laboratory animals:** Rats exposed to vapor in a closed chamber (single dose of 79−39,652 mg/m^3) • Rapid uptake from air with equilibrium achieved at ~2 h. • Inhalation uptake ~2 times that of the *trans* isomer (at equilibrium, the ratio of uptake to exhalation was 20 for *cis* vs. 11.5 for *trans*, and this is consistent with the partition coefficients shown below).	**Humans:** Human subjects (n = 2) exposed to either vapor or aerosol (3,291 and 8,803 mg/m^3 for 30 min) • 72−75% of inhaled amount is absorbed via lungs. **Laboratory animals:** Rats exposed to vapor in a closed chamber (single dose of 79−39,652 mg/m^3) • Rapid uptake from air with equilibrium achieved at ~1.5 h. • Inhalation uptake ~1/2 that for *cis* isomer (at equilibrium, the ratio of uptake to exhalation was 20 for *cis* vs. 11.5 for *trans*, and this is consistent with the partition coefficients shown below).	**Humans:** ND **Laboratory animals:** Rats exposed to vapor (100, 300, 600, or 1,200 mg/m^3 for 3 h) • Rapid uptake from air with substantial levels in venous blood within 2 min and equilibrium blood levels achieved within 45 min (similar pattern at 1,200 mg/m^3, although blood levels continued slowly increasing through exposure so that equilibrium was never achieved). • At equilibrium during the last 90 min of 3-h exposure, systemic uptake was 72−77% at 100−600 mg/m^3 (uptake decreased from ~60% to ~50% over the same time period at 1,200 mg/m^3).	**Humans:** Human subjects (n = 7) exposed to vapor in an open chamber (6.8 mg/m^3 for 6 h) • 64−100% of inhaled amount is absorbed via lungs. • Peak levels in blood occurred near the end of the 6-h period. **Laboratory animals:** Rats exposed via nose-only inhalation (340 or 3,400 mg/m^3 for 2 h) • Rapid uptake from air with substantial levels in arterial blood within 2 min; blood levels increased throughout 2 h exposure, with the rate of increase higher at the higher exposure level.	**Humans:** Human subjects exposed to vapor (376−1,080 mg/m^3 for 30 min−5 h) • 37−64% of inhaled amount is absorbed via lungs. Human subjects (n = 5) exposed via inhalation in a chamber (537 mg/m^3 for 6 h) • Peak levels in blood occurred after 1−2 h. **Laboratory animals:** Rats exposed to vapor (273−2,730 mg/m^3 for 2 h) • Rapid uptake from air with substantial levels in blood within 5 min and equilibrium blood levels achieved within 30 min.	**Humans:** Human subjects exposed to vapor by gas mask (7.5−60 mg/m^3 for 6 h) • Retention (difference between inhaled and exhaled air) averaged 42%, with maximum values reached within 15 min. **Laboratory animals:** Rats exposed to vapor (2,600−18,200 mg/m^3 for 5 h) • Equilibrium blood levels achieved within 30 min. Rats exposed to vapor in a closed system (260 mg/m^3 for 1 h) • ~40% of inhaled [^{14}C] absorbed via the lungs.

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]						
Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Rate and extent of inhalation absorption, continued				• After the first 20 min of exposure, when near-steady-state levels in exhaled breath were reached, systemic uptake was relatively constant at ~50% at 340 mg/m^3 and ~40% at 3,400 mg/m^3.	• At equilibrium during the last 60 min of 2-h exposure, systemic uptake was 69−71%.	
Human blood-gas partition coefficient	9.2−9.85	5.8−6.08	ND	10.3−19.8	8.1−11.7	1.16
Rodent blood-gas partition coefficient	21.6	9.58	5	18.9−33.5	13.3−25.82	1.6−2.8

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Distribution						
Extent of distribution	**Humans and laboratory animals: ND** Rat tissue homogenates exposed to vapor (793−1,586 mg/m^3 for 1−4 h) • The tissue:air partition coefficients determined for rats in vitro were 227 (fat), 15.3 (liver), and 6.09 (muscle), suggesting distribution to the liver and preferentially to fat. Isolated perfused livers from female rats exposed to vapor (180 min, concentrations not reported) • Uptake 3 times faster than for *trans* isomer, consistent with difference in partition coefficients.	**Humans and laboratory animals: ND** Rat tissue homogenates exposed to vapor (793−1,586 mg/m^3 for 1−4 h) • The tissue:air partition coefficients determined for rats in vitro were 148 (fat), 8.96 (liver), and 3.52 (muscle), suggesting distribution to the liver and preferentially to fat. Isolated perfused livers from female rats exposed to vapor (180 min, concentrations not reported) • Uptake 3 times slower than for *cis* isomer, consistent with difference in partition coefficients.	**Humans: ND** **Laboratory animals:** Rats exposed to vapor (40 or 8,000 mg/m^3 for 72 h) • Preferential distribution to liver and kidney, with only small amounts of [^{14}C] in other tissues.	**Humans and laboratory animals:** • Distributed throughout the body, with highest concentrations in fat, liver, brain, and kidney. Rats exposed via nose-only inhalation (340 or 3,400 mg/m^3 for 2 h) • Accumulates in fat; only slowly released from fat with half-time of ~25 h. Pregnant rats exposed to vapor in a closed chamber (136−6,782 mg/m^3 and for 1−6 h) • Found in milk in proportion to fat content (higher in rats vs. humans). Pregnant mice exposed to vapor (100 µCi for 10 min or 1 h; maternal blood concentrations ~230 µmol/L immediately following exposure) • Crosses placenta; distributes to fetus and amniotic fluid. • Crosses blood:brain barrier.	**Humans and laboratory animals:** • Rapidly distributed to brain, liver, lung, and preferential accumulation to fat. • Found in milk. • Crosses placenta; detected in neonatal blood.	**Humans: ND** **Laboratory animals:** Rats exposed to vapor in a closed system (256 mg/m^3 for 6 h) • Rapidly distributed throughout body, with highest levels in liver and kidney. Pregnant rats exposed to vapor (single dose of 511, 1,789, or 3,067 mg/m^3 for 2.5 h) • Crosses placenta; distributes to fetus and amniotic fluid. Rats exposed to vapor (12,781 mg/m^3 for 6 h/d, 5 d/wk for 7 wk) • Not expected to accumulate due to rapid metabolism and elimination.

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Metabolism						
Rate; primary reactive metabolites	**Humans: ND** **Laboratory animals:** • Rapid. • Saturable. • CYP450-mediated oxidation (primarily CYP2E1). Isolated perfused livers from female rats exposed to vapor (180 min, concentrations not reported); liver microsomes from male rats exposed in vitro (7.2 mM for 30 min) • Suicide inhibitor of CYP450 (less potent than *trans* isomer). • Primary oxidation product is an unstable epoxide intermediate that spontaneously rearranges to form 2,2-dichloro-acetaldehyde, which is enzymatically converted to 2,2-dichloroethanol (primarily) and DCA, which may undergo oxidative dechlorination to glyoxylic acid.	**Humans: ND** **Laboratory animals:** • Rapid. • Saturable. • CYP450-mediated oxidation (primarily CYP2E1). Isolated perfused livers from female rats exposed to vapor (180 min, concentrations not reported); liver microsomes from male rats exposed in vitro (7.2 mM for 30 min) • Suicide inhibitor of CYP450 (more potent than *cis* isomer). • Primary oxidation product is an unstable epoxide intermediate that spontaneously rearranges to form 2,2-dichloro-acetaldehyde, which is enzymatically converted to 2,2-dichloroethanol and DCA (primarily), which may undergo oxidative dechlorination to glyoxylic acid.	**Humans and laboratory animals:** • Rapid. • Saturable. • CYP450-mediated oxidation (primarily CYP2E1). • Primary oxidation products are 1,1-dichloroethene-epoxide (major), 2-chloroacetyl chloride (minor), and 2,2-dichloro-acetaldehyde (minor), all of which undergo hydrolysis or conjugation with GSH. • GSH conjugates are catabolized in the kidney to a variety of urinary elimination products.	**Humans and laboratory animals:** • Undergoes only limited metabolism (in humans, >80% of absorbed dose [any route] eliminated as unchanged parent). • Saturable. • Two competing biotransformation pathways: (1) CYP450-mediated oxidation (primary) and (2) GSH conjugation of parent compound. • CYP450-mediated oxidation (primarily CYP2E1): initial product is unstable intermediate (Perc-Fe-O) that is converted to trichloroacetyl chloride (hydrolyzed to TCA with further metabolism to DCA) or oxalic acid, possibly via an unstable epoxide intermediate.	**Humans and laboratory animals:** • Extensively metabolized. • Saturable. • Two competing biotransformation pathways: (1) CYP450-mediated oxidation (primary) and (2) GSH conjugation of parent compound. • CYP450-mediated oxidation (primarily CYP2E1): initial product is unstable intermediate (TCE-O-P450 complex) that spontaneously rearranges to form chloral and unstable TCE oxide, which then forms dichloro-acetyl chloride. Further metabolism yields 2,2,2-trichloro-ethanol, TCA, DCA, and oxalic acid.	**Humans and laboratory animals:** • Rapid. • Saturable. • CYP450-mediated oxidation (primarily CYP2E1). • Primary oxidation product is an unstable epoxide intermediate (2-chloroethylene oxide) that spontaneously rearranges to form 2-chloro-acetaldehyde. • The epoxide and 2-chloroacetaldehyde are both conjugated with GSH to form cysteine derivatives that are excreted in the urine.

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Rate; primary reactive metabolites, continued	• Metabolite production is faster and quantities are greater than for the *trans* isomer (by 4−25 times). • Metabolites are not thought to undergo GSH conjugation to any major extent.	• Metabolite production is slower and quantities are lower than for the *cis* isomer (by 4−25 times). • Metabolites are not thought to undergo GSH conjugation to any major extent.		• GSH conjugation: yields trichlorovinyl cysteine, which can be bioactivated to form reactive species and DCA via beta-lyase or flavin-containing monooxygenases.	• GSH conjugation: yields dichlorovinyl cysteine, which can be bioactivated to form reactive species via beta-lyase or flavin-containing monooxygenases.	
Elimination						
Elimination half-time; route of elimination	**Humans:** Humans (n = 2) exposed to vapor in showers (10 min, absorbed doses = 1.19−2.34 µg) • Elimination half-times of 0.82−2.37 min for blood and 8.96−29.33 min for highly perfused tissues were estimated. **Laboratory animals: ND** • The metabolite, DCA, is expected to be broken down to CO_2 and exhaled, along with trace amounts of 2,2-dichloroethanol.	**Humans and laboratory animals: ND** • The metabolite, DCA, is expected to be broken down to CO_2 and exhaled, along with trace amounts of 2,2-dichloroethanol.	**Humans: ND** **Laboratory animals:** Rats exposed to vapor (40 or 8,000 mg/m^3 for 72 h) • Rapid elimination after inhalation exposure, mostly as metabolites in urine with some unchanged parent compound exhaled in expired air. • Elimination following inhalation was biphasic, with most material eliminated in rapid first phase; elimination half-times were 20 min and 4 h for unchanged parent compound in breath and 3 and 20 h for metabolites in urine.	**Humans:** Human subjects (n = 6) exposed to vapor (488 or 977 mg/m^3 for 4 h) • 80−100% of the total absorbed dose was exhaled as unchanged parent compound in three first-order phases with half-lives of 12−16, 30−40, and 55−65 h. • <2% excreted as metabolites in urine, primarily TCA. Occupationally exposed humans (n = 13) • Biological half-life of Perc was ~6 d Human subjects (n = 6) exposed to vapor in a dynamic chamber (67, 136, or 271 mg/m^3 for 6 h)	**Humans:** Human subjects exposed singly or sequentially to vapor (267−2,042 mg/m^3 for 4 h on 1−5 d) • 11% of the absorbed dose was exhaled unchanged (half-time ~10 h), 2% was exhaled as trichloroethanol (half-time ~20 h), 58% was eliminated as urinary metabolites (primarily trichloroethanol and its glucuronide with half-time of ~10 h and TCA with half-time of ~52 h), and 30% was unaccounted for (likely stored in adipose tissue).	**Humans:** Human subjects exposed to vapor by gas mask (7.5−60 mg/m^3 for 6 h) • 5−7% of the inhaled amount was exhaled as unchanged parent compound. **Laboratory animals:** • Rapid elimination after inhalation exposure, primarily as metabolites in urine up to metabolic saturation, with increasing exhalation of unchanged parent compound above saturation.

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Elimination half-time; route of elimination, continued			Rats exposed to vapor (793 mg/m^3 for 6 h) • 75% of absorbed dose was excreted in urine, 6% in feces, 8% as CO_2 in breath and 4% as unchanged parent compound in breath.	• Elimination half-times were 45.6 h for TCA and 14.1 h for a trichlorovinyl cysteine derivative. **Laboratory animals:** • For some inhalation exposures, rats excrete more than humans as urinary metabolites, with shorter half-times (11 h for TCA and 7.5 h for a trichlorovinyl cysteine derivative at 68−271 mg/m^3 for 6 h), and mice more than rats (62.5% of absorbed dose from a 6-h inhalation exposure of 68 mg/m^3, versus 18.7% in rats). Rats exposed to vapor (68−4,080 mg/m^3 for 6 h) • Elimination is dose-dependent (68% of absorbed dose exhaled as parent compound, 3.6% exhaled as CO_2, and 18.7% excreted as metabolites in urine at 68 mg/m^3 vs. 88, 0.7, and 6%, respectively, at 4,080 mg/m^3).	**Laboratory animals:** Rats and mice exposed to vapor (54 or 3,240 mg/m^3 for 6 h) • Recovery of [^{14}C] was 5% (9%) exhaled as CO_2, 63% (74%) excreted in urine, and 7% (4%) in feces for the low dose, with similar results in both species at the high dose. Rats exposed to vapor (270−1,340 mg/m^3 for 8 h) • Elimination half-time for oxidative metabolites (total trichloro compounds) in urine was 14−17 h.	Rats exposed to vapor (26−13,000 mg/m^3 for 6 h) • In rats exposed for 6 h to 26 mg/m^3, 70% of the initial dose was recovered in urine and 2% was exhaled as the parent compound. Respective recoveries were 56 and 12% at 2,600 mg/m^3 and 27 and >50% at 13,000 mg/m^3. • Elimination half-times were 20−30 min for parent compound in breath and 4.1−4.6 h for metabolites in urine.

Table A-4. ADME Data for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
PBPK models available	Yes	Yes	Yes	Yes	Yes	Yes
References	U.S. EPA (2003); Lilly et al. (1998); Pleil and Lindstrom (1997); Gargas et al. (1989); Gargas et al. (1988); Sato and Nakajima (1987); Costa and Ivanetich (1984, 1982); Filser and Bolt (1979); Henschler and Bonse (1977); Bonse et al. (1975)	U.S. EPA (2003); Lilly et al. (1998); Gargas et al. (1989); Gargas et al. (1988); Sato and Nakajima (1987); Costa and Ivanetich (1984, 1982); Filser and Bolt (1979); Henschler and Bonse (1977); Bonse et al. (1975); Lehmann and Schmidt-Kehl (1936)	Dallas et al. (1983); Jones and Hathway (1978); Mckenna et al. (1978a); Mckenna et al. (1978b); Mckenna et al. (1977)	Chiu et al. (2007); Völkel et al. (1998); Byczkowski and Fisher (1994); Dallas et al. (1994); Ghantous et al. (1986); Schumann et al. (1980); Monster et al. (1979b); Pegg et al. (1979); Ikeda and Imamura (1973)	Dallas et al. (1991); Pellizzari et al. (1982); Monster et al. (1979a); Astrand and Ovrum (1976); Monster et al. (1976); Muller et al. (1974); Ikeda and Imamura (1973); Laham (1970)	Krajewski et al. (1980); Ungváry et al. (1978); Bolt et al. (1977); Bolt et al. (1976); Watanabe et al. (1976); Withey (1976)

[a]When possible, exposure concentrations are reported in units of mg/m^3 to enable interstudy comparisons. Concentrations reported in parts per million were converted to mg/m^3 using: concentration in ppm × molecular weight (g/mol)] ÷ 24.45 (L/mol).

ADME = absorption, distribution, metabolism, and excretion; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; CO_2 = carbon dioxide; CYP450 = cytochrome P450; DCA = 2,2-dichloroacetic acid; GSH = glutathione; ND = no data; Perc = tetrachloroethylene; PBPK = physiologically based pharmacokinetic; TCA = trichloroacetic acid; TCE = trichloroethylene; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

No in vivo human or animal studies reporting distribution of *cis*-1,2-DCE were identified (U.S. EPA, 2020, 2010). Based on tissue:air partition coefficients and in vitro studies, *cis*- and *trans*-1,2-DCE are expected to distribute from the blood to the liver and preferentially to fat (U.S. EPA, 2010). The fat, liver, and muscle tissue:air partition coefficients for *cis*-1,2-DCE are ~2-fold greater than those for the *trans* isomer, suggesting that the *cis* isomer is taken up more efficiently by these tissues (U.S. EPA, 2010). For the candidate analogues with data, distribution is rapid and widespread throughout the body, although differences in partitioning are observed. Perc and TCE primarily accumulate in fat and are also found in milk, which has a high fat content (ATSDR, 2019b, c; U.S. EPA, 2012, 2011d). In contrast, the highest levels of 1,1-DCE and vinyl chloride are found in the liver and kidneys, with only small amounts in other tissues and little to no accumulation in fat (ATSDR, 2019a, 2006; U.S. EPA, 2002b, 2000). Perc, TCE, and vinyl chloride have been shown to cross the placenta. Distribution to the placenta and the fetus has not been evaluated for the other compounds (ATSDR, 2019a; U.S. EPA, 2010).

Similar to *cis*-1,2-DCE, all of the candidate analogues undergo oxidative metabolism mediated by cytochrome P450 (CYP450) enzymes (primarily CYP2E1), and metabolism is saturable. For both *cis*- and *trans*-1,2-DCE, the initial oxidation product is an unstable epoxide intermediate that rearranges to form 2,2-dichloroacetaldehyde, which is then enzymatically converted to 2,2-dichloroethanol and 2,2-dichloracetic acid (U.S. EPA, 2020, 2010). Comparing *cis*- and *trans*-1,2-DCE, quantitative differences in the rate and quantity of metabolites produced have been noted, with the overall rate of metabolism faster and metabolite production greater for the *cis* isomer by approximately 4−25 times (U.S. EPA, 2020, 2010; ATSDR, 1996). In addition, the relative levels of metabolic products differ, so that 2,2-dichloroethanol is the major metabolite for the *cis* isomer, while DCA is the more abundant metabolite for the *trans* isomer (although due to the overall difference in metabolic rate, production of DCA from the *cis* isomer is still greater). Both isomers are capable of irreversible inhibition (i.e., suicide inactivation) via binding to the heme molecule on CYP450s, although *cis*-1,2-DCE is a less potent inhibitor than *trans*-1,2-DCE (U.S. EPA, 2010). Distinct from the other compounds under consideration, the downstream metabolites of the *cis* and *trans* isomers are not thought to undergo GSH conjugation to any major extent. Oxidation of 1,1-DCE generates three products, including an epoxide, and vinyl chloride oxidation generates an epoxide intermediate that rearranges to 2-chloroacetaldehyde; all of these products undergo hydrolysis and/or conjugation with GSH. GSH conjugation has been shown to contribute to the detoxification of 1,1-DCE and vinyl chloride (ATSDR, 2019a, 2006; U.S. EPA, 2002b, 2000). Perc and TCE are the only candidates having a competing GSH conjugation pathway independent of CYP450 oxidation. Metabolites from these GSH conjugation pathways can be bioactivated, yielding reactive species that contribute to the toxicity of these two compounds (ATSDR, 2019b, c). Compared with *cis*-1,2-DCE and to the other candidate analogues, less of the absorbed Perc is metabolized. In humans, 80−100% of the absorbed Perc dose remained unmetabolized and was exhaled as the parent compound (ATSDR, 2019a; U.S. EPA, 2012).

Elimination of *cis*-1,2-DCE is biphasic, with an initial rapid elimination from blood (half-time of 0.82−2.37 minutes in humans) followed by a second only slightly slower phase of elimination from highly perfused tissues (half-time of 8.96−29.33 minutes in humans) (U.S. EPA, 2010). Based on structural and physicochemical similarity to the *cis* isomer, elimination of *trans*-1,2-DCE is also expected to be reasonably rapid, although potentially longer than that of *cis*-1,2-DCE due to its slower rate of metabolism. Data in humans and/or laboratory animals show rapid elimination (minutes to a few hours) following inhalation exposure to 1,1-DCE and

vinyl chloride (ATSDR, 2019a, 2006). Elimination half-times were significantly longer (10 hours to a few days) for Perc and TCE, indicating delayed clearance, presumably due to retention in fat (ATSDR, 2019b, c). For the candidate analogues with data, the primary routes of elimination are as metabolites in urine and via exhalation of unchanged parent compound in breath, with relative importance being dose dependent (increasing exhalation of unchanged parent compound as the exposure level increases above metabolic saturation). Perc differs from the other candidate analogues in that even at low exposure levels below metabolic saturation, elimination occurs primarily by exhalation of parent compound, with lesser amounts excreted as metabolites in the urine (ATSDR, 2019b).

Among the candidate analogues, *trans*-1,2-DCE appears to be the closest metabolic analogue to *cis*-1,2-DCE on the basis of rapid uptake and similarities in distribution and metabolism patterns. However, quantitative differences between the isomers, in uptake and in the rate and quantity of metabolites produced, could have implications for relative toxicity of the two compounds. Although Perc and TCE were identified as candidate analogues for *cis*-1,2-DCE based on the shared DCA metabolite, there are important differences between these candidate analogues and *cis*-1,2-DCE. Unlike *cis*-1,2-DCE, which is rapidly metabolized, Perc undergoes only limited metabolism. Additionally, metabolism of both Perc and TCE includes a direct GSH conjugation pathway independent of CYP450 oxidation that yields reactive species thought to contribute significantly to the toxicity of these two compounds (ATSDR, 2019b, c). Based on these metabolic differences, Perc and TCE are less suitable metabolic analogues for *cis*-1,2-DCE than the other candidate analogues.

Toxicodynamic Similarity Comparisons

Table A-5 summarizes the inhalation toxicity values for the *cis*-1,2-DCE candidate analogues, and Table A-6 shows a comparison of the inhalation toxicity data for the candidate analogues in selected target organs/systems. Because inhalation data for *cis*-1,2-DCE are limited to an acute lethality study, oral data for *cis*-1,2-DCE were also considered when making comparisons across chemicals. Additional information, including more detailed discussions of possible mechanisms of toxicity, can be found in recent assessments for these chemicals (U.S. EPA, 2020; ATSDR, 2019a, b, c; U.S. EPA, 2012, 2011d, 2010; ATSDR, 2006; U.S. EPA, 2002b, 2000; ATSDR, 1996).

Table A-5. Comparison of Available Inhalation Toxicity Values for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

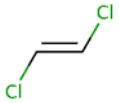
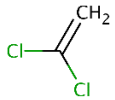
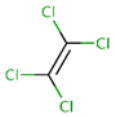
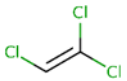
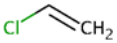
Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Structure						
Role	Target	Analogue	Analogue	Analogue	Analogue	Analogue
DTXSID	2024030	7024031	8021438	2021319	0021383	8021434
Repeat-dose toxicity—subchronic						
POD (mg/m^3)	NA	109	0.170	11.53	0.177 (1st study) 0.020 (2nd study)	2.56
POD type	NA	$BMCL_{1SDHEC}$	$BMCL_{10HEC}$	LOAEL	HEC_{99} (based on calculated idPODs)	LEC_{10HEC}
Subchronic UF_C	NA	300 (UF_A = 3; UF_H = 10; UF_D = 10)	30 (UF_A = 3; UF_H = 10)	300 (UF_H = 10; UF_L = 10; MF = 3 for database deficiencies)	1st study: 100 (UF_L = 10; UF_A = 3.16; UF_H = 3.16) 2nd study: 10 (UF_A = 10)	30 (UF_A = 3; UF_H = 10)
Subchronic p-RfC or Intermediate MRL (mg/m^3)	NA	4×10^{-1} (screening)	4×10^{-3} (provisional)	4×10^{-2}	2×10^{-3} (midpoint RfC from two candidate RfCs)	8×10^{-2}
Critical effects	NA	Decreased WBC and lymphocyte counts	Atrophy in nasal olfactory epithelium	Color vision loss	Decreased thymus weight and fetal heart malformations	Centrilobular hypertrophy
Species	NA	Rat	Rat	Human	Mouse (1st study) Rat (2nd study)	Rat
Duration	NA	90 d	14 wk	Average 106 mo	Simulation-52 wk (1st study) GDs 1−22 (2nd study)	From 10 wk prior to mating through lactation

Table A-5. Comparison of Available Inhalation Toxicity Values for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Route (method)	NA	Inhalation (whole body)	Inhalation (whole body)	Inhalation (worker breathing zone)	Oral (drinking water)	Inhalation (whole body)
Source	NA	U.S. EPA (2020)	ATSDR (2019a)	ATSDR (2019b)	ATSDR (2019c)	ATSDR (2006)
Repeat-dose toxicity—chronic						
POD (mg/m^3)	NA	109	6.9	15 (1st study) 56 (2nd study)	0.177 (1st study) 0.020 (2nd study)	2.5
POD type	NA	$BMCL_{1SDHEC}$	$BMCL_{HEC}$	LOAEL	HEC_{99} (based on calculated idPODs)	$NOAEL_{HEC}$ (based on idPODs)
Chronic UF_C	NA	3,000 (UF_A = 3; UF_H = 10; UF_D = 10; UF_S = 10)	30 (UF_A = 3; UF_H = 10)	1,000 (UF_H = 10; UF_L = 10; UF_S = 10)	1st study: 100 (UF_L = 10; $UF_{A\text{-}pk}$ = 3; $UF_{H\text{-}pk}$ = 3) 2nd study: 10 (UF_A = 3; UF_H = 3)	30 (UF_A = 3; UF_H = 10)
Chronic RfC/p-RfC or chronic MRL (mg/m^3)[b]	NA	4×10^{-2} (screening)	2×10^{-1}	4×10^{-2} (midpoint of the range from two studies)	2×10^{-3} (midpoint RfC from two candidate RfCs)	1×10^{-1}
Critical effects	NA	Decreased WBC and lymphocyte counts	Liver toxicity (fatty change)	Cognitive and reaction time changes and color vision changes	Decreased thymus weight and fetal heart malformations	Liver cell polymorphisms and cysts
Species	NA	Rat	Rat	Human	Mouse (1st study) Rat (2nd study)	Rat
Duration	NA	90 d	up to 18 mo	Mean 8.8 yr (1st study); 15 yr (2nd study)	Simulated 100 wk (1st study); GDs 1−22 (2nd study)	Lifetime
Route (method)	NA	Inhalation (whole body)	Inhalation (whole body)	Inhalation (workplace exposure)	Oral (drinking water)	Oral (feed)
Source	NA	U.S. EPA (2020)	U.S. EPA (2002b)	ATSDR (2019b); U.S. EPA (2012)	ATSDR (2019c); U.S. EPA (2011d)	U.S. EPA (2000)

Table A-5. Comparison of Available Inhalation Toxicity Values for *cis*-1,2-DCE (CASRN 156-59-2) and Candidate Analogues[a]

Chemical CASRN	***cis*-1,2-DCE** 156-59-2	***trans*-1,2-DCE** 156-60-5	**1,1-DCE** 75-35-4	**Perc** 127-18-4	**TCE** 79-01-6	**Vinyl Chloride** 75-01-4
Acute inhalation lethality data (LC_{50})						
Rat inhalation LC_{50} (mg/m^3) (lowest observed)	54,320	95,556	25,178	34,200	67,172	460,113
Mouse inhalation LC_{50} (mg/m^3) (lowest observed)	65,500 (LC_{Lo})	NA	200	35,269	45,408	294,000
Source	NLM (2021b); Kelly et al. (2000); Lehmann and Schmidt-Kehl (1936)	NLM (2021d); Kelly et al. (2000); Lehmann and Schmidt-Kehl (1936)	NLM (2021a); U.S. EPA (2021a); Siegel et al. (1971)	NLM (2021c); Pozzani et al. (1959); Friberg et al. (1953)	NLM (2021e): U.S. EPA CompTox Chemicals Dashboard (trichloroethylene, CASRN 79-01-6); https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID0021383#toxicity-values; accessed July 1, 2021	NLM (2021f); U.S. EPA (2021b); Clark and Tinston (1982)

[a]U.S. EPA derived toxicity values are reported. In instances where no U.S. EPA toxicity value is available, ATSDR MRL values are shown. If U.S. EPA and ATSDR values were the same, both sources are noted.
[b]For 1,1-DCE, the U.S. EPA chronic RfC is shown. However, a more recent ATSDR assessment (ATSDR, 2019a) was done that reviewed new studies not available in the U.S. EPA (2002b) Toxicological Review. One of these new studies was used to derive a chronic MRL of 2×10^{-3} mg/m^3; POD = 0.67 mg/m^3 ($BMCL_{10HEC}$); UF_C = 30; based on metaplasia in nasal olfactory epithelium in a 105-wk whole-body inhalation study in mice.

1,1-DCE = 1,1-dichloroethylene; ATSDR = Agency for Toxic Substances and Disease Registry; BMCL = benchmark concentration lower confidence limit; $BMCL_{10}$ = 10% benchmark concentration lower confidence limit; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; DTXSID = DSSTox substance identifier; GD = gestation day; HEC = human equivalent concentration; HEC_{99} = 99th percentile human equivalent concentration; idPOD = internal dose points of departure; LC_{50} = median lethal concentration; LC_{Lo} = lowest lethal concentration; LEC_{10} = 10% lowest effect concentration; LOAEL = lowest-observed-adverse-effect level; MF = modifying factor; MRL = minimal risk level; NA = not applicable; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration; Perc = tetrachloroethylene; pk = uncertainty based on pharmacokinetic component; POD = point of departure; RfC = reference concentration; SD = standard deviation; TCE = trichloroethylene; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor; U.S. EPA = U.S. Environmental Protection Agency; WBC = white blood cell.

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Liver	In 14- and 90-d studies in rats (10/sex/dose; Sprague Dawley) exposed orally (gavage; 0−1,940 mg/kg-d; 97% purity), relative increases in liver weight were observed (3−39% increases). In the 14-d study, statistically significant increases were observed in both absolute and relative liver weights (15−21%) in females and in relative liver weights (16%) in males at ≥97 mg/kg-d. In the 90-d study, relative liver weight increases (14−15%) were statistically significant in both females and males at ≥97 mg/kg-d. Refer to Table 3 in the main document for more details. (*rat, oral, short-term and subchronic*)	In 8- and 16-wk studies in rats (6 females/dose; SPR Wistar) exposed to vapor (793 mg/m^3; 8 h/d, 5 d/wk), fatty degeneration of the liver lobule and Kupffer cells were observed. In the 8-wk study, 3 of 6 exposed rats showed slight changes in the liver lobules and severe changes in the Kupffer cells, while severe fat accumulation was also noted in the Kupffer cells in 1 of 6 controls. In the 16-wk study, 3 of 6 exposed rats showed severe changes in liver lobules and slight changes in Kupffer cells and 2 of the other exposed rats showed slight changes in both the liver lobules and Kupffer cells. Of the 6 controls, 2 also showed slight changes in both the liver lobules and Kupffer cells in the 16-wk study. (*rat, inhalation, subchronic and chronic*)	In a 14-wk study, male rats (10/sex/dose; F344/N) exposed to vapor (0−396 mg/m^3; 6 h/d, 5 d/wk) exhibited hepatic centrilobular cytoplastic alterations at ≥50 mg/m^3. (*rat, inhalation, chronic*) **In 6-, 12-, and 18-mo studies, rats (86/group; Sprague Dawley) exposed to vapor (40 and 160 mg/m^3 for the first 5 wk, then 100 and 300 mg/m^3 for the remainder; 6 h/d, 5 d/wk) exhibited hepatocellular midzonal fatty changes at the high dose after 6 and 12 mo (males and females), and at the high dose at 18 mo (females only); changes were reversible. (*rat, inhalation, chronic*)[h]**	In a population of 27 dry cleaners (107 mg/m^3 8-h TWA exposure; 12-yr mean duration) and 26 nonexposed laundry workers, a higher prevalence of diffuse parenchymal changes was observed among the laundry workers (67 vs. 38% in the control group). (*human*) In a 30-d study, mice (10−12/sex/dose; NMRI) exposed to vapor (0−1,017 mg/m^3; 24 h/d, continuous) exhibited liver enlargement and vacuolization of hepatocytes at ≥61 mg/m^3. (*mouse, inhalation, short-term*)	In a 30-d study, male mice (10−20/sex/dose; NMRI) exposed to vapor (0−1,612 mg/m^3; 24 h/d, continuous) exhibited increased liver weight and increased BuChE activity, accompanied by misshapen, enlarged and vacuolated hepatocytes at ≥403 mg/m^3 (in female mice, these effects occurred at 1,612 mg/m^3). (*mouse, inhalation, short-term*)	**In a 19-wk study in rats (30/sex/dose; Sprague Dawley) exposed to vapor (0−2,812 mg/m^3; 6 h/d, 10 wk prior to mating through lactation), centrilobular hypertrophy was observed in F_1 female rats at ≥26 mg/m^3. (*rat, inhalation, reproductive*)[i]**

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Liver, continued			In a 12-d study, mice (10/sex/dose; Ha[ICR]) exposed to vapor (0−793 mg/m^3; 6 h/d, 5 d/wk) exhibited increased relative liver weights (by 20−24%) at ≥218 mg/m^3. (*mouse, inhalation, short-term)* In a 5-d study, mice (4−10 males/dose; CD-1) exposed to vapor (0−238 mg/m^3; 22−23 h/d) exhibited hepatocellular degeneration at ≥59 mg/m^3. (*mouse, inhalation, short-term*)			

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Kidney	**In 14- and 90-d studies in rats (10/sex/dose; Sprague Dawley) exposed orally (gavage; 0−1,940 mg/kg-d; 97% purity), relative increases in kidney weight were observed (12−27% increases). In the 14-d study, absolute and relative kidney weights were statistically significantly increased in females (14−20%) at ≥970 mg/kg-d; in males, increases in absolute and relative kidney weights did not reach statistical significance at any dosing level (97−1,940 mg/kg-d).**	In a 90-d study in rats (15/sex/dose; Crl:CD BR) exposed to vapor (793−15,860 mg/m^3; 6 h/d, 5 d/wk; >99.4% purity), increases in relative kidney weights for male and females were <10% and not generally dose-related. (*rat, inhalation, subchronic*)	In a 14-wk study, female mice (10/sex/dose; B6C3F1/N) exposed to vapor (0−396 mg/m^3; 6 h/d, 5 d/wk) exhibited increased relative kidney weights (by 11%) at ≥25 mg/m^3. (*mouse, inhalation, chronic*) Enzyme changes (↓ kidney monooxygenase and epoxide hydrolase levels), tubular alterations, and kidney histopathology were observed at higher exposure levels.	In a population of 57 dry cleaners (68 mg/m^3; 8-h TWA exposure; 13.9-yr mean duration; mostly females), 30 unexposed workers (mostly females), and 81 unexposed workers (mostly males), a 50% increase in creatinine-adjusted geometric mean concentration of urinary β2 glucuronidase and a 100% increase in geometric mean urinary lysozyme were observed in dry cleaners compared with either control group. (*human*)	In a 30-d study, male mice (10−20/sex/dose; NMRI) exposed to vapor (0−1,612 mg/m^3; 24 h/d, continuous) exhibited increased kidney weight (by 39%) at ≥403 mg/m^3 (in female mice, the effect occurred at 1,612 mg/m^3). (*mouse, inhalation, short-term*) ↑ Urinary glucose and proteins, serum gamma-glutamyl transpeptidase; and blood urea nitrogen, and kidney histopathology were observed at higher exposure levels.	In a 12-mo study, male rats (75/dose; Wistar) exposed to vapor (0−7,668 mg/m^3; 6 h/d, 6 d/wk) exhibited increased kidney weights at ≥256 mg/m^3. (*rat, inhalation, chronic*) No histopathology at highest exposure levels.

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Kidney, continued	**In the 90-d study, increases in relative and absolute kidney weights (3−23%) did not reach statistical significance in females; however, in males, increases in relative (but not absolute) kidney weight (14%) were statistically significant at ≥32 mg/kg-d. Refer to Table 3 in the main document for more details. (*rat, oral, short-term and subchronic*)[j]**			In a 103-wk study, mice (49−50/sex/dose; B6C3F1) exposed to vapor (0−1,356 mg/m^3; 6 h/d, 5 d/wk) exhibited nephrosis at ≥678 mg/m^3. (*mouse, inhalation, chronic*) ↑ Kidney weight and histopathology were observed at higher exposure levels.		
Respiratory	In a 14-d study, rats (5/sex/group; strain not specified) exposed to vapor (to 0−91,900 mg/m^3 for 4 h) exhibited irregular respiration at ≥53,400 mg/m^3 immediately following exposure. (*rat, inhalation, acute*)	In 1-, 2-, 8- and 16-wk studies in rats (6 females/dose; SPR Wistar) exposed to vapor (793 mg/m^3; 8 h/d, 5 d/wk), slight pulmonary capillary hyperemia and alveolar septum distension were observed in all six rats in all four exposure duration groups. (*rat, inhalation, acute and subchronic*)	**In a 14-wk study, rats (10/sex/dose; F344/N) exposed to vapor (0−396 mg/m^3; 6 h/d, 5 d/wk) exhibited olfactory epithelium mineralization at 25 mg/m^3; olfactory epithelium atrophy was also observed in males at ≥25 mg/m^3. (*rat, inhalation, subchronic*)[k]**	In a 103-wk study, mice (49−50/sex/dose; B6C3F1) exposed to vapor (0−1,356 mg/m^3; 6 h/d, 5 d/wk) exhibited acute passive congestion of the lungs at ≥678 mg/m^3. (*mouse, inhalation, chronic*)	In 28- and 90-d studies, rats (Wistar) exposed to vapor (0−2,021 mg/m^3; 4 h/d, 5 d/wk) exhibited lung lesions (bronchiolitis and alveolitis) at 2,021 mg/m^3. (*rat, inhalation, short-term and subchronic*)	In a 5- to 6-mo study, male mice (3−13/dose; CD-1) exposed to vapor (0−15,337 mg/m^3; 5 h/d, 5 d/wk) exhibited proliferation and hypertrophy of bronchial epithelium, hypersecretion of mucin, and hyperplasia of alveolar epithelium at ≥6,390 mg/m^3. (*mouse, inhalation, chronic*)

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Respiratory, continued		In a 90-d study, rats (15/sex/group; Crl:CD [SD] BR) exposed to vapor (0−16,000 mg/m^3; 6 h/d, 5 d/wk) exhibited no upper or lower respiratory lesions. (*rat, inhalation, subchronic*)	**In a 105-wk study, mice (50/sex/dose; B6C3F1/N) exposed to vapor (0−100 mg/m^3; 6 h/d, 5 d/wk) exhibited nasal turbinate atrophy, hyperostosis, and metaplasia of the respiratory olfactory epithelium at ≥25 mg/m^3. (*mouse, inhalation, chronic*)[k]** In a 14-wk study, female mice (10/sex/dose; B6C3F1/N) exposed to vapor (0−396 mg/m^3; 6 h/d, 5 d/wk) exhibited increased relative lung weights (by 12−16%) at ≥50 mg/m^3. (*mouse, inhalation, chronic*) Hyperostosis, turbinate atrophy, chronic lung inflammation, respiratory epithelium hyperplasia, metaplasia, and necrosis and laryngeal lesions were noted at higher levels.	Erosion of the nasal mucosa, thrombosis, and squamous metaplasia in the nasal cavity were observed at higher levels.	No noncancer lung effects were observed in chronic studies at higher levels.	

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Neurological	ND	ND	ND	**In 65 households in buildings collocated with dry cleaners (65 children; geometric mean exposure 0.34 mg/m^3; 10-yr mean duration of residence) and 61 households in residential buildings without dry cleaners (71 children), decreased visual contrast sensitivity and color vision impairment was observed for exposed subjects compared to controls. (*human*)[l]** In a 90-d study, gerbils (4/sex/dose; Mongolian) exposed to vapor (0−407 mg/m^3; 24 h/d, continuous) exhibited decreased DNA content in the frontal cortex at ≥407 mg/m^3. (*gerbil, inhalation, subchronic*)	In a 13-wk study, male rats (5/dose; JCL-Wistar) exposed to vapor (0−1,612 mg/m^3; 8 h/d, 5 d/wk) exhibited decreased wakefulness during exposure and a decreased postexposure sleeping heart rate at ≥269 mg/m^3. (*rat, inhalation, chronic*) ↓ Swimming speed, ↑ auditory threshold, depressed amplitude of auditory-evoked potentials, latency in visual discrimination response, ↓ shock avoidance and startle response, behavioral changes, and astroglial hypertrophy were observed at higher exposure levels.	In a 20-wk study, rats (90/sex/dose; F344) exposed to vapor (0−128 mg/m^3; 1 h/d, 5 d/wk) exhibited no neurological effects. (*rat, inhalation, chronic*)

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Neurological, continued				Changes in fatty acid composition in the brain, ↓ brain weight, ↓ activity, changes in auditory response, and ↑ amplitude of flash evoked potential peak N3 were observed at higher exposure levels.		
Hematological (red cell)	In 14- and 90-d studies in rats (10/sex/dose; Sprague Dawley) exposed orally (gavage; 0−1,940 mg/kg-d; 97% purity), small decreases in RBC, hematocrit and hemoglobin—not deemed to be biologically significant—were observed. In the 14-d study, no significant changes in hemoglobin or RBC counts were observed at any dose level (97−1,940 mg/kg-d), but significant decreases (11%) in hematocrit were observed in females at 291 mg/kg-d.	In a 90-d study, rats (15/sex/dose; Crl:CD BR) exposed to vapor (0−15,860 mg/m^3; 6 h/d, 5 d/wk; >99.4% purity) showed decreased mean hemoglobin (in males) at ≥3,965 mg/m^3 after 45 d. In females, mean monocyte count was decreased at 15,860 mg/m^3 after 45 d; these changes were not considered toxicologically important and did not occur at the 90-d sampling time. (*rat, inhalation, subchronic*)	In 6-, 12-, and 18-mo studies in rats (86/group; Sprague Dawley) exposed to vapor (40 and 160 mg/m^3 for the first 5 wk, then 100 and 300 mg/m^3 for the remainder; 6 h/d, 5 d/wk), no hematological effects were observed. (*rat, inhalation, chronic*)	In a population of dry cleaners (135 mg/m^3, 8-h TWA geometric mean exposure; 1- to 12-mo duration; 29 men and 27 women), and unexposed workers (30 men and 35 women), no hematological effects were observed. (*human*) In a 104-wk study in rats (50/sex/dose; F344) exposed to vapor (0−4,070 mg/m^3; 6 h/d, 5 d/wk), the only hematology change noted was an increase in mean corpuscular hemoglobin in female rats exposed to 4,070 mg/m^3. (*rat, inhalation, chronic*)	In a 4-wk study, female rats (8/dose; Sprague Dawley) exposed to vapor (0−5,374 mg/m^3; 6 h/d, 4 d/wk; 99.99% purity) showed no hematological effects at 5,374 mg/m^3. (*rat, inhalation, short-term*)	In an 8-wk study, male mice (4/dose; CD-1) exposed to vapor (0−2,600 mg/m^3; 6 h/d, 5 d/wk) showed no hematological effects at 2,600 mg/m^3. (*mouse, inhalation, subchronic*)

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Hematological (red cell), continued	In the 90-d study, decreases in hemoglobin and RBC counts (6−8%) were significant at 291 mg/kg-d in females; decreases in hematocrit in females (10%) and hemoglobin in males (6%) were significant at ≥291 mg/kg-d. Refer to Table 3 in the main document for more details. (*rat, oral, short-term and subchronic*)					
Immunological	ND	In 8- and 16-wk studies in rats (6 females/dose; SPR Wistar) exposed to vapor (793 mg/m^3; 8 h/d, 5 d/wk), severe pneumonic infiltration (not further characterized) was observed in the lungs of 3/6 exposed rats at both exposure durations but not in controls. (*rat, inhalation, subchronic and chronic*)	ND	In a 4-wk study in female rats (8/dose; Sprague Dawley) exposed to vapor (0−6,793 mg/m^3; 6 h/d, 5 d/wk; 99.98% purity), no immunological effects were observed. (*rat, inhalation, short-term*)	In a 30-d study, mice (10−20/sex/dose; NMRI) exposed to vapor (0−1,612 mg/m^3; 24 h/d, continuous) exhibited decreased spleen weights (by 24−41%) at ≥1,612 mg/m^3. (*mouse, inhalation, short-term)* ↓ Splenic anti-sRBC IgM response and ↓ serum IgG were observed at higher exposure levels.	In an 8-wk study, male mice (4/dose; CD-1) exposed to vapor (0−2,600 mg/m^3; 6 h/d, 5 d/wk) exhibited an increase in spontaneous lymphocyte proliferation at ≥26 mg/m^3. (*mouse, inhalation, subchronic*) ↑ Spleen weight and ↓ WBC counts were observed at higher exposure levels.

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Immunological, continued		In a 90-d study in rats (15/sex/dose; Crl:CD BR) exposed to vapor (0−15,860 mg/m^3; 6 h/d, 5 d/wk; >99.4% purity), decreased WBC and lymphocyte counts (18−25%) were observed in exposed animals, reaching statistical significance in males at 15,860 mg/m^3 after 45 d (WBC and lymphocyte counts) and 90 d (lymphocyte counts only). (*rat, inhalation, subchronic*)[m]				

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
Developmental	ND	In a developmental study in rats (24 dams/dose; Crl:CD BR) exposed to vapor (0−47,580 mg/m^3; 6 h/d, GDs 7−16), decreased fetal weight (by 4−6%) and a nonsignificant increase in hydrocephalus were observed at 47,580 mg/m^3. (*rat, inhalation, developmental*)	In a developmental study in mice (15−65 dams/dose; CD-1) exposed to vapor (0−1,189 mg/m^3; 22−23 h/d, GDs 6−16), incidence of fetuses with unossified incus and incompletely ossified sternebrae was increased at ≥59 mg/m^3. (*mouse, inhalation, developmental*)	In developmental studies in rats (17−30 dams/dose; Sprague Dawley) and mice (17−30 dams/dose; Swiss-Webster) exposed to vapor (0−2,035 mg/m^3; 7 h/d, GDs 6−15), increased fetal resorptions in rats and decreased fetal weight and delayed ossification in mice were observed at 2,035 mg/m^3. (*rat and mouse, inhalation, developmental*)	In a developmental study in rats (30 dams/dose; Long-Evans) exposed to vapor (0−9,673 mg/m^3; 6 h/d, 7 d/wk; GDs 0−20), decreased fetal weight and incomplete skeletal ossification were observed at 9,673 mg/m^3. (*rat, inhalation, developmental*)	In developmental studies in mice (30−40 dams/dose; CF-1) exposed to vapor (0−1,278 mg/m^3; 7 h/d, 10 d; GDs 6−15) and in rabbits (15−20 dams/dose; New Zealand) exposed to vapor (0−1,278 mg/m^3; 7 h/d, 13 d; GDs 6−18), delayed ossification was observed at 1,278 mg/m^3. (*mouse and rabbit, inhalation, developmental*)

Table A-6. Comparison of Effects on Target Organs/Systems Following Short-term, Subchronic, and Chronic Exposure to *cis*-1,2-DCE (Oral) and Candidate Analogues (Inhalation)[a,b]

Target Organ/ System	*cis*-1,2-DCE[c]	*trans*-1,2-DCE	1,1-DCE	Perc	TCE[d]	Vinyl Chloride[d]
	Effect[e,f,g] (species)					
References	DuPont Haskell Lab (1999); McCauley et al. (1995); McCauley et al. (1990)	Kelly (1998); Hurtt et al. (1993); DuPont (1988); Haskell Laboratories (1988); Freundt et al. (1977)	NTP (2015); Quast et al. (1986); Henck et al. (1979); Rampy et al. (1977); Short et al. (1977c); Short et al. (1977b); Short et al. (1977a)	Boverhof et al. (2013); Mcdermott et al. (2005); Brodkin et al. (1995); JISA (1993); Cai et al. (1991); Karlsson et al. (1987); Mennear et al. (1986); NTP (1986); Kjellstrand et al. (1984); Franchini et al. (1983); Schwetz et al. (1975); Storm et al. (2011)	Boverhof et al. (2013); Kumar et al. (2002); Arito et al. (1994); Kjellstrand et al. (1983); Dorfmueller et al. (1979)	Thornton et al. (2002); Bi et al. (1985); Hehir et al. (1981); John et al. (1981); Suzuki (1981); Sharma and Gehring (1979); Suzuki (1978); John et al. (1977)

[a]When possible, exposure concentrations are reported in units of mg/m^3 to enable interstudy comparisons. Concentrations reported in parts per million were converted to mg/m^3 using: concentration in ppm × molecular weight (g/mol)] ÷ 24.45 (L/mol).
[b]Duration categories are defined as follows: acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days to ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002a).
[c]No subchronic- or chronic inhalation data available; effects listed are following acute inhalation or oral exposure as noted.
[d]The subchronic and chronic inhalation toxicity values for TCE and the chronic toxicity value for vinyl chloride were derived following route-to-route extrapolations from oral studies (see Table A-5). Effects from oral studies on candidate analogues are not included here.
[e]The lowest LOAELs or highest NOAELs for effects on the target organ/system are shown; ≥ indicates that other effects were reported at concentrations greater than or equal to the lowest LOAEL. Selected effects observed at higher exposure concentrations are listed.
[f]Species where effects in the target organ/system were observed are shown in parentheses.
[g]Effects used for derivation of toxicity values shown in Table A-5 are in bold.
[h]Midzonal fatty changes, listed as an observed effect at higher exposure levels, formed the basis for the inhalation chronic RfC (U.S. EPA, 2002b), see Table A-5. The lowest LOAEL value shown is from new data reported in ATSDR (2019a).
[i]Basis for the inhalation intermediate MRL (ATSDR, 2006).
[j]Basis for chronic RfD derived by IRIS (U.S. EPA, 2010) and subchronic provisional p-RfD derived in a previous PPRTV assessment for *cis*-1,2-DCE (U.S. EPA, 2011c).
[k]Basis for the inhalation intermediate and chronic MRLs (ATSDR, 2019a). See Table A-5 footnote b regarding the chronic toxicity value for 1,1-DCE.
[l]Basis for the inhalation intermediate MRL and the chronic MRL and RfC (ATSDR, 2019b; U.S. EPA, 2012).
[m]Basis for the inhalation screening subchronic and chronic RfCs (U.S. EPA, 2020).

↑ = increased; ↓ = decreased; 1,1-DCE = 1,1-dichloroethylene; BuChE = plasma butyrylcholinesterase; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; DNA = deoxyribonucleic acid; GD = gestation day; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; ND = not determined; NOAEL = no-observed-adverse-effect level; Perc = tetrachloroethylene; PPRTV = Provisional Peer-Reviewed Toxicity Value; RBC = red blood cell; RfC = reference concentration; RfD = reference dose; sRBC = sheep red blood cell; TCE = trichloroethylene; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; WBC = white blood cell.

Acute Effects

The lowest observed inhalation median lethal concentration (LC_{50}) values for *cis*-1,2-DCE are 54,320 and 65,500 mg/m^3, in rats exposed for 4 hours and mice exposed for 2 hours, respectively (Kelly et al., 2000; Lehmann and Schmidt-Kehl, 1936). Inhalation LC_{50} values for candidate analogues ranged from 25,178 mg/m^3 (1,1-DCE) to 460,113 mg/m^3 (vinyl chloride) in rats and 200 mg/m^3 (1,1-DCE) to 294,000 mg/m^3 (vinyl chloride) in mice (see Table A-5). Although limited conclusions can be drawn from acute data, it is clear that the acute potency of *cis*-1,2-DCE is greater than that of vinyl chloride for exposure via inhalation. The LC_{50} value for *trans*-1,2-DCE (95,556 mg/m^3) is within twofold of the LC_{50} value for *cis*-1,2-DCE (54,320 mg/m^3) in rats exposed for 4 hours (Kelly et al., 2000).

Liver Effects

No inhalation studies evaluating the potential for *cis*-1,2-DCE to promote liver effects are available. Oral exposure to *cis*-1,2-DCE produced dose-related increases in absolute and/or relative liver weights in rats treated for 14 or 90 days, albeit without accompanying changes in serum chemistry or histopathology, even at the highest doses tested. Findings after oral exposure to *trans*-1,2-DCE were similar to those for the *cis* isomer, primarily involving increases in absolute and relative liver weight with limited clinical chemistry changes and no accompanying histopathology. Hepatic effects, including increases in absolute and relative liver weight, fatty changes, necrosis, and altered hepatocyte morphology, were also observed for the other candidate analogues by the oral route.

Liver effects have also been observed following inhalation exposure to each candidate analogue. Fatty degeneration in the liver lobule was observed in rats following repeated inhalation exposure to *trans*-1,2-DCE vapors. A supporting in vitro study on liver perfusates supplemented with either *cis*- or *trans*-1,2-DCE in the gas phase showed increasing levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in the perfusate with time, indicative of liver damage (Bonse et al., 1975). The enzyme levels were higher in the *cis*-1,2-DCE-exposed perfusate compared with the *trans*-1,2-DCE-exposed perfusate. Acute oral and injection studies that tested liver and plasma enzyme levels in rats exposed to the *cis*- and *trans*-1,2-DCE isomers also showed somewhat greater effects from the *cis* isomer (Mcmillan, 1986; Jenkins et al., 1972).

For 1,1-DCE, prolonged inhalation exposure has been shown to produce liver lesions ranging from fatty change to necrosis in rats and mice, and hepatotoxicity was identified as the critical effect for derivation of the 1,1-DCE chronic reference concentration (RfC). Increased liver weight also was noted. Hepatotoxicity of 1,1-DCE has been attributed to metabolites that do not undergo GSH conjugation in the liver and covalently bind with tissue macromolecules. The 1,1-DCE metabolites 1,1-dichloroethene epoxide, 2-chloroacetyl chloride, and 2,2-dichloroacetaldehyde, when unconjugated, are presumed hepatic toxicants (ATSDR, 2019a). The 1,1-DCE oxidation product 2,2-dichloroacetaldehyde is shared with *cis*-1,2-DCE. Toxicity of 1,1-DCE is correlated with CYP2E1 concentrations and increases under conditions of GSH depletion; however, fatty change, primarily in the centrilobular region, was observed in the absence of GSH depletion.

Hepatic lesions, such as centrilobular hypertrophy, and increased relative liver weight have also been reported for subchronic inhalation exposure to vinyl chloride, and this is the basis for the ATSDR intermediate minimal risk level (MRL). The chronic RfC is also based on hepatic

effects, although by route-to-route extrapolation from chronic oral data. Vinyl chloride liver toxicity is thought to be related to the production of the reactive intermediate metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, which are known to bind to liver proteins and macromolecules in liver tissue (ATSDR, 2006; U.S. EPA, 2000). Reactive intermediates from metabolism of *cis*- and *trans*-1,2-DCE are known to bind to the heme moiety of CYP450 molecules, and other data also show protein and lipid binding by metabolites of 1,2-DCE (isomer not stated) in liver microsomes (U.S. EPA, 2020). Both 1,2-DCE isomers and vinyl chloride have structural alerts for protein binding (see Figure A-1).

Both TCE and Perc have also been found to produce liver effects. Perc inhalation exposure resulted in parenchymal changes in humans and liver enlargement and vacuolization of hepatocytes in laboratory animals, while inhalation exposure to TCE caused increased liver weights, serum chemistry changes, and enlarged vacuolated hepatocytes. The Perc and TCE metabolite, DCA, which is also a metabolite of *cis*-1,2-DCE, has been linked to liver toxicity (ATSDR, 2019b), but Perc and TCE also generate other reactive metabolites that likely contribute to hepatotoxicity. Perc hepatotoxicity occurs even when CYP450 pathways are perturbed, suggesting that the alternative GSH conjugation pathway (and subsequent formation of reactive metabolites) likely contributes to this toxicity (ATSDR, 2019b). Much like Perc, reactive metabolites from the oxidation-independent GSH conjugation pathway also likely contribute to TCE hepatotoxicity (ATSDR, 2019c). Direct GSH conjugation of parent compound, as occurs for Perc and TCE, is not known to occur for *cis*-1,2-DCE.

Kidney Effects

No data are available on the potential for *cis*-1,2-DCE to cause kidney effects following inhalation exposure. In orally exposed rats, *cis*-1,2-DCE produced an increase in relative kidney weights in males not accompanied by supporting effects (e.g., histopathology or clinical chemistry changes), even at the highest dose. The increase in kidney weight is the basis for both the subchronic provisional reference dose (p-RfD) derived in a previous PPRTV assessment and the chronic reference dose (RfD) derived by IRIS for *cis*-1,2-DCE. Results similar to *cis*-1,2-DCE (increases in kidney weights without supporting changes in serum chemistry or histopathology) were observed following oral exposure to *trans*-1,2-DCE. Renal effects, including increases in kidney weight, increased blood urea nitrogen (BUN), cytomegaly, and toxic nephropathy were observed for the other candidate analogues by the oral route.

Increased kidney weights following inhalation exposure were observed for all candidate analogues except *trans*-1,2-DCE. Kidney weight increases were accompanied by additional evidence of renal toxicity, such as histological, serum chemistry, and/or urinalysis changes for 1,1-DCE, Perc, and TCE. 1,1-DCE kidney toxicity is thought to be associated with β-lyase bioactivation of hepatic GSH conjugates and/or their derivatives to reactive species (ATSDR, 2019a). For Perc and TCE, the toxic renal effects are thought to be due to the formation of reactive GSH-dependent metabolites following nonoxidative GSH conjugation with the parent compounds. Data suggest that GSH conjugation and the formation of GSH-dependent metabolites such as *S*-(1,2-dichlorovinyl)cysteine (1,2-DCVC) play a significant role in both Perc and TCE-induced renal toxicity (ATSDR, 2019b, c). GSH conjugation of the parent compound and formation of reactive GSH-dependent metabolites are not observed for *cis*-1,2-DCE.

Respiratory Effects

No subchronic- or chronic inhalation studies evaluating the potential for *cis*-1,2-DCE to cause respiratory effects are available, although irregular respiration was reported immediately after acute inhalation exposure to lethal levels of *cis*-1,2-DCE in rats (DuPont Haskell Lab, 1999). Following oral exposure, no clinical signs of respiratory distress or histopathology in the lung were observed; lungs were not weighed in the available study (McCauley et al., 1995; McCauley et al., 1990). Limited information is available about respiratory effects of candidate analogues following oral exposure, although gavage administration of TCE has been reported to cause dyspnea and pulmonary vasculitis.

Lung effects, including capillary hyperemia (vinyl chloride and *trans*-1,2-DCE) alveolar septum distention (TCE, vinyl chloride, and *trans*-1,2-DCE) congestion (vinyl chloride) bronchiolitis and alveolitis (Perc, TCE, vinyl chloride, and 1,1-DCE) and hyperplasia (Perc, TCE, and vinyl chloride) were observed in inhalation studies of all candidate analogues but only sporadically. 1,1-DCE and Perc were the only candidate analogues reported to produce upper respiratory effects following inhalation exposure, primarily lesions such as hyperplasia, metaplasia, and erosion of the nasal mucosa. Mineralization and atrophy of the olfactory epithelium in rodents was the basis for the intermediate and chronic inhalation MRL values for 1,1-DCE. Nasal lesions were not observed in rats exposed to *trans*-1,2-DCE at concentrations up to 15,860 mg/m^3 for 90 days in a study that included histopathological examination of upper and lower respiratory tract tissues at all exposure levels (U.S. EPA, 2020).

Neurological Effects

No subchronic or chronic inhalation studies evaluating the potential for *cis*-1,2-DCE to cause neurological effects are available. Animals acutely exposed to lethal concentrations of *cis*-1,2-DCE vapors showed signs of CNS depression (DuPont Haskell Lab, 1999). No behavioral clinical signs or changes in brain weight or histopathology were observed in animals treated for 90 days with doses up to 872 mg/kg-day of *cis*-1,2-DCE by gavage (McCauley et al., 1995; McCauley et al., 1990).

Among candidate analogues, no data are available on neurological effects for *trans*-1,2-DCE or 1,1-DCE following repeated inhalation exposure, and negative results were observed in neurotoxicity testing on vinyl chloride. In contrast, neurotoxicity is a sensitive endpoint for Perc and has been demonstrated in humans. The intermediate inhalation MRL for Perc is based on color vision changes, while both the chronic inhalation MRL and the chronic RfC are based on cognitive and reaction time changes and color vision changes in humans. In animals, Perc induced various neurotoxic effects, including electrophysiological changes, auditory changes, and effects on the brain (ATSDR, 2019b). In general, the neurotoxic effects of Perc are thought to be due to the parent compound rather than metabolites (ATSDR, 2019b). TCE has also been shown to induce neurological effects, such as decreased wakefulness and sleeping heart rate, auditory changes, behavioral changes, visual changes, and astroglial hypertrophy in animal studies. The TCE metabolite, chloral hydrate, has been shown to act as a CNS depressant through inhibition of neuronal receptors (ATSDR, 2019c).

Hematological Effects (Red Blood Cell [RBC] Parameters)

No inhalation studies on *cis*-1,2-DCE evaluating hematological effects were identified. In oral studies, decreases in RBC, hemoglobin, and/or hematocrit were reported, but these changes were small in magnitude, not clearly related to dose, within the normal range of variation (U.S.

EPA, 2010), and possibly reflective of increased water intake observed in the treated rats. They were not considered biologically significant or indicative of an effect of *cis*-1,2-DCE exposure (U.S. EPA, 2010). Similar to *cis*-1,2-DCE, slight decreases of uncertain biological significance were observed in RBC parameters in one study of rats orally exposed to *trans*-1,2-DCE (out of several available) and in an oral study of a 50:50 mixture of the 1,2-DCE isomers. Hematological effects, including decreases in RBC, hemoglobin, and clotting time of blood were observed for the TCE and vinyl chloride by the oral route.

No changes in RBC parameters were observed for any candidate analogue by inhalation exposure.

Immunological Effects (Including White Blood Cell [WBC] Parameters)

No inhalation studies evaluating the potential for *cis*-1,2-DCE to cause immunological effects are available. In an oral study in which female rats were administered *cis*-1,2-DCE for 90 days, no significant changes in WBC parameters were observed; however, significantly increased absolute and relative thymus weights (by 13 and 17%, respectively) were observed in females at the highest dose (872 mg/kg-day). Decreases in thymus weights were observed in female animals orally dosed with the *trans* isomer at concentrations ≥224 mg/kg-day (U.S. EPA, 2020). The chronic RfD for *trans*-1,2-DCE is immune-related, based on suppression of spleen cell antibody production against sheep red blood cells (sRBCs) in mice (U.S. EPA, 2010). Evidence of immunosuppression and immunotoxicity, including decreases in humoral immunity, increased T-cell hyperactivity, and decreased spleen cellularity is observed following oral exposure to TCE. Limited information is available about immunological effects of other candidate analogues following oral exposure.

No studies are available that evaluate immune functional changes in response to *cis*-1,2-DCE by any route of exposure. The *trans*-1,2-DCE screening subchronic and chronic p-RfCs are based on decreased WBC and lymphocyte counts in rats. These changes were not associated with histopathology in immune system organs (thymus, spleen, and bone marrow); the weights of these organs were not measured. Although reductions in lymphocyte counts following exposure to *trans*-1,2-DCE have been hypothesized to reflect a stress-related increase in glucocorticoid levels, no direct evidence supporting this hypothesis is available. Upon further evaluation, the U.S. EPA concluded that the effect on WBC and lymphocyte counts were related to exposure to *trans*-1,2-DCE (U.S. EPA, 2020). Pneumonic infiltration and severe fatty degeneration in Kupffer cells following inhalation exposure to *trans*-1,2-DCE could also be considered immune-related—Kupffer cells are highly phagocytic macrophages known to protect systemic circulation from gastrointestinal bacteria (ATSDR, 1996). In inhalation studies of TCE, mice exhibited significant reductions in spleen weight and serum immunoglobulin G (IgG) levels. Exposed rats had a reduced splenic anti-sRBC IgM response (ATSDR, 2019c). In addition to fetal heart malformations, the intermediate and chronic inhalation MRLs and the chronic RfC value for TCE are based on decreased thymus weights in mice exposed to TCE in drinking water (route-to-route extrapolation). Inhalation exposure to vinyl chloride resulted in increases in spleen weights in multiple species and in spontaneous proliferation/transformation of lymphocytes isolated from the spleens of exposed mice. A decrease in WBC counts was observed at higher exposure levels (ATSDR, 2006). No immune-related effects have been observed for Perc following inhalation exposure, and no long-term inhalation studies on 1,1-DCE evaluating immunotoxicity endpoints were identified.

Developmental Effects

No inhalation or oral studies on *cis*-1,2-DCE that evaluated the potential for developmental effects were identified. Developmental effects, including decreased litter sizes, anophthalmia, and increased collagen content of the skin, were observed following oral exposure to Perc, TCE, and vinyl chloride. Limited information is available about developmental effects following oral exposure to *trans*-1,2-DCE or 1,1-DCE.

Developmental effects indicative of developmental delay (reduced fetal weights and incomplete or delayed ossification) were reported for every candidate analogue following inhalation exposure, in most cases at exposure levels also causing maternal toxicity. The intermediate and chronic inhalation MRLs and the chronic RfC for TCE were based, in part, on fetal heart malformations in mice exposed to TCE in drinking water (route-to-route extrapolation). Studies in humans offer some support for a potential association between projected TCE exposure via vapor intrusion and cardiac birth defects (ATSDR, 2019c). No laboratory inhalation studies on any candidate analogue, including TCE, reported fetal heart effects.

Summary

In summary, limited data (no subchronic- or chronic inhalation studies, and only a single subchronic oral study) are available on *cis*-1,2-DCE for inhalation toxicity comparisons with the candidate analogues. The sensitive effects of subchronic oral exposure to *cis*-1,2-DCE were mild increases in liver and kidney weights, with limited accompanying serum chemistry or histopathology changes up to the highest doses tested. The liver and kidney were identified as target organs for the other candidate analogues following inhalation exposure, generally showing a variety of lesions and related changes in addition to increases in organ weights. Other potentially relevant endpoints identified for candidate analogues following inhalation exposure include upper respiratory lesions (1,1-DCE, Perc), neurological effects (Perc, TCE), immunological effects (*trans*-1,2-DCE, TCE), and developmental effects (all candidates).

Weight-of-Evidence Approach

A tiered weight-of-evidence (WOE) approach as described in Wang et al. (2012) was used to select the overall best analogue chemical. The approach focuses on identifying a preferred candidate for three types of analogues: structural analogues, toxicokinetic or metabolic analogues, and toxicity-like analogues. Selection of the overall best analogue chemical is then based on all of the information from the three analogue types, and the following considerations used in a WOE approach: (1) lines of evidence from U.S. EPA assessments are preferred; (2) biological and toxicokinetic data are preferred over the structural similarity comparisons; (3) lines of evidence that indicate pertinence to humans are preferred; (4) chronic studies are preferred over subchronic studies when selecting an analogue for a chronic value; (5) chemicals with more conservative/health-protective toxicity values may be favored; and (6) if there are no clear indications as to the best analogue chemical based on the other considerations, then the candidate analogue with the most structural similarity may be preferred.

Fifteen unique analogues were identified as part of this assessment: six structural analogues, eight metabolism-related analogues, and one compound identified on the basis of both structural and metabolic similarities (*trans*-1,2-DCE). Of the candidate analogues, *trans*-1,2-DCE is the most appropriate structural and metabolic analogue for *cis*-1,2-DCE, with the same shared structural features (i.e., an alkene and two vinylic chlorine atoms), shared

structural alerts, similar physicochemical properties, and common metabolic pathways (i.e., CYP450-mediated metabolism resulting in an unstable epoxide intermediate that rearranges to form 2,2-dichloroacetaldehyde, which is then enzymatically converted to 2,2-dichloroethanol and DCA with little downstream GSH conjugation). That quantitative differences exist between the 1,2-DCE isomers in uptake, overall rate of metabolism, and relative amounts of unique metabolites produced is acknowledged, although data were not located to inform the impact of these toxicokinetic differences on toxicological potency or effect. Major toxicokinetic differences, including longer clearance times, GSH conjugation pathways that yield reactive metabolites, and primary elimination route of exhalation, suggest that Perc and TCE are less suitable analogues for *cis*-1,2-DCE.

Limitations in the toxicity data available for *cis*-1,2-DCE, including lack of inhalation data, pose challenges for evaluating analogues on the basis of toxicodynamic comparisons. Target organs/systems identified from oral studies with *cis*-1,2-DCE are the liver and kidney (organ weight increases with limited serum chemistry or histopathological changes), and the derivation of the chronic and subchronic RfD values was based on kidney effects. Although the relevance of directly comparing oral and inhalation data is uncertain, the liver and/or kidney were also identified as relevant target organs for all of the analogues following inhalation exposure. Other relevant toxicity targets of inhalation exposure shared among the analogues include upper respiratory lesions (1,1-DCE, Perc), neurological effects (Perc, TCE), immunological effects (*trans*-1,2-DCE, TCE), and developmental effects (all candidates). Although toxicity comparisons revealed commonality among oral exposure to *cis*-1,2-DCE and inhalation exposure to candidate analogues, several notable differences were also apparent. Both Perc and TCE have an oxidation-independent GSH conjugation pathway, not observed in *cis*-1,2-DCE metabolism, that produces reactive metabolites thought to contribute to liver and kidney toxicity. In addition, the neurotoxic effects of Perc are thought to be due to the parent compound rather than to any metabolites shared with *cis*-1,2-DCE. Similarly, the TCE neurotoxic effects are thought to be mediated partially by the nonshared metabolite, chloral hydrate. Based on major differences in both toxicodynamics and toxicokinetics, Perc and TCE are not suitable analogues for *cis*-1,2-DCE and were not considered further.

From the remaining candidates (*trans*-1,2-DCE, 1,1-DCE, and vinyl chloride), *trans*-1,2-DCE is selected as the source analogue for the derivation of inhalation toxicity values primarily on the basis of structural and metabolic considerations, with some support from limited oral toxicity data comparisons. Table A-7 presents oral toxicity values and data for *cis*- and *trans*-1,2-DCE. *cis*-1,2-DCE and *trans*-1,2-DCE elicited similar, mild effects on the liver and kidney after subchronic oral exposure (organ weight increases with limited serum chemistry and histopathological changes). Differences in RfD values point to potential differences in potency, which could be related to the differences in uptake and metabolism described above. Still, the subchronic point of departure (POD) for *trans*-1,2-DCE is only ~threefold higher than the subchronic POD for *cis*-1,2-DCE, and critical effects (mild liver and kidney effects) were similar across isomers. Subchronic human equivalent dose (HED) PODs for the two isomers are within twofold of each other. For chronic PODs, the potency difference is more pronounced (the POD is ~13-fold higher and HED POD is ~7-fold higher for *trans*-1,2-DCE compared with *cis*-1,2-DCE) and the critical effects are different (immunotoxicity for *trans*-1,2-DCE and increased kidney weight for *cis*-1,2-DCE).

Table A-7. Comparison of Subchronic and Chronic Oral Toxicity Values and Effects on Target Organs/Systems Following Oral Exposure to *cis*-1,2-DCE and *trans*-1,2-DCE[a]

Chemical	*cis*-1,2-DCE	*trans*-1,2-DCE
Repeat-dose toxicity—subchronic		
POD (mg/kg-d); [HED POD (mg/kg-d)][b]	5.1; (1.3)	17; (2.4)
POD type	$BMDL_{10}$	NOAEL
Intermediate UF_C	300 (UF_A = 10; UF_H = 10; UF_D = 3)	100 (UF_A = 10; UF_H = 10)
Subchronic RfD/p-RfDs or intermediate MRL (mg/kg-d)	2×10^{-2}	2×10^{-1}
Critical effects	Increased relative kidney weight	Increased serum ALP
Species	Rat	Mouse
Duration	90 d	90 d
Route (method)	Oral (gavage)	Oral (drinking water)
Source	U.S. EPA (2011c)	ATSDR (1996)
Repeat-dose toxicity—chronic		
POD (mg/kg-d)	5.1; (1.3)	65; (9.1)
POD type	$BMDL_{10}$	$BMDL_{1SD}$
Chronic UF_C	3,000 (UF_A = 10; UF_H = 10; UF_D = 3; UF_S = 10)	3,000 (UF_A = 10; UF_H = 10; UF_D = 3; UF_S = 10)
Chronic RfD/p-RfD (mg/kg-d)	2×10^{-3}	2×10^{-2}
Critical effects	Increased relative kidney weight	Suppression of the humoral immune system (decreased spleen antibody production against sRBCs)
Species	Rat	Mouse
Duration	90 d	90 d
Route (method)	Oral (gavage)	Oral (drinking water)
Source	U.S. EPA (2010)	U.S. EPA (2010)

Table A-7. Comparison of Subchronic and Chronic Oral Toxicity Values and Effects on Target Organs/Systems Following Oral Exposure to *cis*-1,2-DCE and *trans*-1,2-DCE[a]

Chemical	*cis*-1,2-DCE	*trans*-1,2-DCE
Effects on target organs/systems in subchronic and chronic studies		
Target organ/system	**Effect (species)[b,c,d]**	
Liver	≥97 mg/kg-d ↑ relative liver weight, ↑ absolute liver weight; 90 d (*rat*) Doses up to 872 mg/kg-d tested: no changes in AST or histopathology	≥175 mg/kg-d ↑ serum ALP; ↑ relative liver weight; 90 d (*mouse, rat*) Observations at higher doses: ↑ absolute and relative liver weight No clinical chemistry changes in other studies up to 3,760 mg/kg-d. No histopathology.
Kidney	≥32 mg/kg-d ↑ relative kidney weight; 90 d (*rat*) Doses up to 872 mg/kg-d tested: No adverse clinical chemistry changes or histopathology.	≥1,257 mg/kg-d ↑ absolute kidney weight and kidney:brain weight ratio, nonsignificant increase in kidney:body weight ratio; 90 d (*rat, mouse*) No clinical chemistry or histopathology at higher doses.
Respiratory	No clinical signs or lung histopathology up to 872 mg/kg-d (lung weight not measured); 90 d (*rat*)	452 mg/kg-d ↓ lung weight; 90 d (*mouse*) No histopathology at higher doses.
Neurological	No clinical signs or changes in brain weight or histopathology up to 872 mg/kg-d; 90 d (*rat*)	No clinical signs, changes in brain weight or histopathology up to 3,245 mg/kg-d (*rat*) or 8,065 mg/kg-d (*mouse*); 14 wk

Table A-7. Comparison of Subchronic and Chronic Oral Toxicity Values and Effects on Target Organs/Systems Following Oral Exposure to *cis*-1,2-DCE and *trans*-1,2-DCE[a]

Chemical	*cis*-1,2-DCE	*trans*-1,2-DCE
Hematological (red cell)	≥97 mg/kg-d ↓ hematocrit; 90 d (*rat*) Doses up to 872 mg/kg-d tested: ↓ hemoglobin and RBC count Observed changes were small and not biologically significant.	≥380 mg/kg-d ↓ RBC counts; 90 d (*rat, mouse*)
Immunological	872 mg/kg-d (highest dose) ↑ relative thymus weight in females; 90 d (*rat*) No changes in relative spleen weight. No histopathology in spleen or thymus.	≥175 mg/kg-d Significant decrease in sRBC-responsive cells; 90 d (*mouse*) Observations at higher doses: ↓ absolute and relative thymus weight No histopathology at highest dose.
Developmental	ND	ND

[a]U.S. EPA-derived toxicity values are reported. In instances where no U.S. EPA toxicity value is available, ATSDR MRL values are shown.
[b]HED PODs were calculated using: HED POD = POD × $(BW_A/BW_H)^{1/4}$. Reference body weights were taken from U.S. EPA (1988). Because data for CD-1 mice were not available, a reference body weight for the average (based on BAF1 and B6C3F1) mouse was used in the HED POD calculations for *trans*-1,2-DCE.
[c]The lowest LOAELs or highest NOAELs for effects on the target organ/system are shown; ≥ indicates that other effects were reported at doses greater than or equal to the lowest LOAEL. Selected effects observed at higher doses are listed.
[d]Species for which effects in the target organ/system were observed are shown in parentheses. The lowest LOAEL was observed in the first species listed.

↑ = increased; ↓ = decreased; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ATSDR = Agency for Toxic Substances and Disease Registry; BMDL = benchmark dose lower confidence limit; $BMDL_{10}$ = 10% benchmark dose lower confidence limit; BW_A = animal body weight; BW_H = human body weight; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; MRL = minimal risk level; ND = not determined; NOAEL = no-observed-adverse-effect level; p-RfD = provisional reference dose; POD = point of departure; RBC = red blood cell; RfD = reference dose; SD = standard deviation; sRBC = sheep red blood cell; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor; U.S. EPA = U.S. Environmental Protection Agency.

Although the liver and kidney were determined to be targets of toxicity of both *cis*- and *trans*-1,2-DCE, immunological effects were determined to be a more sensitive endpoint for *trans*-1,2-DCE and are used as the critical effect in deriving its screening p-RfC value. Immune-related responses were observed for *trans*-1,2-DCE by oral and inhalation exposure. Limited data are available to evaluate potential immune-related effects caused by *cis*-1,2-DCE by either oral or inhalation exposure. However, relative thymus weights increased in female rats orally exposed to *cis*-1,2-DCE for 90 days. The direction of effect was opposite in mice orally exposed to *trans*-1,2-DCE, which showed decreased absolute and relative thymus weights after 90 days. Of note is that organ-weight changes are not the most sensitive effects for detecting immunotoxicity. Thus, immunotoxicity cannot be ruled out for *cis*-1,2-DCE as a potential target organ effect because immune functional measures have not been evaluated via either oral or inhalation routes of exposure for this chemical.

Differences in oral POD values for *cis*- and *trans*-1,2-DCE described above potentially imply that the RfC values for *trans*-1,2-DCE might not be adequately protective for inhalation exposure to *cis*-1,2-DCE. However, an examination of measured rat and human blood-gas partition coefficients for the two isomers reveals subtle differences that ultimately enhance confidence in this case the screening p-RfC values for *trans*-1,2-DCE are likely to be protective for any effects from *cis*-1,2-DCE. On the basis of guidelines described in U.S. EPA (1994), human equivalent concentrations (HECs) for systemic effects from a Category 3 gas (i.e., a gas that has its effects outside the respiratory tract, such as *cis*-1,2-DCE and *trans*-1,2-DCE) are calculated by multiplying the critical concentration in the animal study by the ratio of blood-gas partition coefficients for the chemical (animal/human), with the stipulation that a value of 1 is used if the animal value exceeds the human value. For *trans*-1,2-DCE, the rat value (9.58) is greater than the human value (5.8−6.08), so the default coefficient of 1 was used in the calculation, rather than the calculated value of ~1.6. This means that the HEC used as the POD for derivation of the screening p-RfCs for *trans*-1,2-DCE is lower, and therefore more protective, than it would have been based strictly on the ratio of partition coefficients (~60% of what it would have been). For *cis*-1,2-DCE, the rat and human blood-gas partition coefficients are 21.6 and 9.2–9.85, for a ratio of ~2.2. Because the ratio of coefficients is larger for *cis*-1,2-DCE than for *trans*-1,2-DCE, use of the default ratio of 1 in the derivation of the screening RfC is even more protective for this isomer (an HEC calculated for this isomer would be ~45% of the value it would be based strictly on the ratio of partition coefficients). Also of note is that the screening chronic p-RfC for *trans*-1,2-DCE is lower than the RfC values of all other candidate analogues except TCE, which was determined a less appropriate analogue due to significant toxicokinetic and toxicodynamic differences. Thus, use of the screening inhalation toxicity values for *trans*-1,2-DCE can reasonably be expected to be protective for *cis*-1,2-DCE toxicity within the rough order of magnitude margin of error associated with screening toxicity values.

INHALATION NONCANCER TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Concentration

On the basis of the overall analogue approach presented in this PPRTV assessment, *trans*-1,2-DCE was selected as the most appropriate analogue for *cis*-1,2-DCE for deriving screening subchronic and chronic p-RfCs. The study used for the U.S. EPA screening subchronic and chronic p-RfC values for *cis*-1,2-DCE is a 90-day inhalation study of *trans*-1,2-DCE in rats (Kelly 1998 as cited in U.S. EPA, 2020). The PPRTV assessment for *trans*-1,2-DCE (U.S. EPA, 2020) provided the following study summary:

The toxicity of trans-1,2-DCE (99.86% purity) was evaluated in groups of DCrl:CD (SD) BR rats (15 males and 15 females/group) in an unpublished study following OECD Guideline No. 413 (Kelly, 1998) and complying with Quality Assurance and Good Laboratory Practice (GLP) standards. Rats (approximately 7 weeks old) were exposed, whole body, to analytical concentrations (mean ± standard error [SE], reported by the study author to two significant figures) of 0, 200 ± 0.48, 1,000 ± 1.3, or 4,000 ± 4.7 ppm of trans-1,2-DCE vapor 6 hours/day, 5 days/week, for 90 days (these concentrations correspond to 0, 790, 4,000, and 16,000 mg/m^3, maintaining the stated significant figures). Ten rats/sex/group were designated for toxicological evaluations and the remaining five rats/sex/group were designated for cell proliferation evaluations. Clinical signs were observed during exposure and immediately after the rats were returned to their cages. Alerting response to an auditory stimulus was checked approximately every 2 hours during each exposure and immediately after. Body weights and food consumption were measured in all animals weekly.

In the toxicology evaluation group, blood samples were collected for hematology and serum chemistry measurements on approximate Test Days 45 and 90 from 10 male and 10 female rats from each exposure group. Urinalysis was performed on the same rats on the same day as the blood draw. One day after the final exposure, 10 rats per sex/exposure concentration were sacrificed for pathological evaluations; the remaining rats (~5 rats/sex/exposure concentration) were allowed to recover for approximately 1 month prior to sacrifice. Gross examinations were done at necropsy; liver, kidneys, lungs, testes, ovaries, adrenal glands, and brain were weighed, and samples from >45 tissues from 10 males and 10 females from the control and high-exposure groups were fixed in formalin or Bouin's solution, embedded in paraffin, stained with H & E, and examined microscopically. For low- and mid-exposure groups, the nose, pharynx/larynx, lungs, liver, kidneys, heart, and reproductive organs were microscopically examined. No histopathology was done on recovery animals owing to the lack of treatment-related lesions in the nonrecovery, high-exposure group. Ophthalmological evaluations were done on all rats in the toxicological group at the start of the study and at the end of the exposure period.

In the cell proliferation group, five rats/sex/exposure concentration were sacrificed after approximately 7 and 90 days of exposure for hepatic cell proliferation evaluations. Three days prior to each sacrifice, osmotic pumps filled with 20 mg/mL 5-bromo-2'-deoxyuridine (BrdU) were implanted subcutaneously in designated rats. At sacrifice, the liver and duodenum were collected and processed for immunohistochemical analysis of BrdU incorporation into deoxyribonucleic acid (DNA). Hepatic labeling indices were evaluated only for the control and high-exposure groups.

Statistical analyses of the data performed by the study author included analysis of variance (ANOVA), Dunnett's test for multiple pairwise comparisons, Bartlett's test for homogeneity, Cochran-Armitage test for trend, and when results of Bartlett's test were significant, Kruskal-Wallis and Mann-Whitney U tests. One-way ANOVA tests for linear trend were conducted for the purposes of this

assessment using GraphPad Prism software (Version 8.4.2) to evaluate potential treatment-related hematological changes (i.e., WBC and lymphocyte counts) (GraphPad, 2018).

One death (a female in the 4,000-mg/m^3 cell proliferation group) was reported; the animal was sacrificed on Test Day 85 due to an ulcer/erosion of the skin on the tail. There were significant increases in incidences of stained or wet perineum in female rats in the 4,000- and 16,000-mg/m^3 toxicology evaluation groups, but the effects were described as transient and likely related to the stresses of exposure. No other clinical signs or significant differences in mean body weights, body-weight gains, or food consumption between the control and exposed were observed. Minor ophthalmologic lesions were determined to be incidental and not compound related.

Hematology and clinical chemistry examinations revealed statistically significant changes in some parameters, including hemoglobin (Hb), hematocrit (Hct), white blood cell (WBC), lymphocytes, monocytes, alkaline phosphatase (ALP), aspartate aminotransferase (AST), sorbitol dehydrogenase (SDH), albumin, and glucose (see Tables B-3 and B-4). The study author discounted these changes because they either did not increase (or decrease) consistently with increasing exposure concentration, appeared to be transient (observed at 45 days but not 90 days) and/or were small in magnitude compared with historical controls. However, the alterations in WBC and lymphocyte counts appeared to be treatment related. Decreased WBC and lymphocyte counts were observed in exposed animals, reaching statistical significance in males at the highest exposure concentration (16,000 mg/m^3) after the 45-day (WBC and lymphocyte counts) and 90-day (lymphocyte counts only) sampling time points. The toxicological significance of the WBC and lymphocyte responses were further questioned by the study author, arguing that the observed changes were small compared with historical controls but provided no further details. Kelly (1998) also indicated that leukopenia (low WBC count and differentials) could be due to a secondary stress response related to elevation of endogenous glucocorticoids, a phenomenon that has been associated with exposure to irritants in inhalation toxicity studies (Brondeau et al., 1990). However, the cause of the stress was not identified, and there is no direct evidence to support the hypothesis of glucocorticoid-dependent leukopenia following trans-1,2-DCE exposure. The effects on WBC and lymphocytes were generally concentration-related and of similar magnitude across sexes at the 16,000-mg/m^3 dose group (decreases of 18−20 and 22−26% compared with controls for WBC and lymphocytes, respectively). Statistical analysis performed by the U.S. EPA for the purposes of this assessment provided further evidence in support of the biological significance of the hematological findings, revealing a significant decreased trend in WBC and lymphocyte counts in males at 45 and 90 days and in WBC counts at 45 days, and lymphocyte counts at 90 days in females. As such, U.S. EPA considers these effects to be related to exposure to trans-1,2-DCE. No significant urinalysis findings were identified.

There were no statistically significant organ-weight changes in either sex, and absolute and relative liver and kidney weights were within 10% of control values in all groups (see Table B-5). Incidence data reported in the study showed no significant gross or microscopic lesions in any tissues that were attributable to trans-1,2-DCE exposure.

In the cell proliferation group, no differences in the hepatic labeling indices were observed between the control and 16,000-mg/m^3 rats of either sex (lower exposure groups were not evaluated).

A no-observed-adverse-effect level (NOAEL) of 4,000 mg/m^3 and lowest-observed-adverse-effect level (LOAEL) of 16,000 mg/m^3 were identified from this study on the basis of statistically significant decreases in WBCs and lymphocytes at 45 days and decreased WBC counts at 90 days in male rats exposed to *trans*-1,2-DCE vapors for up to 90 days under the study conditions described (U.S. EPA, 2020). Also noted was that trend tests supported concentration-related decreases in WBC and lymphocyte counts in both sexes. The reported study concentrations of 0, 790, 4,000, and 16,000 mg/m^3 were converted to corresponding HEC_{ER} (human equivalent concentration for extrarespiratory effects) values of 0, 140, 710, and 2,800 mg/m^3, respectively, by U.S. EPA (2020). The 90-day WBC and lymphocyte count data for both males and females for these endpoints were evaluated via benchmark dose (BMD) modeling.

The benchmark concentration lower confidence limit 1 standard deviation ($BMCL_{1SD}$) human equivalent concentration (HEC) of 109 mg/m^3 for decreased lymphocyte counts in male rats was identified as the most sensitive point of departure (POD) for deriving screening-level p-RfC values for trans-1,2-DCE.

The screening subchronic p-RfC for *trans*-1,2-DCE was derived from the $BMCL_{1SD}$ of 109 mg/m^3 by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10) to the selected POD of 109 mg/m^3 (U.S. EPA, 2020). Wang et al. (2012) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are the same as those applied to the analogue unless additional information is available.

$$\begin{aligned} \textbf{Screening Subchronic p-RfC} &= \text{Analogue POD} \div UF_C \\ &= 109\ \text{mg/m}^3 \div 300 \\ &= \mathbf{4 \times 10^{-1}\ mg/m^3} \end{aligned}$$

Table A-8 summarizes the UFs for the screening subchronic p-RfC for *cis*-1,2-DCE.

Table A-8. Uncertainty Factors for the Screening Subchronic p-RfC for *cis*-1,2-DCE (CASRN 156-59-2)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans, using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a Category 3 gas, as specified in U.S. EPA (1994) guidelines for deriving p-RfCs.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability in humans.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the *trans*-1,2-DCE analogue database and absence of toxicity data for *cis*-1,2-DCE.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL.
UF_S	1	A UF_S of 1 is applied because the POD for the subchronic p-RfC was derived from subchronic data.
UF_C	300	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Concentration

trans-1,2-DCE was also selected as the analogue for *cis*-1,2-DCE for derivation of a screening chronic p-RfC. The key study and calculation of the POD were described above for the subchronic p-RfC. The screening chronic p-RfC for *trans*-1,2-DCE was derived by applying a UF_C of 3,000 (UF_A = 3, UF_H = 10, UF_D = 10, and a subchronic-to-chronic extrapolation uncertainty factor [UF_S] of 10 for use of a subchronic BMCL as a POD) to the selected POD of 109 mg/m^3. In deriving the screening chronic p-RfC for *cis*-1,2-DCE, the same uncertainty factors were used.

$$\textbf{Screening Chronic p-RfC} = \text{Analogue POD} \div UF_C$$
$$= 109 \text{ mg/m}^3 \div 3{,}000$$
$$= \mathbf{4 \times 10^{-2} \text{ mg/m}^3}$$

Table A-9 summarizes the uncertainty factors for the screening chronic p-RfC for *cis*-1,2-DCE.

Table A-9. Uncertainty Factors for the Screening Chronic p-RfC for *cis*-1,2-DCE (CASRN 156-59-2)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans, using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a Category 3 gas, as specified in U.S. EPA (1994) guidelines for deriving p-RfCs.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability in humans.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the *trans*-1,2-DCE analogue database and absence of toxicity data for *cis*-1,2-DCE.
UF_L	1	A UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a BMCL.
UF_S	10	A UF_S of 10 is applied because the POD for the chronic p-RfC was derived from subchronic data.
UF_C	3,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; *cis*-1,2-DCE = *cis*-1,2-dichloroethylene; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX B. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2020). 1,2-Dichloroethylene, all isomers (156-59-2; 156-60-5; 540-59-0) [TLV/BEI]. In 2020 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices (pp. 26). Cincinnati, OH. https://portal.acgih.org/s/store#/store/browse/detail/a154W00000BOag6QAD

Anders, MW. (1985). Bioactivation of foreign compounds. New York, NY: Academic Press.

Arito, H; Takahashi, M; Ishikawa, T. (1994). Effect of subchronic inhalation exposure to low-level trichloroethylene on heart rate and wakefulness-sleep in freely moving rats. Sangyo Igaku 36: 1-8.

Astrand, I; Ovrum, P. (1976). Exposure to trichloroethylene I. Uptake and distribution in man. Scand J Work Environ Health 2: 199-211.

ATSDR (Agency for Toxic Substances and Disease Registry). (1996). Toxicological profile for 1,2-dichloroethene [ATSDR Tox Profile]. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/ToxProfiles/tp87.pdf

ATSDR (Agency for Toxic Substances and Disease Registry). (2006). Toxicological profile for vinyl chloride [ATSDR Tox Profile]. Atlanta, GA. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=282&tid=51

ATSDR (Agency for Toxic Substances and Disease Registry). (2019a). Toxicological profile for 1,1-dichloroethene: draft for public comment [ATSDR Tox Profile]. Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp39.pdf

ATSDR (Agency for Toxic Substances and Disease Registry). (2019b). Toxicological profile for tetrachloroethylene [ATSDR Tox Profile]. Atlanta, GA: U.S. Department of Health and Human Services. https://www.atsdr.cdc.gov/ToxProfiles/tp18.pdf

ATSDR (Agency for Toxic Substances and Disease Registry). (2019c). Toxicological profile for trichloroethylene [ATSDR Tox Profile]. Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp19.pdf

Barton, HA; Creech, JR; Godin, CS; Randall, GM; Seckel, CS. (1995). Chloroethylene mixtures: Pharmacokinetic modeling and in vitro metabolism of vinyl chloride, trichloroethylene, and trans-1,2-dichloroethylene in rat. Toxicol Appl Pharmacol 130: 237-247. http://dx.doi.org/10.1006/taap.1995.1029

Bi, WF; Wang, YS; Huang, MY; Meng, DS. (1985). Effect of vinyl chloride on testis in rats. Ecotoxicol Environ Saf 10: 281-289. http://dx.doi.org/10.1016/0147-6513(85)90074-0

Bingham, E; Cohrssen, B. (2012). Patty's toxicology (6th ed.). Hoboken, NJ: John Wiley & Sons.

Bolt, HM; Kappus, H; Buchter, A; Bolt, W. (1976). Disposition of [1,2-14C] vinyl chloride in the rat. Arch Toxicol 35: 153-162.

Bolt, HM; Laib, RJ; Kappus, H; Buchter, A. (1977). Pharmacokinetics of vinyl chloride in the rat. Toxicology 7: 179-188.

Bonse, G; Urban, T; Reichert, D; Henschler, D. (1975). Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem Pharmacol 24: 1829-1834. http://dx.doi.org/10.1016/0006-2952(75)90468-2

Boverhof, DR; Krieger, SM; Hotchkiss, J; Stebbins, KE; Thomas, J; Woolhiser, MR. (2013). Assessment of the immunotoxic potential of trichloroethylene and perchloroethylene in rats following inhalation exposure. J Immunotoxicol 10: 311-320. http://dx.doi.org/10.3109/1547691X.2012.735275

Brodkin, CA; Daniell, W; Checkoway, H; Echeverria, D; Johnson, J; Wang, K; Sohaey, R; Green, D; Redlich, C; Gretch, D. (1995). Hepatic ultrasonic changes in workers exposed to perchloroethylene. Occup Environ Med 52: 679-685.

Byczkowski, JZ; Fisher, JW. (1994). Lactational transfer of tetrachloroethylene in rats. Risk Anal 14: 339-349. http://dx.doi.org/10.1111/j.1539-6924.1994.tb00250.x

Cai, SX; Huang, MY; Chen, Z; Liu, YT; Jin, C; Watanabe, T; Nakatsuka, H; Seiji, K; Inoue, O; Ikeda, M. (1991). Subjective symptom increase among dry-cleaning workers exposed to tetrachloroethylene vapor. Ind Health 29: 111-121. http://dx.doi.org/10.2486/indhealth.29.111

CalEPA (California Environmental Protection Agency). (2018). Cis- and trans-1,2-dichloroethylene in drinking water. Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. https://oehha.ca.gov/media/downloads/water/chemicals/phg/phg12-dce072018.pdf

CalEPA (California Environmental Protection Agency). (2021). OEHHA chemical database: 1,2-dichloroethylene, cis. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. https://oehha.ca.gov/chemicals/12-dichloroethylene-cis

ChemIDplus. (2021). ChemIDplus advanced. Available online at https://chem.nlm.nih.gov/chemidplus/

Chiu, WA; Micallef, S; Monster, AC; Bois, FY. (2007). Toxicokinetics of inhaled trichloroethylene and tetrachloroethylene in humans at 1 ppm: Empirical results and comparisons with previous studies. Toxicol Sci 95: 23-36. http://dx.doi.org/10.1093/toxsci/kfl129

Clark, DG; Tinston, DJ. (1982). Acute inhalation toxicity of some halogenated and non-halogenated hydrocarbons. Hum Exp Toxicol 1: 239-247. http://dx.doi.org/10.1177/096032718200100306

Clewell, HJ; Andersen, ME. (1994). Physiologically-based pharmacokinetic modeling and bioactivation of xenobiotics [Review]. Toxicol Ind Health 10: 1-24. http://dx.doi.org/10.1177/074823379401000101

Costa, AK; Ivanetich, KM. (1982). The 1,2-dichloroethylenes: their metabolism by hepatic cytochrome p-450 in vitro. Biochem Pharmacol 31: 2093-2102. http://dx.doi.org/10.1016/0006-2952(82)90426-9

Costa, AK; Ivanetich, KM. (1984). Chlorinated ethylenes: their metabolism and effect on DNA repair in rat hepatocytes. Carcinogenesis 5: 1629-1636. http://dx.doi.org/10.1093/carcin/5.12.1629

Dallas, C; Gallo, J; Ramanathan, R; Muralidhara, S; Bruckner, J. (1991). Physiological pharmacokinetic modeling of inhaled trichloroethylene in rats. Toxicol Appl Pharmacol 110: 303-314. http://dx.doi.org/10.1016/S0041-008X(05)80013-4

Dallas, CE; Muralidhara, S; Chen, XM; Ramanathan, R; Varkonyi, P; Gallo, JM; Bruckner, JV. (1994). Use of a physiologically based model to predict systemic uptake and respiratory elimination of perchloroethylene. Toxicol Appl Pharmacol 128: 60-68. http://dx.doi.org/10.1006/taap.1994.1180

Dallas, CE; Weir, FW; Feldman, S; Putcha, L; Bruckner, JV. (1983). The uptake and disposition of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol Appl Pharmacol 68: 140-151. http://dx.doi.org/10.1016/0041-008X(83)90363-0

Davis, AP; Grondin, CJ; Johnson, RJ; Sciaky, D; Wiegers, J; Wiegers, TC; Mattingly, CJ. (2021). The comparative toxicogenomics database. Davis, AP; Grondin, CJ; Johnson, RJ; Sciaky, D; Wiegers, J; Wiegers, TC; Mattingly, CJ. http://ctdbase.org/

Dorfmueller, MA; Henne, SP; York, RG; Bornschein, RL; Manson, JM. (1979). Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology 14: 153-166. http://dx.doi.org/10.1016/0300-483X(79)90061-1

Dow Chemical (Dow Chemical Company). (1994). The toxicity of 1,2-dichloroethylene as determined by repeated exposures on laboratory animals, with cover letter dated 05/10/94 (sanitized) [TSCA Submission]. (OTS0557247. 86940000837S. TSCATS/442717).

Dreher, EL; Beutel, KK; Myers, JD; Lübbe, T; Krieger, S; Pottenger, LH. (2014). Chloroethanes and chloroethylenes. In B Elvers (Ed.), Ullmann's Encyclopedia of Industrial Chemistry (6th ed., pp. 1-81). Hoboken, NJ: Wiley-VCH Verlag GmbH & Co. http://dx.doi.org/10.1002/14356007.o06_o01.pub2

DuPont (E. I. du Pont de Nemours & Company). (1988). Teratogenicity study of trans-1,2-dichloroethylene in rats with cover letter dated 05/10/94 (sanitized) [TSCA Submission]. (OTS0557175. 86940000765S. TSCATS/442645). E. I. du Pont de Nemours and Company.

DuPont Haskell Lab (DuPont Haskell Laboratory). (1999). Initial submission: Letter from DuPont Haskell Laboratory to USEPA RE results of 4-hour inhalation median lethality study (LC50) in rats w/cis-1,2-dichloroethylene, dated 8/26/99 [TSCA Submission]. (OTS0559785. 88990000257. 8EHQ-0899-14538. TSCATS/446080). DuPont Chem.

ECHA (European Chemicals Agency). (2020). Substance infocard: cis-dichloroethylene. https://echa.europa.eu/substance-information/-/substanceinfo/100.005.328

Filser, JG; Bolt, HM. (1979). Pharmacokinetics of halogenated ethylenes in rats. Arch Toxicol 42: 123-136. http://dx.doi.org/10.1007/BF00316492

Foster, AB. (1984). Deuterium isotope effects in studies of drug metabolism. Trends Pharmacol Sci 5: 524-527. http://dx.doi.org/10.1016/0165-6147(84)90534-0

Franchini, I; Cavatorta, A; Falzoi, M; Lucertini, S; Mutti, A. (1983). Early indicators of renal damage in workers exposed to organic solvents. Int Arch Occup Environ Health 52: 1-9. http://dx.doi.org/10.1007/BF00380601

Freundt, KJ; Leibaldt, GP; Lieberwirth, E. (1977). Toxicity studies on trans-1,2-dichloroethylene. Toxicology 7: 141-153. http://dx.doi.org/10.1016/0300-483X(77)90059-2

Freundt, KJ; Macholz, J. (1972). Cis-1,2-dichloroethylene and trans-1, 2-dichloroethylene - 2 new inhibitors of microsomal enzymes [Abstract]. Naunyn-Schmiedebergs Arch Pharmacol 274: R37.

Freundt, KJ; Macholz, J. (1978). Inhibition of mixed function oxidases in rat liver by trans- and cis-1,2-dichloroethylene. Toxicology 10: 131-140. http://dx.doi.org/10.1016/0300-483X(78)90063-X

Friberg, L; Kylin, B; Nystrom, A. (1953). Toxicities of trichlorethylene and tetrachloroethylene and Fujiwara's pyridine-alkali reaction. Basic Clin Pharmacol Toxicol 9: 303-312.

Gargas, ML; Burgess, RJ; Voisard, DE; Cason, GH; Andersen, ME. (1989). Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98: 87-99. http://dx.doi.org/10.1016/0041-008x(89)90137-3

Gargas, ML; III, CH; Andersen, ME. (1990). Gas uptake inhalation techniques and the rates of metabolism of chloromethanes, chloroethanes, and chloroethylenes in the rat. Inhal Toxicol 2: 295-319. http://dx.doi.org/10.3109/08958379009145260

Gargas, ML; Seybold, PG; Andersen, ME. (1988). Modeling the tissue solubilities and metabolic rate constant (Vmax) of halogenated methanes, ethanes, and ethylenes. Toxicol Lett 43: 235-256. http://dx.doi.org/10.1016/0378-4274(88)90031-8

Ghantous, H; Danielsson, BRG; Dencker, L; Gorczak, J; Vesterberg, O. (1986). Trichloroacetic acid accumulates in murine amniotic fluid after tri- and tetrachloroethylene inhalation. Acta Pharmacol Toxicol 58: 105-114. http://dx.doi.org/10.1111/j.1600-0773.1986.tb00078.x

Hanioka, N; Jinno, H; Nishimura, T; Ando, M. (1998). Changes in hepatic cytochrome P450 enzymes by cis- and trans-1,2-dichloroethylenes in rat. Xenobiotica 28: 41-51. http://dx.doi.org/10.1080/004982598239740

Haskell Laboratories. (1988). Initial submission: Teratogenicity study of trans-1,2-dichloroethylene in rats (final report) with attachments and cover letter dated 032792 [TSCA Submission]. (88-920001531. 8EHQ-0392-2889. TSCATS/422945). E. I. du Pont de Nemours and Company, Inc. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0535915.xhtml

Hehir, RM; Mcnamara, BP; Mclaughlin, J, Jr; Willigan, DA; Bierbower, G; Hardisty, JF. (1981). Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. Environ Health Perspect 41: 63-72.

Henck, JW; Quast, JF; Rampy, LW. (1979). A comparison of four mouse strains exposed to subchronically inhaled vinylidene chloride (VDC). Henck, JW; Quast, JF; Rampy, LW.

Henschler, D; Bonse, G. (1977). Metabolic activation of chlorinated ethylenes: Dependence of mutagenic effect on electrophilic reactivity of the metabolically formed epoxides. Arch Toxicol 39: 7-12. http://dx.doi.org/10.1007/BF00343270

Henschler, D; Bonse, G. (1979). Metabolic activation of chlorinated ethylene derivatives. In Y Cohen (Ed.), Advances in Pharmacology and Therapeutics: Volume 9: Toxicology (pp. 123-130). New York, NY: Pergamon Press.

Hurtt, ME; Valentine, R; Alvarez, L. (1993). Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat. Fundam Appl Toxicol 20: 225-230. http://dx.doi.org/10.1006/faat.1993.1030

IARC (International Agency for Research on Cancer). (2021). Agents classified by the IARC monographs. Lyon, France. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf

Ikeda, M; Imamura, T. (1973). Biological half-life of trichloroethylene and tetrachloroethylene in human subjects [Review]. Int Arch Occup Environ Health 31: 209-224. http://dx.doi.org/10.1007/BF00539241

Jenkins, LJ; Trabulus, MJ; Murphy, SD. (1972). Biochemical effects of 1,1-dichloroethylene in rats - Comparison with carbon-tetrachloride and 1,2-dichloroethylene. Toxicol Appl Pharmacol 23: 501-510. http://dx.doi.org/10.1016/0041-008X(72)90052-X

JISA (Japan Industrial Safety Association). (1993). Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice. Hadano, Japan. https://www.epa.gov/iris/supporting-documents-tetrachloroethylene-perchloroethylene

John, JA; Smith, FA; Leong, BKJ; Schwetz, BA. (1977). The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39: 497-513. http://dx.doi.org/10.1016/0041-008X(77)90141-7

John, JA; Smith, FA; Schwetz, BA. (1981). Vinyl chloride: inhalation teratology study in mice, rats and rabbits. Environ Health Perspect 41: 171-177. http://dx.doi.org/10.2307/3429312

Johnson, P; Dawson, B; Goldberg, S. (1998). A review: Trichloroethylene metabolites: Potential cardiac teratogens [Review]. Environ Health Perspect 106: 995-999. http://dx.doi.org/10.2307/3434143

Jones, BK; Hathway, DE. (1978). The biological fate of vinylidene chloride in rats. Chem Biol Interact 20: 27-41. http://dx.doi.org/10.1016/0009-2797(78)90078-9

Karlsson, JE; Rosengren, LE; Kjellstrand, P; Haglid, KG. (1987). Effects of low-dose inhalation of three chlorinated aliphatic organic solvents on deoxyribonucleic acid in gerbil brain [Comment]. Scand J Work Environ Health 13: 453-458. http://dx.doi.org/10.5271/sjweh.2015

Kelly, DP. (1998). trans-1,2-Dichloroethylene: 90-day inhalation toxicity study in rats. (Laboratory Project ID HL-1998-00952). Newark, DE: E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine.

Kelly, DP. (1999). Trans-1,2-dichloroethylene and cis-1,2-dichloroethylene: Inhalation median lethal concentration (LC50) study in rats. (Laboratory Project ID: DuPont-2806). Newark, DE: E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine.

Kelly, DP; Hansen, J; Brock, W; Barter, J; Burleigh-Flayer, H. (2000). Acute inhalation toxicity of cis and trans isomers of 1,2-dichloroethylene in rats [Abstract]. Toxicologist 54: pg. 20.

Kjellstrand, P; Holmquist, B; Alm, P; Kanje, M; Romare, S; Jonsson, I; Månsson, L; Bjerkemo, M. (1983). Trichloroethylene: Further studies of the effects on body and organ weights and plasma butyrylcholinesterase activity in mice. Acta Pharmacol Toxicol 53: 375-384. http://dx.doi.org/10.1111/j.1600-0773.1983.tb03438.x

Kjellstrand, P; Holmquist, B; Kanje, M; Alm, P; Romare, S; Jonsson, I; Mansson, L; Bjerkemo, M. (1984). Perchloroethylene: Effects on body and organ weights and plasma butyrylcholinesterase activity in mice. Acta Pharmacol Toxicol 54: 414-424. http://dx.doi.org/10.1111/j.1600-0773.1984.tb01951.x

Krajewski, J; Dobecki, M; Gromiec, J. (1980). Retention of vinyl chloride in the human lung. Occup Environ Med 37: 373-374.

Kumar, P; Purohit, DC; Prasad, AK; al, e. (2002). Histobiochemical alterations in rat lungs induced by inhalation of trichloroethylene. J Ecophys Occup Health 2: 265-274.

Laham, S. (1970). Studies on placental transfer: Trichlorethylene. Ind Med Surg 39: 46-49.

Lehmann, KB; Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116: 131-268.

Lilly, PD; Thornton-Manning, JR; Gargas, ML; Clewell, HJ; Andersen, ME. (1998). Kinetic characterization of CYP2E1 inhibition in vivo and in vitro by the chloroethylenes. Arch Toxicol 72: 609-621. http://dx.doi.org/10.1007/s002040050551

Mathews, JM; Etheridge, AS; Raymer, JH; Black, SR; Pulliam, DW; Bucher, JR. (1998). Selective inhibition of cytochrome P450 2E1 in vivo and in vitro with trans-1,2-dichloroethylene. Chem Res Toxicol 11: 778-785. http://dx.doi.org/10.1021/tx970227g

McCauley, PT; Robinson, M; Condie, LW; Parnell, M. (1990). The effects of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in rats [unpublished report]. U.S. Environmental Protection Agency, U.S. Air Force.

McCauley, PT; Robinson, M; Daniel, FB; Olson, GR. (1995). The effects of subacute and subchronic oral exposure to cis-1,2-dichloroethylene in Sprague-Dawley rats. Drug Chem Toxicol 18: 171-184. http://dx.doi.org/10.3109/01480549509014319

Mcdermott, MJ; Mazor, KA; Shost, SJ; Narang, RS; Aldous, KM; Storm, JE. (2005). Tetrachloroethylene (PCE, Perc) levels in residential dry cleaner buildings in diverse communities in New York City. Environ Health Perspect 113: 1336-1343. http://dx.doi.org/10.1289/ehp.7414

Mckenna, MJ; Watanabe, PG; Gehring, PJ. (1977). Pharmacokinetics of vinylidene chloride in the rat. Environ Health Perspect 21: 99-105. http://dx.doi.org/10.1289/ehp.772199

Mckenna, MJ; Zempel, JA; Madrid, EO; Braun, WH; Gehring, PJ. (1978a). Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration. Toxicol Appl Pharmacol 45: 821-835. http://dx.doi.org/10.1016/0041-008X(78)90173-4

Mckenna, MJ; Zemple, JA; Madrid, EO; Gehring, PJ. (1978b). The pharmacokinetics of [14C] vinylidene chloride in rats following inhalation exposure. Toxicol Appl Pharmacol 45: 599-610. http://dx.doi.org/10.1016/0041-008x(78)90121-7

Mcmillan, DA. (1986) Toxicity of the cis- and trans-isomers of 1,2-dichloroethylene. (Doctoral Dissertation). University of Nebraska Medical Center, Omaha, NE. Retrieved from https://dialog.proquest.com/professional/pqdtftprofmodule/docview/303446721/fulltextPDF/178313B913C6B59B493/1?accountid=102841

Mennear, J; Maronpot, R; Boorman, G; Eustis, S; Huff, J; Haseman, J; Mcconnell, E; Ragan, H; Miller, R. (1986). Toxicologic and carcinogenic effects of inhaled tetrachloroethylene in rats and mice. In New concepts and developments in toxicology: Proceedings of the Fourth International Congress of toxicology held in Tokyo, Japan, July 21-25, 1986. New York: Elsevier Science Publishers.

Mertens, JA. (2000). Dichloroethylene. In C Ley (Ed.), Kirk-Othmer encyclopedia of chemical technology. New York, NY: John Wiley & Sons, Inc. http://dx.doi.org/10.1002/0471238961.0409030813051820.a01

Monster, AC; Boersma, G; Duba, WC. (1976). Pharmacokinetics of trichloroethylene in volunteers, influence of workload and exposure concentration. Int Arch Occup Environ Health 38: 87-102. http://dx.doi.org/10.1007/BF00378619

Monster, AC; Boersma, G; Duba, WC. (1979a). Kinetics of trichloroethylene in repeated exposure of volunteers. Int Arch Occup Environ Health 42: 283-292. http://dx.doi.org/10.1007/BF00377782

Monster, AC; Boersma, G; Steenweg, H. (1979b). Kinetics of tetrachloroethylene in volunteers; influence of exposure concentration and work load. Int Arch Occup Environ Health 42: 303-309.

Muller, G; Spassovski, M; Henschler, D. (1974). Metabolism of trichloroethylene in man: II. Pharmacokinetics of metabolites. Arch Toxicol 32: 283-295. http://dx.doi.org/10.1007/BF00330110

Nakahama, T; Sarutani, S; Inouye, Y. (2000). Effects of chlorinated ethylenes on expression of rat CYP forms: Comparative study on correlation between biological activities and chemical structures. J Health Sci 46: 251-258. http://dx.doi.org/10.1248/jhs.46.251

Nakajima, T. (1997). Cytochrome P450 isoforms and the metabolism of volatile hydrocarbons of low relative molecular mass. J Occup Health 39: 83-91. http://dx.doi.org/10.1539/joh.39.83

NIOSH (National Institute for Occupational Safety and Health). (2014). 1,2-Dichloroethylene. Immediately Dangerous to Life or Health (IDLH) concentrations. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health, Education and Welfare. https://www.cdc.gov/niosh/idlh/540590.html

NIOSH (National Institute for Occupational Safety and Health). (2019). NIOSH pocket guide to chemical hazards: 1,2-Dichloroethylene. Atlanta, GA: U.S. Department of Health, Education and Welfare, Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/niosh/npg/npgd0195.html

NLM (National Library of Medicine). (2021a). ChemIDplus: 1,1-Dichloroethylene. Available online at https://chem.nlm.nih.gov/chemidplus/rn/75-35-4

NLM (National Library of Medicine). (2021b). ChemIDplus: cis-1,2-Dichloroethylene. Available online at https://chem.nlm.nih.gov/chemidplus/rn/156-59-2

NLM (National Library of Medicine). (2021c). ChemIDplus: Tetrachloroethylene [USP]. Available online at https://chem.nlm.nih.gov/chemidplus/rn/127-18-4

NLM (National Library of Medicine). (2021d). ChemIDplus: trans-1,2-Dichloroethylene. Available online at https://chem.nlm.nih.gov/chemidplus/rn/156-60-5

NLM (National Library of Medicine). (2021e). ChemIDplus: Trichloroethylene [INN:NF]. Available online at https://chem.nlm.nih.gov/chemidplus/rn/79-01-6

NLM (National Library of Medicine). (2021f). ChemIDplus: Vinyl chloride. Available online at https://chem.nlm.nih.gov/chemidplus/rn/75-01-4

NLM (National Library of Medicine). (2021g). PubChem: cis-1,2-Dichloroethylene. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/643833

NLM (National Library of Medicine). (2021h). PubChem: trans-1,2-Dichloroethylene. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/638186

NLM (National Library of Medicine). (2021i). PubChem: Vinyl chloride. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/6338

NLM (National Library of Medicine). (2021j). PubChem: Vinylidene chloride. Available online at https://pubchem.ncbi.nlm.nih.gov/compound/6366

NTP (National Toxicology Program). (1986). Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344 rats and B6C3F1 mice (inhalation studies). (NTP TR 311). Research Triangle Park, NC: U.S. Department of Health and Human Services. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr311.pdf

NTP (National Toxicology Program). (2015). NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (Inhalation studies). https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr582_508.pdf. May 8, 2018

NTP (National Toxicology Program). (2016). 14th Report on carcinogens. Research Triangle Park, NC. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html

O'Brien, PJ. (1988). Radical formation during the peroxidase catalyzed metabolism of carcinogens and xenobiotics: The reactivity of these radicals with GSH, DNA, and unsaturated lipid [Review]. Free Radic Biol Med 4: 169-183. http://dx.doi.org/10.1016/0891-5849(88)90025-1

OECD (Organisation for Economic Co-operation and Development). (2022). The OECD QSAR toolbox [version 4.5] [Database]. Retrieved from http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

OSHA (Occupational Safety & Health Administration). (2020a). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC. https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286

OSHA (Occupational Safety & Health Administration). (2020b). Safety and health regulations for construction: Occupational health and environmental controls: Gases, vapors, fumes, dusts, and mists: Appendix A. Available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10629

OSHA (Occupational Safety & Health Administration). (2020c). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. Available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

Parkinson, A. (2001). Biotransformation of xenobiotics. In CD Klaassen (Ed.), Casarett and Doull's toxicology: The basic science of poison (6th ed., pp. 133-224). New York, NY: McGraw-Hill.

Pegg, DG; Zempel, JA; Braun, WH; Watanabe, PG. (1979). Disposition of tetrachloro(14C)ethylene following oral and inhalation exposure in rats. Toxicol Appl Pharmacol 51: 465-474. http://dx.doi.org/10.1016/0041-008X(79)90371-5

Pellizzari, ED; Hartwell, TD; Harris, BS, III; Waddell, RD; Whitaker, DA; Erickson, MD. (1982). Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28: 322-328. http://dx.doi.org/10.1007/BF01608515

Plaa, GL; Larson, RE. (1965). Relative nephrotoxic properties of chlorinated methane, ethane, and ethylene derivatives in mice. Toxicol Appl Pharmacol 7: 37-44. http://dx.doi.org/10.1016/0041-008X(65)90072-4

Pleil, JD; Lindstrom, AB. (1997). Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compounds. Clin Chem 43: 723-730.

Pozzani, UC; Weil, CS; Carpenter, CP. (1959). The toxicological basis of threshold limit values. 5: The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Am Ind Hyg Assoc J 20: 364-369. http://dx.doi.org/10.1080/00028895909343733

Quast, JF; Mckenna, MJ; Rampy, LW; Norris, JM. (1986). Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. Toxicol Sci 6: 105-144. http://dx.doi.org/10.1016/0272-0590(86)90269-1

Rampy, LW; Quast, JF; Humiston, CG; Balmer, MF; Schwetz, BA. (1977). Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking water or administered by repeated inhalation. Environ Health Perspect 21: 33-43. http://dx.doi.org/10.1289/ehp.772133

Sato, A; Nakajima, T. (1987). Pharmacokinetics of organic solvent vapors in relation to their toxicity [Review]. Scand J Work Environ Health 13: 81-93. http://dx.doi.org/10.5271/sjweh.2075

Schumann, AM; Quast, JF; Watanabe, PG. (1980). The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. Toxicol Appl Pharmacol 55: 207-219. http://dx.doi.org/10.1016/0041-008X(80)90082-4

Schwetz, BA; Leong, BKJ; Gehring, PJ. (1975). The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol Appl Pharmacol 32: 84-96. http://dx.doi.org/10.1016/0041-008X(75)90197-0

Sharma, RP; Gehring, PJ. (1979). Immunologic effects of vinyl chloride in mice. Ann N Y Acad Sci 320: 551-563.

Short, RD, Jr; Minor, JL; Winston, JM; Ferguson, B; Unger, T; Lee, CC. (1977a). Toxicity studies of selected chemicals Task II: the developmental toxicity of vinylidene chloride inhaled by rats and mice during gestation. Short, RD, Jr; Minor, JL; Winston, JM; Ferguson, B; Unger, T; Lee, CC.

Short, RD; Winston, JM; Minor, JL; Hong, CB; Seifter, J; Lee, CC. (1977b). Toxicity of vinylidene chloride in mice and rats and its alteration by various treatments. J Toxicol Environ Health 3: 913-921. http://dx.doi.org/10.1080/15287397709529625

Short, RD; Winston, JM; Minor, JL; Seifter, J; Lee, CC. (1977c). Effect of various treatments on toxicity of inhaled vinylidene chloride. Environ Health Perspect 21: 125-129. http://dx.doi.org/10.1289/ehp.7721125

Siegel, J; Jones, RA; Coon, RA; Lyon, JP. (1971). Effects on experimental animals of acute, repeated and continuous inhalation exposures to dichloroacetylene mixtures. Toxicol Appl Pharmacol 18: 168-174. http://dx.doi.org/10.1016/0041-008X(71)90326-7

Simmonds, AC; Reilly, CA; Baldwin, RM; Ghanayem, BI; Lanza, DL; Yost, GS; Collins, KS; Forkert, PG. (2004). Bioactivation of 1,1-dichloroethylene to its epoxide by CYP2E1 and CYP2F enzymes. Drug Metab Dispos 32: 1032-1039.

Storm, JE; Mazor, KA; Aldous, KM; Blount, BC; Brodie, SE; Serle, JB. (2011). Visual contrast sensitivity in children exposed to tetrachloroethylene. Arch Environ Occup Health 66: 166-177. http://dx.doi.org/10.1080/19338244.2010.539638

Suzuki, Y. (1978). Pulmonary tumors induced in mice by vinyl chloride monomer. Environ Res 16: 285-301.

Suzuki, Y. (1981). Neoplastic and nonneoplastic effects of vinyl chloride in mouse lung. Environ Health Perspect 41: 31-52. http://dx.doi.org/10.1289/ehp.814131

Thornton, SR; Schroeder, RE; Robison, RL; Rodwell, DE; Penney, DA; Nitschke, KD; Sherman, WK. (2002). Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68: 207-219. http://dx.doi.org/10.1093/toxsci/68.1.207

U.S. EPA (U.S. Environmental Protection Agency). (1988). Recommendations for and documentation of biological values for use in risk assessment [EPA Report]. (EPA600687008). Cincinnati, OH. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA600890066F). Research Triangle Park, NC. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317

U.S. EPA (U.S. Environmental Protection Agency). (2000). Toxicological review of vinyl chloride [EPA Report]. (EPA635R00004). Washington, DC. http://www.epa.gov/iris/toxreviews/1001tr.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2002a). A review of the reference dose and reference concentration processes. (EPA630P02002F). Washington, DC. https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2002b). Toxicological review of 1,1-dichloroethylene (CAS No. 75-35-4) [EPA Report]. (EPA635R02002). https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0039tr.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2003). Toxicological review of dichloroacetic acid (CAS No. 79-43-6) [EPA Report]. (EPA635R03007). Washington, DC. http://www.epa.gov/iris/toxreviews/0654tr.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA630P03001F). Washington, DC. https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2008). 1,2-Dichloroethene (CAS reg. no. 540-59-0), cis-1,2-dichloroethene (CAS reg. no. 156-59-2), trans-1,2-dichloroethene (CAS reg. no. 156-60-5): Acute exposure guideline levels (AEGLs), final. Washington, DC: National Advisory Committee for Acute Exposure Guideline Levels. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2014-11/documents/1_1_and_1_2_dichloroethylene.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2010). Toxicological review of cis-1,2-dichloroethylene and trans-1,2-dichloroethylene (CAS nos. cis: 156-592-2: trans- 156-60-5: mixture: 540-59-0). In support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA635R09006F). Washington, DC. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0418tr.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2011a). Chemical assessment clustering engine (ChemACE). Retrieved from https://www.epa.gov/tsca-screening-tools/chemical-assessment-clustering-engine-chemace

U.S. EPA (U.S. Environmental Protection Agency). (2011b). Health effects assessment summary tables (HEAST) for superfund [EPA Report]. Washington, DC. https://epa-heast.ornl.gov/heast.php

U.S. EPA (U.S. Environmental Protection Agency). (2011c). Provisional peer-reviewed toxicity values for cis-1,2-Dichloroethylene (CASRN 156-59-2) [EPA Report]. Cincinnati, OH. http://hhpprtv.ornl.gov/issue_papers/Dichloroethylene12cis.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2011d). Toxicological review of trichloroethylene (CAS No. 79-01-6) in support of summary Information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA635R09011F). Washington, DC. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100CB6V.txt

U.S. EPA (U.S. Environmental Protection Agency). (2012). Toxicological review of tetrachloroethylene (Perchloroethylene) (CASRN 127-18-4) in support of summary information on the Integrated Risk Information System (IRIS) [EPA Report]. (EPA635R08011F). Washington, DC: National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0106tr.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2018a). 2018 Edition of the drinking water standards and health advisories tables [EPA Report]. (EPA822F18001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2018b). Compiled AEGLs (Acute Exposure Guideline Levels) values. Washington, DC: US Environmental Protection Agency. https://www.epa.gov/aegl/compiled-acute-exposure-guideline-values-aegls

U.S. EPA (U.S. Environmental Protection Agency). (2019). CompTox Chemicals Dashboard [Database]. Research Triangle Park, NC. Retrieved from https://comptox.epa.gov/dashboard

U.S. EPA (U.S. Environmental Protection Agency). (2020). Provisional peer-reviewed toxicity values for trans-1,2-dichloroethylene (CASRN 156-60-5). (EPA/690/R-20/006F). Washington, DC: Center for Public Health and Environmental Assessment, U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/pprtv/recordisplay.cfm?deid=349934

U.S. EPA (U.S. Environmental Protection Agency). (2021a). CompTox chemicals dashboard: 1,1-Dichloroethylene. Available online at https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8021438

U.S. EPA (U.S. Environmental Protection Agency). (2021b). CompTox chemicals dashboard: Vinyl chloride. Available online at https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8021434

U.S. EPA (U.S. Environmental Protection Agency). (2021c). TSCA chemical substance inventory. Download the non-confidential TSCA inventory. Available online at https://www.epa.gov/tsca-inventory/how-access-tsca-inventory

Ungváry, G; Hudák, A; Tátrai, E; Lörincz, M; Folly, G. (1978). Effects of vinyl chloride exposure alone and in combination with trypan blue--applied systematically during all thirds of pregnancy on the fetuses of CFY rats. Toxicology 11: 45-54.

Völkel, W; Friedewald, M; Lederer, E; Pähler, A; Parker, J; Dekant, W. (1998). Biotransformation of perchloroethene: Dose-dependent excretion of trichloroacetic acid, dichloroacetic acid, and N-acetyl-S-(trichlorovinyl)-L-cysteine in rats and humans after inhalation. Toxicol Appl Pharmacol 153: 20-27. http://dx.doi.org/10.1006/taap.1998.8548

von Oettingen, WF. (1937). The halogenated hydrocarbons: Their toxicity and potential dangers. J Ind Hyg Toxicol 19: 349-448.

von Oettingen, WF. (1955). The halogenated aliphatic, olefinic, cyclic, aromatic, and aliphatic-aromatic hydrocarbons including the halogenated insecticides, their toxicity and potential dangers. In Public Health Service publication, no 414. (Public Health Service Publication 414). Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service.

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

Watanabe, PG; Mcgowan, GR; Madrid, EO; Gehring, PJ. (1976). Fate of [14C]vinyl chloride following inhalation exposure in rats. Toxicol Appl Pharmacol 37: 49-59. http://dx.doi.org/10.1016/s0041-008x(76)80007-5

Withey, JR. (1976). Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J Toxicol Environ Health 1: 381-394. http://dx.doi.org/10.1080/15287397609529338

Yamano, T; Morita, S. (1992). Hepatotoxicity of trichlorfon and dichlorvos in isolated rat hepatocytes. Toxicology 76: 69-77.