EPA/690/R-20/006F | September 2020 | FINAL

United States
Environmental Protection
Agency

Provisional Peer-Reviewed Toxicity Values for

trans-1,2-Dichloroethylene
(CASRN 156-60-5)

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

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https://www.epa.gov/pprtv

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[Noncancer Inhalation Values]

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
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 *TRANS*-1,2-DICHLOROETHYLENE (CASRN 156-60-5)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations.

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. Environmental Protection Agency'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 Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

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 Center for Public Health and Environmental Assessment (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 Office of Research and Development (ORD) CPHEA website at https://www.epa.gov/pprtv/forms/contact-us-about-pprtvs.

INTRODUCTION

trans-1,2-Dichloroethylene (*trans*-1,2-DCE), CASRN 156-60-5, belongs to the chloroethylene class of compounds (Dreher et al., 2014). *trans*-1,2-DCE is an isomer of dichloroethylene. The *cis*- isomer (CASRN 156-59-2) and the *trans*- isomer of 1,2-dichloroethylene have different physical, chemical, and biological properties. *trans*-1,2-DCE, the focus of this report, is used as a solvent for waxes, resins, lacquers, and thermoplastics; for the extraction of rubber; as a refrigerant, an extractant of oil and fats from fish and meat, a degreasing agent, a surface cleaning agent, and a foam blowing additive; and in pharmaceutical manufacturing and silicone etching as a source of HCl (Dreher et al., 2014). *trans*-1,2-DCE is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2017a), is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018), and was assessed by the U.S. EPA in a High Production Volume (HPV) Hazard Characterization report (U.S. EPA, 2015).

trans-1,2-DCE is a byproduct of vinyl chloride, trichloroethylene (TCE), and tetrachloroethylene production. It can be withdrawn and purified from the waste streams of these processes (Dreher et al., 2014). *trans*-1,2-DCE can also be synthesized by thermal cracking of 1,1,2-trichloroethane or by chlorination of acetylene.

The empirical formula for *trans*-1,2-DCE is $C_2H_2Cl_2$ and its structure is shown in Figure 1. A table of physicochemical properties for *trans*-1,2-DCE is provided below (see Table 1). *trans*-1,2-DCE is a liquid with high vapor pressure and water solubility. Volatilization of *trans*-1,2-DCE from water and dry surfaces is expected based on the measured Henry's law constant of 9.38×10^{-3} atm-m^3/mol and vapor pressure of 331 mm Hg. In the air, *trans*-1,2-DCE will exist in the vapor phase. *trans*-1,2-DCE will degrade in the atmosphere by reacting with photochemically produced hydroxyl radicals, nitrate radicals, and ozone; estimated half-lives based on these reactions are 6.6, 310, and 5.7 days, respectively (HSDB, 2013). High mobility is expected in soil based on a measured K_{oc} of 59. In an Organisation for Economic Co-operation and Development (OECD) 301D test and other closed bottle biodegradation studies, *trans*-1,2-DCE was not readily biodegradable; however, multiple studies indicate that *trans*-1,2-DCE may be degraded under anaerobic conditions. For example, 73% of the initial *trans*-1,2-DCE was removed when incubated for 6 months under anaerobic conditions with organic sediment obtained from the Florida Everglades; vinyl chloride was generated as a degradation product (HSDB, 2013). Furthermore, the blood-air partition coefficients determined for *trans*-1,2-DCE in humans and rats are 6.04 (± 0.38) and 9.58 (± 0.94) (Gargas et al., 1989), respectively, which are important for understanding regional deposition/absorption of this chemical and for dosimetry conversions (see section on "Animal Studies" for more details).

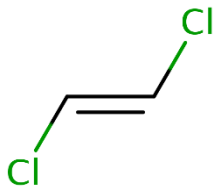

Figure 1. *trans*-1,2-DCE (CASRN 156-60-5) Chemical Structure

Table 1. Physicochemical Properties of *trans*-1,2-DCE (CASRN 156-60-5)[a]

Property (unit)	Value
Physical state	Liquid
Boiling point (°C)	48.7
Melting point (°C)	−49.8
Density (g/cm^3 at 20°C)	1.2565
Vapor pressure (mm Hg at 25°C)	331
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mg/L at 25°C)	4,520
Octanol-water partition constant (log K_{ow})	2.06
Henry's law constant (atm-m^3/mol at 24°C)	9.38×10^{-3}
Soil adsorption coefficient (K_{oc})	59
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	2.34×10^{-12}
Atmospheric half-life (d)	6.6 (calculated based on the compound's measured OH rate constant)
Relative vapor density (air = 1)	3.67
Molecular weight (g/mol)	96.94
Flash point (closed cup in °C)	6
Blood-air partition coefficient (human)[b]	6.04 ± 0.38
Blood-air partition coefficient (rat)[b]	9.58 ± 0.94

[a]HSDB (2013); all values are measured unless otherwise noted.
[b]Gargas et al. (1989).

NA = not applicable; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

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

Table 2. Summary of Available Toxicity Values for *trans*-1,2-DCE (CASRN 156-60-5)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
Noncancer			
IRIS (RfC)	NV	Information reviewed but value not derived	U.S. EPA (2010)
IRIS (RfD)	0.02 mg/kg-d	Based on decrease in number of antibody-forming cells against sRBCs in male mice	
DWSHA (RfD)	0.02 mg/kg-d	NA	U.S. EPA (2012a)
HEAST (subchronic RfD)	0.2 mg/kg-d	Based on increased serum ALP in a 90-d drinking water study in mice	U.S. EPA (2011)
ATSDR (MRL, inhalation acute)	0.2 ppm	Based on fatty degeneration of the liver in rats exposed for 8 hr	ATSDR (1996)
ATSDR (MRL, inhalation intermediate)	0.2 ppm	Based on fatty degeneration of the liver in rats exposed for 8 or 16 wk	
ATSDR (MRL, oral intermediate)	0.2 mg/kg-d	Based on increased serum ALP in male mice exposed for 90 d	
CalEPA (ADD)	0.0048 mg/kg-d	Based on decreased antibody response to sRBCs	CalEPA (2018b)
IPCS	NV	NA	IPCS (2018)
AEGL (AEGL-1)	10 min: 280 ppm 30 min: 280 ppm 60 min: 280 ppm 4 hr: 280 ppm 8 hr: 280 ppm	Based on ocular irritation in humans	U.S. EPA (2017b); U.S. EPA (2008)
AEGL (AEGL-2)	10 min: 1,000 ppm 30 min: 1,000 ppm 60 min: 1,000 ppm 4 hr: 690 ppm 8 hr: 450 ppm	Based on narcosis in rats (4 and 8 hr) or anesthetic effects in humans (10, 30, and 60 min)	
AEGL (AEGL-3)	10 min: 1,700 ppm 30 min: 1,700 ppm 60 min: 1,700 ppm 4 hr: 1,200 ppm 8 hr: 620 ppm	Based on a no-effect level for death in rats (4 and 8 hr) or dizziness, intracranial pressure, and nausea in humans (10, 30, and 60 min)	
ACGIH (TLV-TWA)	200 ppm	Based on CNS impairment and eye irritation	ACGIH (2018)
OSHA (PEL)	200 ppm (790 mg/m^3)	8-hr TWA for general industry, construction, and shipyard employment	OSHA (2017a); OSHA (2020); OSHA (2017b)
NIOSH (REL)	200 ppm (790 mg/m^3)	TWA for up to a 10-hr workday during a 40-hr workweek	NIOSH (2016)
NIOSH (IDLH)	1,000 ppm	Based on acute inhalation toxicity data in humans	NIOSH (2016); NIOSH (2014)

Table 2. Summary of Available Toxicity Values for *trans*-1,2-DCE (CASRN 156-60-5)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference[c]
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 (2012a)
HEAST	NV	NA	U.S. EPA (2011)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2017)
CalEPA	NV	NA	CalEPA (2011); CalEPA (2017); CalEPA (2018a)

[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; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.
[b]Parameters: ADD = acceptable daily dose; AEGL = acute exposure guideline levels; IDLH = immediately dangerous to life or health concentrations; MRL = minimum risk level; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = reference concentration; RfD = reference dose; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.
[c]Reference date is the publication date for the database and not the date the source was accessed.

ALP = alkaline phosphatase; CNS = central nervous system; NA = not applicable; NV = not available; sRBC = sheep red blood cell; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Non-date-limited literature searches were conducted in October 2017 and updated in April 2020 for studies relevant to the derivation of noncancer inhalation provisional toxicity values for *trans*-1,2-DCE (CASRN 156-60-5). The database searches for PubMed, TOXLINE (including TSCATS1), and Web of Science were conducted by an information specialist and records stored in the U.S. EPA's Health and Environmental Research Online (HERO) database. The following additional databases were searched for health-related data: 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 Health Effects Assessment Summary Tables (HEAST), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2, International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), OECD Existing Chemicals Database, OECD Screening Information Data Set (SIDS) High Production Volume Chemicals via IPCS INCHEM, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

REVIEW OF POTENTIALLY RELEVANT DATA FOR DERIVATION OF NONCANCER INHALATION REFERENCE VALUES

The primary focus of this PPRTV assessment is to evaluate the feasibility of deriving provisional inhalation reference values. As such, Table 3 provides an overview of the noncancer inhalation database for *trans*-1,2-DCE, and includes all potentially relevant acute, short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. An oral reference dose (RfD) of 0.02 mg/kg-day and a weight-of-evidence (WOE) descriptor of *"Inadequate Information to Assess Carcinogenic Potential"* is available for *trans*-1,2-DCE from the U.S. EPA's IRIS (U.S. EPA, 2010). Toxicity data for other routes (including oral exposure) are briefly summarized as supplemental information for hazard identification (see "Other Data" section for more details). Principal studies are identified in bold. The phrase "statistical significance" or the term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3. Summary of Potentially Relevant Noncancer Data for *trans*-1,2-DCE (CASRN 156-60-5)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Concentrations, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[f]
Human							
			1. Inhalation (mg/m^3)				
Acute	2 M, 5−30 min Reported concentrations: 275, 825, 950, 1,000, 1,200, 1,700, or 2,200 ppm	1,090, 3,270, 3,770, 3,960, 4,758, 6,740, 8,723	Dizziness (self-report) at 3,270 mg/m^3 after 5 min. At higher exposure concentrations, slight burning of eyes, drowsiness, "intracranial pressure," and nausea that persisted for 0.5 hr after exposure. No self-reported effects at 1,090 mg/m^3.	1,090	3,270	Lehmann and Schmidt-Kehl (1936) as cited in U.S. EPA (2008)	SS
Animal							
			1. Inhalation (mg/m^3)				
Short term	6 F, Wistar, rat, 8 hr/d, 5 d/wk, 1 or 2 wk Reported concentrations: 0 or 200 ppm	HEC_{ER} = 0, 189[c] HEC_{PU} = 0, 2,500[d]	Significant increase in capillary hyperemia and alveolar septum distension in the lung at 1 wk; incidence was elevated, but not significant, at 2 wk because the effect was also observed in 2/6 controls at that time. At 1 and 2 wk, incidences of fat accumulation in the liver lobule and in Kupffer cells were higher than controls but were not statistically significant.	NDr	189[e]	Freundt et al. (1977)	PR

Table 3. Summary of Potentially Relevant Noncancer Data for *trans*-1,2-DCE (CASRN 156-60-5)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Concentrations, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[f]**
Subchronic	6 F, Wistar, rat, 8 hr/d, 5 d/wk, 8 or 16 wk Reported concentrations: 0 or 200 ppm	HEC_{ER} = 0, 189[c] HEC_{PU} = 0, 2,500[d]	Significant increase in capillary hyperemia and alveolar septum distension in the lung at 8 and 16 wk. At 8 and 16 wk, incidences of fat accumulation in the liver lobule and in Kupffer cells were higher than controls but were not statistically significant.	NDr	189	Freundt et al. (1977)	PR
Subchronic	**15 M/15 F Crl:CD (SD) BR, rat, 6 hr/d, 5 d/wk for 90 d** **Reported concentrations: 0, 200, 1,000, or 4,000 ppm**	**HEC_{ER} = 0, 140, 710, 2,800[c]**	**Concentration-related decreases in WBC and lymphocyte counts in rats with statistically significant changes in males after 45-d (WBC and lymphocyte counts) and 90-d (WBC counts) sampling time points.**	**710**	**2,800**	**Kelly (1998)**	**PS, NPR**

Table 3. Summary of Potentially Relevant Noncancer Data for *trans*-1,2-DCE (CASRN 156-60-5)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Concentrations, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[f]
Reproductive/ Developmental	24 F, Crl:CD BR, rat, 6 hr/d, GDs 7−16 Reported concentrations: 0, 2,000, 6,000, or 12,000 ppm	HEC_{ER} = 0, 1,980, 5,950, 11,890[c]	Maternal: ocular irritation (i.e., increased lacrimation). At higher concentrations (≥5,950), periocular stain (brown), lethargy, salivation, wet perinasal hair, and mild effects on maternal body weights were also reported. Fetal: Decreased fetal body weights (4−6%) and nonsignificant increase in the incidence of hydrocephalus.	Maternal: NDr Fetal: 5,950	Maternal: 1,980 Fetal: 11,890	Hurtt et al. (1993); Haskell Laboratories (1988)	PR

[a]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% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: The units for inhalation concentrations are expressed as mg/m^3. Concentration is calculated as concentration in ppm × molecular weight of *trans*-1,2-DCE (96.9438 g/mol) ÷ 24.45 L/mol. Concentrations from animal studies are presented as HECs (in mg/m^3) for PU and ER using the equations recommended by the U.S. EPA (1994) (see Footnotes C and D).
[c]HEC_{ER} = concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air partition coefficient of 9.58 is greater than the human blood-air partition coefficient of 6.04 as indicated by Gargas et al. (1989).
[d]HEC_{PU} = concentration (mg/m^3) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{PU}$. $RGDR_{PU}$ is the pulmonary regional gas dose ratio (animal:human); see Equations 4−28 in U.S. EPA (1994) for calculation of $RGDR_{PU}$ and default values for variables.
[e]Although the study authors considered the lung lesions systemic in nature based on similar observations after i.p. and oral exposure routes, the potential contribution of airway exposure cannot be ruled out [see study summary for Freundt et al. (1977) in the "Animal Studies" section for more details]; therefore, the vapor concentration of 793 mg/m^3 was converted to HECs for both extrarespiratory (HEC_{ER}) and airway exposure pulmonary effects (HEC_{PU}). The estimated HEC_{ER} of 182 mg/m^3 was ultimately selected for all lesions because it is more health-protective.
[f]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study; SS = data from secondary source.

ER = extrarespiratory effects; F = female(s); GD = gestation day; HEC = human equivalent concentration; i.p. = intraperitoneal;
LOAEL = lowest-observed-adverse-effect level; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; RGDR = regional gas dose ratio;
PU = pulmonary effects; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; WBC = white blood cell.

HUMAN STUDIES

Inhalation Exposures

Acute Studies

Lehmann and Schmidt-Kehl (1936) as cited in U.S. EPA (2008)

In an acute exposure study, two male graduate students were exposed themselves to concentrations of *trans*-1,2-DCE vapors of 275, 825, 950, 1,000, 1,200, 1,700, or 2,200 ppm (1,090, 3,270, 3,770, 3,960, 4,758, 6,740, or 8,723 mg/m^3)[1] in a closed-room environment for 5−30 minutes. The concentrations of *trans*-1,2-DCE within the chamber were determined analytically, and the effects of exposure were self-reported. No effects were reported following 5 minutes of exposure to 1,090 mg/m^3 (see Table B-1). At higher concentrations, dizziness, burning of eyes, and drowsiness were reported. At 6,740 and 8,723 mg/m^3, symptoms included "intracranial pressure" and nausea that persisted for approximately 30 minutes after the exposure period. A no-observed-adverse-effect level (NOAEL) of 1,090 mg/m^3 and a lowest-observed-adverse-effect level (LOAEL) of 3,270 mg/m^3 are identified for clinical symptoms after acute exposure to *trans*-1,2-DCE in humans.

Short-Term, Subchronic, and Chronic Studies

No repeated inhalation exposure studies on *trans*-1,2-DCE in humans have been identified.

ANIMAL STUDIES

Inhalation Exposures

Short-Term and Subchronic Studies

Freundt et al. (1977)

In a published, peer-reviewed study, Freundt et al. (1977) evaluated toxicity in rats following short-term and subchronic-duration exposures to *trans*-1,2-DCE vapors (purity not reported). Groups of mature female SPF Wistar rats weighing 180−200 g at the start of the study were exposed to *trans*-1,2-DCE at nominal concentrations of 0 or 200 ppm (0 or 793 mg/m^3)[1] 8 hours/day, 5 days/week for 1, 2, 8, or 16 weeks (six rats/group). Exposure concentrations were monitored via gas chromatography. Monitoring of clinical signs and measurements of body weights, feed consumption, serum chemistry, and organ weights were either not reported or were not included in the study design. At the appropriate times of sacrifice, gross necropsies were performed. Lung, liver, kidney, spleen, brain, muscle (quadriceps), and sciatic nerve tissues from six rats and their concurrent controls were fixed and stained with scarlet red (a lipid stain) or hematoxylin and eosin (H & E) for histological examination. No statistical analyses on histopathology incidences were reported.

Histopathological findings included capillary hyperemia[2] and distension of the alveolar septum in the lungs of all the rats exposed to 793 mg/m^3 *trans*-1,2-DCE at each exposure duration (increases in the incidence of lung lesions were statistically significant at 1, 8, and 16 weeks) (see Table B-2). There were no lung lesions in the concurrent controls at 8 and 16 weeks; however, capillary hyperemia and distension of the alveolar septum were observed in 1/6 and 2/6 controls at 1 and 2 weeks, respectively. The lung lesions were graded as "slight

[1]Concentration in mg/m^3 is calculated as concentration in ppm × molecular weight of *trans*-1,2-DCE (96.9438 g/mol) ÷ 24.45 L/mol.

[2]Capillary hyperemia refers to the enlargement of blood vessels due to an increase in the arterial blood supply to a tissue (active hyperemia) or a decrease in blood flow out of the tissue (congestion) (Mosier, 2017).

changes" for all exposure groups. Severe pneumonic infiltration (not further characterized) was observed in the lungs of 3/6 exposed rats at both 8 and 16 weeks, but not in the controls.

These same researchers also observed pulmonary capillary hyperemia and alveolar septum distension significantly increased in rats exposed to *trans*-1,2-DCE by acute inhalation exposure and at low incidence in rats acutely administered *trans*-1,2-DCE via intraperitoneal (i.p.) injection or gavage (see Table 4 in the "Other Studies" section below).

Fatty accumulation in the liver lobules and Kupffer cells was seen at all exposure durations at higher incidence than in the corresponding control, but differences from controls were not statistically significant at any duration, either because incidence in the treated group was low or because the lesions were also seen in the matched control group (see Table B-2). In addition, the study had low power to detect statistically significant differences because of the small group sizes. Lesions were graded as either "slight" or "severe," with no middle category. At 1- and 2-week exposure durations, all liver lesions were graded as "slight changes." "Severe" lesions were only seen in Kupffer cells at 8 weeks (in both treated and control animals) and in the liver lobule in three of the five treated rats showing lesions at 16 weeks (total number of rats examined per group was six).

Low incidences of fat accumulation in the liver lobules and Kupffer cells were also observed following acute inhalation and oral exposures, and no liver lesions were seen after i.p. injection (see Table 4).

Short-term and subchronic LOAELs of 793 mg/m^3 (the only concentration evaluated) were identified based on significantly increased incidence of pulmonary capillary hyperemia and distension of the alveolar septum in female Wistar rats exposed to *trans*-1,2-DCE vapors for 8 hours/day, 5 days/week, for 1, 2, 8, or 16 weeks. Although the study authors considered the lung lesions to be systemic because similar observations were made after i.p. and oral exposure routes, a blood-air partition coefficient of 9.58 in rats suggests that inhaled *trans*-1,2-DCE is likely to penetrate the alveolar region. Therefore, the potential contribution of airway exposure cannot be ruled out, and the vapor concentration of 793 mg/m^3 (8 hours/day, 5 days/week) was converted to human equivalent concentrations for both extrarespiratory (HEC_{ER} of 189 mg/m^3)[3] and airway exposure pulmonary effects (HEC_{PU} of 2,500 mg/m^3).[4]

Kelly (1998)

The toxicity of *trans*-1,2-DCE (99.86% purity) was evaluated in groups of Crl: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

[3]HEC for extrarespiratory effects was calculated by treating *trans*-1,2-DCE as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air coefficient of 9.58 is greater than the human blood-air coefficient of 6.04, as indicated by Gargas et al. (1989).

[4]HEC for airway exposure pulmonary effects was calculated using the following equation from U.S. EPA (1994) methodology: HEC_{PU} = concentration (mg/m^3) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{PU}$. $RGDR_{PU}$ is the pulmonary regional gas dose ratio (RGDR) (animal:human); see Equations 4−28 in U.S. EPA (1994) for calculation of $RGDR_{PU}$ and default values for variables.

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).[1] 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

groups 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 NOAEL of 4,000 mg/m^3 (HEC: 710 mg/m^3) and a LOAEL of 16,000 mg/m^3 (HEC: 2,800 mg/m^3) were identified from this study based on statistically significant decreases in WBC and lymphocyte counts in male rats exposed to *trans*-1,2-DCE vapor for up to 90 days under the study conditions described. Although statistically significant changes were not observed at specific exposure levels, concentration-related decreases in WBC at 45 days and lymphocytes at 90 days also occurred in females according to trend test results. The reported concentrations of 0, 790, 4,000, and 16,000 mg/m^3 correspond to HEC_{ER} values of 0, 140, 710, and 2,800 mg/m^3, respectively (maintaining the stated two significant figures).[3]

Reproductive/Developmental Studies

Hurtt et al. (1993); Haskell Laboratories (1988)

Mated and presumed pregnant female Crl:CD BR rats (24/group) were exposed by inhalation to nominal *trans*-1,2-DCE vapor (99.64% purity) concentrations of 0, 2,000, 6,000, or 12,000 ppm (equivalent to 0, 7,930, 23,800, or 47,580 mg/m^3)[1] for 6 hours daily on Gestation Days (GDs) 7−16. Measured exposure concentrations were within 5% of nominal values throughout the study. Animals were monitored twice daily (pre-and postexposure) for clinical signs. Observations were also recorded during exposure to assess the overall state of the animals, including response to a sound stimulus, but were limited to those visible in the front half of the exposure chamber. Body weights were recorded on GDs 1, 7−17, and 22. Feed consumption was measured on alternating days from GDs 1−19 and on GD 22. At sacrifice (GD 22), dams were examined for gross pathologic changes. Liver and gravid and empty uterus weights were measured, and the numbers of live, dead, or resorbed fetuses and corpora lutea were determined. Fetal parameters recorded included fetal weights, sex, external alterations, and mean litter weights, which were calculated after omitting any fetuses considered stunted (i.e., fetuses weighing the same or less than the maximum stunted weight). Half of the fetuses in each litter, and all those appearing malformed or stunted, were examined for visceral alterations. The remaining fetuses were examined for skeletal alterations. Statistical analysis was performed by the study authors. ANOVA, Jonckheere's, or Cochran-Armitage tests were used to test for linear trends. Where appropriate, Fisher's exact, Dunnett's, or Mann-Whitney U tests were used for pairwise comparisons. For fetal effects, the litter (i.e., the proportion of affected fetuses per litter or the litter mean) was used as the unit of comparison.

No dams died prior to the scheduled sacrifice. Observations during exposure (6 hours daily) showed that *trans*-1,2-DCE had a narcotizing effect on dams at ≥23,800 mg/m^3 (incidence data were not provided). Outside of the daily exposure period, there were significant, dose-related increases in incidences of dams showing clinical signs (see Table B-6). Increased lacrimation indicative of ocular irritation was observed at all exposure levels (≥7,930 mg/m^3) with incidence rates of 54−100%. Other clinical signs included brown periocular staining and alopecia at ≥23,800 mg/m^3, and lethargy, salivation, and wet perinasal hair at 47,580 mg/m^3.

Maternal body-weight gain was significantly reduced by 33% during the exposure period in the 47,580-mg/m^3 group, relative to controls, with the biggest difference occurring on the first days of exposure (GDs 7−9; see Table B-7). Maternal body-weight gain was also significantly reduced during GDs 11−13 of the exposure period in the 23,800-mg/m^3 group. Conversely, mean maternal body weights were reduced relative to controls at the highest concentration (47,580 mg/m^3) throughout the exposure periods, but the reductions were small (4−6%) and not statistically significant. Food consumption was significantly reduced in both the 47,580- and 23,800-mg/m^3 groups during the total exposure period, and also at the 7,390-mg/m^3 group during GDs 13−15 (see Table B-8); however, decreases in food intake at the lowest exposure concentration were not accompanied by any changes in maternal weights. Further, the biological significance of the reductions in body-weight gain was unclear, given that mean body weights were mostly unchanged in the dams. Postmortem examinations found no significant effect on absolute or relative maternal liver weights in any group.

Significant increases in the mean number of early resorptions per litter were observed in dams in the 23,800- and 47,580-mg/m^3 exposure groups (see Table B-9). The study authors reported that the resorption rate in the control animals was unusually low and that the observed

responses, even in the high-exposure group, fell within the range of historical control data collected from the same laboratory during the previous 2 years (historical mean resorptions per litter were 1.0, 0.8, 1.5, 0.6, and 0.9; no further details were provided). These uncertainties combined with the lack of changes in other reproductive parameters (i.e., pregnancy rate, corpora lutea, number of fetuses per litter) evaluated in the study question the biological significance of the increased resorptions.

A statistically significant decrease in litter-adjusted mean fetal weight was seen in the 47,580-mg/m^3 group, primarily in the female fetuses (see Table B-9). Fetal weights were reduced by 6% in female fetuses and by 4% in all fetuses, compared with controls. Incidences of malformations (external, head, visceral, skeletal) in treated groups did not differ significantly from controls. A nonsignificant increase was found for incidence of hydrocephalus (accumulation of fluid within the brain), which was seen in five fetuses from four litters in the 47,580-mg/m^3 group and one fetus in the control group.

Data on variations in the published version of the study (Hurtt et al., 1993) only partially match the data from the unpublished report (Haskell Laboratories, 1988). According to the unpublished report, the incidence of fetal variations (mean percent of fetuses affected per litter) was significantly increased in all treated groups relative to controls, due to significant increases in visceral variations (primarily distended ureter and small renal papilla) in the low- and mid-exposure groups (but not in the high-exposure group) and skeletal variations (primarily rudimentary lumbar ribs) in the high-exposure group. In contrast, the published report omits the data for distended ureter and rudimentary lumbar ribs (data for "rudimentary ribs" in this report correspond to data for rudimentary cervical ribs in the unpublished report) and finds no effect on variations per litter based on a combined analysis of variations and retardations (analyzed separately in the unpublished report) using different incidence values than the unpublished report. No discussion of these data or explanation for the discrepancy is provided in the published report, so it is unclear how to interpret these results.

A maternal LOAEL of 7,930 mg/m^3 (the lowest concentrated tested) was determined for *trans*-1,2-DCE in this study based on a significant increase in ocular irritation (i.e., lacrimation) in the dams. A NOAEL could not be determined. At higher exposure concentrations (≥23,800 mg/m^3), brown periocular staining, alopecia, lethargy, salivation, wet perinasal hair, and mild effects on maternal body weight (significant reductions in body-weight gain and food consumption but not mean body weight) were reported. A fetal NOAEL of 23,800 mg/m^3 and LOAEL of 47,580 mg/m^3 were determined based on significantly reduced fetal weight. A nonsignificant increase in hydrocephalus at the 47,580-mg/m^3 concentration was also suggestive of a chemical-related effect. The nominal exposure concentrations of 7,930, 23,800, and 47,580 mg/m^3 correspond to HEC_{ER} values of 0, 1,980, 5,950, and 11,890 mg/m^3, respectively.[3]

OTHER DATA

Other relevant data for *trans*-1,2-DCE include acute inhalation studies, oral studies, and studies by other routes. The findings from these studies are briefly summarized below as supplemental information for hazard identification. More detailed descriptions of the individual studies are provided in Table 4.

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Effects in animals following acute inhalation exposure				
Acute	OF1SPF mice (number and sex unknown) were exposed to *trans*-1,2-DCE vapors for 6 hr.	Mortality. Causes of death not reported.	Mouse LC_{50} (6 hr) = 86,131 mg/m^3	Gradiski et al. (1978) as cited in U.S. EPA (2008)
Acute	Crl:CD (SD) BR rats (5 M and 5 F) were exposed to *trans*-1,2-DCE vapors for 4 hr at concentrations ranging from 12,300 to 34,100 ppm (48,770−135,200 mg/m^3).	Observed effects during exposure included prostration, decreased responsiveness, and death. Effects in survivors after exposure included lethargy, irregular respiration, weakness, and transitory weight loss.	Rat LC_{50} (4 hr) = 95,556 mg/m^3	Kelly (1999) as cited in U.S. EPA (2008)
Acute	Three mice (sex and strain unknown) were exposed to *trans*-1,2-DCE vapors for 30−155 min at 45,000−129,000 mg/m^3.	Disequilibrium and lethargy were observed at all tested concentrations. 100% mortality at ≥75,000 mg/m^3.	The low concentration of 45,000 mg/m^3 is associated with neurological effects (CNS depression).	Lehmann and Schmidt-Kehl (1936) as cited in U.S. EPA (2008)
Acute	2−3 M or F cats were exposed to *trans*-1,2-DCE vapors for 22−348 min at 72,000−189,200 mg/m^3 or for 10−390 min at 43,000−191,000 mg/m^3.	Disequilibrium and lethargy were observed at all tested concentrations; the time to effect decreased with increasing exposure concentrations. Narcosis was observed at ≥72,000 mg/m^3.	The low concentration of 43,000 mg/m^3 is associated with neurological effects (CNS depression).	Lehmann and Schmidt-Kehl (1936) as cited in U.S. EPA (2008)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Acute	Female Wistar rats (6/group) were exposed to *trans*-1,2-DCE vapors for 8 hr at concentrations of 793, 3,960, or 11,900 mg/m^3, each with a matched air-exposed control group.	Significant increases were seen in incidence of capillary hyperemia and alveolar septum distension in the lung in all treated groups relative to their matched controls. Severity of the lesion was graded as "slight" in most affected rats, but "severe" in two rats each at 3,960 and 11,900 mg/m^3 (no middle grade was used). Low incidences of fat accumulation in the liver lobule and Kupffer cells were reported in all treated groups (1 or 2/6), but also one of the matched control groups. Fibrous swelling and hyperemia of the cardiac muscle (graded as "severe") was seen in 2/6 rats at 11,900 mg/m^3. No signs of CNS depression were observed in any group.	The low concentration of 793 mg/m^3 is associated with histopathological changes in the lung.	Freundt et al. (1977)
Effects in humans following oral exposure				
Case-control study at the Marine Corps base at Camp Lejeune; children from mothers who resided at Camp Lejeune at any time during pregnancy between 1968−1985 Cases: neural tube defects (*n* = 15); oral clefts (*n* = 24); childhood cancer (*n* = 13) Controls: 526 children	Estimated monthly exposure levels of *trans*-1,2-DCE from contaminated drinking water at Camp Lejeune were based on water modeling, residential history, and family housing records. Unexposed: no residential exposure Low: >0 to <5 ppb High: ≥5 ppb Exposed: had residential exposure Other contaminants in drinking water included perchloroethylene, trichloroethylene, vinyl chloride, and benzene.	ORs (95% CI) Exposed Neural tube defects: 1.1 (0.4−3.1) Oral clefts: 0.5 (0.2−1.3) Childhood cancers: 1.5 (0.5−4.7) Similar results were observed with adjustments for other potential risk factors or when comparisons were made between high and unexposed categories.	No associations were found between *trans*-1,2-DCE exposure in utero or during early childhood and cases of neural tube defects, oral clefts, or childhood cancers.	Ruckart et al. (2013)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Case-control study at the Marine Corps base at Camp Lejeune; males born prior to 1969 and diagnosed with cancer between 1995−2013 Male breast cancer cases at VA hospital: *n* = 71 Facility controls (patients with cancer not known to be associated with solvent exposure): *n* = 373	Estimated cumulative and monthly exposure levels to *trans*-1,2-DCE from contaminated drinking water at Camp Lejeune: Cumulative low: >0 to <472 ppb Cumulative high: ≥472 ppb Monthly low: >0 to <94 ppb Monthly high: ≥94 ppb Other contaminants in drinking water included perchloroethylene, trichloroethylene, vinyl chloride, and benzene.	Adjusted ORs (95% CI) for association between *trans*-1,2-DCE and breast cancer. Cumulative Low: 0.56 (0.02−3.83) High: 1.50 (0.30−6.11) Adjusted hazard ratio (95% CI) for age at onset of breast cancer by exposure level. Cumulative Low: 0.64 (0.06−7.01) High: 2.72 (0.52−14.18)	Suggestive evidence of a possible association between exposure to *trans*-1,2-DCE and early age at onset of male breast cancer. Study was limited to a small number of participants in the cumulative high-exposure group (*n* = 3), which resulted in a large CI. Similar results for perchloroethylene and vinyl chloride.	Ruckart et al. (2015)
Effects in animals following oral exposure				
Acute	Female Wistar rats (10/dose) were treated by gavage with single doses of 0.5, 0.75, 0.9, 1.0, 1.1, or 1.25 mL/kg *trans*-1,2-DCE in olive oil.	Deaths recorded at ≥0.75 mL/kg. Clinical symptoms were not reported. Two rats in each of the 0.9, 1.0, and 1.1 mL/kg groups showed capillary hyperemia and alveolar septal distension in the lung and fibrous swelling and hyperemia in cardiac muscle (all changes graded as "severe"). Two rats in the 0.9 mL/kg group showed "severe" fatty infiltration of the liver lobules and Kupffer cells.	Rat LD_{50}: 1.0 (0.9−1.1) mL/kg [equivalent to 1,256 mg/kg][b]	Freundt et al. (1977)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Acute	Male and female S-D CD rats (10/sex/group) received single oral doses of *trans*-1,2-DCE by gavage in corn oil.	Deaths occurred within 30 hr after dosing. CNS depression, ataxia, and depressed respiration were observed at all doses; the severity was dose dependent. No compound-related gross pathological findings were observed.	Rat male LD_{50}: 7,902 (6,805−9,175) mg/kg Rat female LD_{50}: 9,939 (6,494−15,213) mg/kg	Hayes et al. (1987)
Acute	Male and female CD-1 mice received single oral doses of *trans*-1,2-DCE by gavage in emulphor.	Deaths occurred over a 10-d period following administration. Dead animals had hyperemia of mucosal surfaces of the stomach and small intestines. Decreased activity, ruffled fur, ataxia, loss of righting reflex, hunchbacked appearance, and death were noted at ≥1,600 mg/kg; the severity was dose dependent.	Mouse male LD_{50}: 2,122 (1,874−2,382) mg/kg Mouse female LD_{50}: 2,391 (2,055−2,788) mg/kg	Barnes et al. (1985)
Short term	Male mice (9−10/group) were dosed daily with 0, 21, or 210 mg/kg *trans*-1,2-DCE for 14 d by gavage in emulphor. Endpoints evaluated included body weights, select organ weights, hematology and serum chemistry analysis, and functional immunological assessments (e.g., immune responses to sRBCs, and delayed hypersensitivity responses).	No notable exposure-related changes in any of the endpoints evaluated.	No evidence of systemic or immune effects at doses up to 210 mg/kg-d.	Barnes et al. (1985); Shopp et al. (1985); Munson et al. (1982)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Subchronic	Groups of S-D CD rats (20/sex/dose) were administered *trans*-1,2-DCE in 1% emulphor in drinking water at 0, 402, 1,314, or 3,114 mg/kg-d (males) or 0, 353, 1,257, or 2,809 mg/kg-d (females) for 90 d. Endpoints evaluated included body weights, hematology and serum chemistry analysis, urinalysis, select organ weights, and histopathology.	Statistically significant increases in absolute kidney weight (13−15%) and kidney:brain weight ratio (11%), and nonsignificant increase in kidney:body weight ratio (10−11%), in females at 1,257 and 2,809 mg/kg-d. No significant effect on kidney weight in males, and no corresponding pathological or clinical chemistry changes. No notable exposure-related changes in any of the other endpoints evaluated.	Limited evidence for an effect on kidneys in females at ≥1,257 mg/kg-d.	Hayes et al. (1987)
Subchronic	Groups of CD-1 mice (15−23/sex/dose) were administered *trans*-1,2-DCE in 1% emulphor in drinking water for 90 d at doses of 0, 17, 175, or 387 mg/kg-d (males) or 0, 23, 224, or 452 mg/kg-d (females). Endpoints evaluated included body weights, gross pathology, organ weights, hematology, serum and liver chemistry, histopathology, and functional immunological assessments (e.g., immune responses to sRBCs, and delayed hypersensitivity responses).	Absolute and/or relative thymus weights significantly decreased in females at ≥224 mg/kg-d. No significant effect on thymus weight in males, and no corresponding pathological or clinical chemistry changes. Significant decrease in sRBC-responsive cells in males at ≥175 mg/kg-d. No corresponding effect in females. No notable exposure-related changes in any of the other endpoints evaluated.	Limited evidence for an effect on the thymus in females at ≥224 mg/kg-d and humoral immune response in males at ≥175 mg/kg-d.	Barnes et al. (1985); Shopp et al. (1985)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity				
Test[a]	**Materials and Methods**	**Results**	**Conclusions**	**References**
Subchronic	Groups of F344/N rats (10/sex/dose) were administered *trans*-1,2-DCE by microcapsule in feed at average daily doses of 0, 190, 380, 770, 1,540, or 3,210 mg/kg-d (males) or 0, 190, 395, 780, 1,580, or 3,245 mg/kg-d (females) for 14 wk. Endpoints evaluated included: clinical signs, FOB neurological tests (on Wk 4 and 13), body weights, hematology and biochemistry parameters, organ weights, and gross and microscopic examinations.	Absolute and relative liver weights significantly increased in females at ≥395 mg/kg-d, although magnitude did not increase with dose. No effect on liver weight in males, and no corresponding pathological or clinical chemistry changes. No notable exposure-related changes in any of the other endpoints evaluated.	Limited evidence for an effect on the liver in females at ≥395 mg/kg-d.	NTP (2002)
Subchronic	Groups of B6C3F1 (10/sex/dose) mice were administered *trans*-1,2-DCE by microcapsule in feed at average daily doses of 0, 480, 920, 1,900, 3,850, or 8,065 mg/kg-d (males) or 0, 450, 915, 1,830, 3,760, or 7,925 mg/kg-d (females) for 14 wk. Endpoints evaluated included: clinical signs, FOB neurological tests (on Wk 4 and 13), body weights, hematology and biochemistry parameters, organ weights, and gross and microscopic examinations.	Relative liver weight significantly increased in males at ≥1,900 mg/kg-d and in females at ≥3,760 mg/kg-d, although the magnitude did not necessarily increase with dose. No effect on absolute liver weights, and no corresponding pathological or clinical chemistry changes. No notable exposure-related changes in any of the other endpoints evaluated.	Limited evidence for an effect on liver in males at ≥1,900 mg/kg-d and females at ≥3,760 mg/kg-d.	NTP (2002)
Effects in animals following i.p. exposure				
Acute	Female Wistar rats (10/dose) were administered *trans*-1,2-DCE i.p. at doses ranging from 4.0−10.0 mL/kg.	Deaths occurred at all doses. Clinical symptoms were not reported. One rat in the 6.0 mL/kg group and two rats in the 10.0 mL/kg group showed capillary hyperemia and alveolar septal distension in the lung and fibrous swelling and hyperemia in cardiac muscle (all changes graded as “severe”).	Rat i.p. LD_{50}: 6.0 (5.1−7.1) mL/kg [equivalent to 7,680 mg/kg]	Freundt et al. (1977)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Acute	Female NMRI mice (10/dose) were administered *trans*-1,2-DCE i.p. at doses ranging from 2.0−8.0 mL/kg.	Deaths occurred at all doses. Symptoms following injection included motor excitement, convulsions, narcosis, compulsory walking during narcosis, and increased respiratory rate. Gross pathology observations included hyperemia of the liver, kidneys, urinary bladder, and intestines; intestinal hemorrhage; and hematuria.	Mouse i.p. LD_{50}: 3.2 (2.8−3.7) mL/kg [equivalent to 4,096 mg/kg]	Freundt et al. (1977)
Effects in animals following dermal/ocular exposure				
Acute (dermal lethality study)	NZW rabbits (2 M and 3 F) received a single dose of 13 mL (5,000 mg/kg) *trans*-1,2-DCE applied neat to clipped, intact skin for 24 hr under occlusion and were observed for 14 d.	No rabbits died during the study. Three of the rabbits lost weight after dosing. The only clinical signs were skin reactions at the application site. Dermal irritation progressed from mild erythema and edema at 24 hr to severe erythema and edema with necrosis and fissuring of the skin at 7 d.	Rabbit dermal LD_{50}: >5,000 mg/kg	DuPont (1988a)
Acute (dermal irritation study)	NZW rabbits (5 M and 1 F) received a single dose of 0.5 mL *trans*-1,2-DCE applied neat to clipped, intact skin for 24 hr under occlusion and were observed for 72 hr.	No to moderate erythema was observed 24, 48, and 72 hr after application. No edema was observed throughout the study.	*trans*-1,2-DCE was a moderate skin irritant under the conditions of this study.	DuPont (1988c)

Table 4. Other Studies on *trans*-1,2-DCE Toxicity

Test[a]	Materials and Methods	Results	Conclusions	References
Acute (ocular irritation study)	NZW rabbits (2 F) received a single dose of 0.01 mL *trans*-1,2-DCE applied neat to the right eye (left eyes acted as controls). The eyes of one rabbit were washed with water 20 sec after application; the other rabbit's eyes remained unwashed. The rabbits were observed for 3 d.	Both treated eyes exhibited moderate iritis, conjunctival redness, copious blood-tinged discharge, and chemosis. The effects were more severe in the washed eye, which also showed severe corneal opacity and moderate to severe microscopic corneal injury. Recovery in both eyes occurred within 3 d.	*trans*-1,2-DCE was a severe eye irritant under the conditions of this study.	DuPont (1988b)

[a]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% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dose in mg/kg is calculated as dose in mL/kg × density of *trans*-1,2-DCE (1,256 mg/mL).

CI = confidence interval; CNS = central nervous system; F = female(s); FOB = functional observation battery; i.p. = intraperitoneal; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); NZW = New Zealand White; OR = odds ratio; S-D = Sprague-Dawley; sRBC = sheep red blood cell; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; VA = Veterans Affairs.

Inhalation Toxicity Studies

Acute Animal Studies

Acute lethality studies reported median lethal concentration (LC_{50}) values of 95,556 mg/m^3 in rats after 4 hours of exposure and 86,131 mg/m^3 in mice after 6 hours of exposure to *trans*-1,2-DCE vapor [Kelly (1999) and Gradiski et al. (1978) as cited in U.S. EPA (2008)]. Effects indicative of central nervous system (CNS) depression were reported in the rat study, including prostration and decreased responsiveness during exposure and lethargy, irregular respiration, and weakness in survivors after exposure [Kelly (1999) as cited in U.S. EPA (2008)]. Disequilibrium and lethargy were observed in mice and cats at *trans*-1,2-DCE vapor concentrations around 43,000 mg/m^3, with narcosis and death first occurring at around 72,000 mg/m^3 [Lehmann and Schmidt-Kehl (1936) as cited in U.S. EPA (2008)].

No signs of CNS depression were seen in rats exposed to *trans*-1,2-DCE vapor concentrations up to 11,900 mg/m^3 for 8 hours (Freundt et al., 1977). Histological findings in this study were similar to those observed by the same researchers in short- and long-term experiments described above: significantly increased capillary hyperemia and alveolar septum distension in the lung at ≥793 mg/m^3 (graded as "slight" in most animals, but "severe" in two rats, each at 3,960 and 11,900 mg/m^3) and low incidence of fat accumulation in the liver lobule and Kupffer cells in all treated groups (but also one of the matched air-exposed control groups). An additional finding in the acute study was fibrous swelling and hyperemia of cardiac muscle in 2/6 rats at 11,900 mg/m^3. All of these lesions were also seen at low incidence in acute oral and i.p. injection studies by these same researchers, described in more detail below and in Table 4.

Oral Toxicity Studies

Human Studies

Residents living at specific sites within the Marine Corp base at Camp Lejeune from the 1968 through 1985 were exposed to contaminated drinking water containing TCE (1,400 ppb highest level detected) and the TCE degradation products, vinyl chloride and *trans*-1,2-DCE (407 ppb highest level tested) (Ruckart et al., 2013; Sonnenfeld, 1998). Ruckart et al. (2013) found no associations between residents with high monthly exposures to *trans*-1,2-DCE (≥5 ppb) in utero and early childhood and developmental effects, including oral clefts and neural tube defects, or with presence of childhood cancers. A follow-up study (Ruckart et al., 2015) found suggestive evidence of a potential association between early age onset of male breast cancer and estimated high cumulative (≥472 ppb) exposure to *trans*-1,2-DCE. The study reported similar results for other contaminants (i.e., perchloroethylene and vinyl chloride), but the study was limited by the small number of participants in the high-exposure group (n = 3).

Animal Studies

Due to the limited data available on *trans*-1,2-DCE inhalation toxicity, evidence from oral animal studies was considered as supplementary data for the inhalation assessment. Oral exposure studies include acute oral lethality studies in rats and mice (Hayes et al., 1987; Barnes et al., 1985; Freundt et al., 1977), a short-term range-finding study in mice (Barnes et al., 1985; Shopp et al., 1985; Munson et al., 1982), and four subchronic toxicity studies (two each in rats and mice) (NTP, 2002; Hayes et al., 1987; Barnes et al., 1985; Shopp et al., 1985) (see Table 4).

Short-Term Studies

A 14-day range-finding study in mice found no notable exposure-related systemic or immune effects at doses up to 210 mg/kg-day (Barnes et al., 1985; Shopp et al., 1985; Munson et

al., 1982). In addition to a standard array of systemic endpoints, the study included investigation of functional immune humoral and cell-mediated responses.

Subchronic Studies

Subchronic studies performed by the administration of *trans*-1,2-DCE in 1% emulphor in drinking water for 90 days found evidence of potential treatment-related effects, including significantly increased kidney weight in rats and decreased thymus weight in mice (both changes in females only, with no corroborating changes in pathology or clinical chemistry endpoints) (Hayes et al., 1987; Barnes et al., 1985; Shopp et al., 1985). The mouse study also included an assessment of immune function and showed a statistically significant decrease (26%) in the number of Immunoglobulin M (IgM) antibody-forming cells (AFC) in the spleen after challenge with sheep red blood cells (sRBC) in males at ≥175 mg/kg day (Shopp et al., 1985). Subchronic studies featuring exposure to *trans*-1,2-DCE by microcapsules in the feed for 14 weeks in mice and rats showed significant increases in liver weight (female rats at ≥395 mg/kg-day and in male and female mice at ≥1,900 mg/kg-day), but these increases were not accompanied by related pathological or clinical chemistry changes (NTP, 2002). The IRIS assessment on *trans*-1,2-DCE considered the decreased AFCs in male mice as biologically significant and indicative of a functional suppression of the humoral immune system, establishing an RfD based on this effect (U.S. EPA, 2010).

Acute Studies

Acute oral LD_{50} values for *trans*-1,2-DCE were 1,256 mg/kg in female Wistar rats treated by gavage in olive oil (Freundt et al., 1977), 7,902 and 9,939 mg/kg, respectively, in male and female Sprague-Dawley (S-D) rats treated by gavage in corn oil (Hayes et al., 1987), and 2,122 and 2,391 mg/kg, respectively, in male and female CD-1 mice treated by gavage in emulphor (Barnes et al., 1985). Signs of CNS depression were associated with animal deaths, including decreased activity, ataxia, depressed respiration, and loss of righting reflex (Hayes et al., 1987; Barnes et al., 1985). In female Wistar rats, Freundt et al. (1977) reported low incidences in treated groups of capillary hyperemia and alveolar septal distension in the lung, fatty infiltration of the liver lobules and Kupffer cells, and fibrous swelling and hyperemia in cardiac muscle, the same lesions seen in inhalation studies by these researchers.

Other Route Toxicity Studies

Intraperitoneal Injection

LD_{50} values from injection studies were 7,680 mg/kg in rats and 4,096 mg/kg in mice (Freundt et al., 1977). After injection, the mice exhibited clinical signs indicative of neurological effects, including motor excitement, convulsions, narcosis, and increased respiratory rate. Clinical signs were not reported for rats. As in the oral lethality study, treated rats showed low incidence of capillary hyperemia and alveolar septal distension in the lung and fibrous swelling and hyperemia in cardiac muscle, lesions also seen in inhalation studies performed by these researchers. Mice showed a different set of lesions, including hyperemia in the liver, kidney, urinary bladder, and intestine, as well as intestinal hemorrhage and hematuria.

Dermal Exposure

trans-1,2-DCE was only moderately irritating to the skin in a dermal irritation study in rabbits conducted using an undiluted dose of 0.5 mL (DuPont, 1988c), but produced severe erythema and edema with necrosis and fissuring of the skin after 7 days in a dermal toxicity

study conducted using a much larger undiluted dose of 13 mL (5,000 mg/kg) (DuPont, 1988a). Still, no animals died in this study, indicating that the dermal LD_{50} was >5,000 mg/kg.

Ocular Exposure

trans-1,2-DCE was found to be a severe eye irritant in an ocular irritation study in rabbits conducted using an undiluted dose of 0.01 mL (DuPont, 1988b). Effects included corneal injury.

Absorption, Distribution, Metabolism, and Excretion Studies

Absorption

Experimental data show inhaled *trans*-1,2-DCE to be well absorbed through the lungs, a result that is consistent with the blood-air partition coefficients estimated in humans and rats for this chemical [6.08 and 9.58, respectively; Gargas et al. (1989)]. Approximately 72−75% of inhaled *trans*-1,2-DCE is estimated to be absorbed into the lungs in humans [Lehmann and Schmidt-Kehl (1936) as cited in ATSDR (1996)]. Closed-chamber gas uptake studies in rats have shown rapid absorption of *trans*-1,2-DCE over the first 1.5−2 hours of exposure, followed by leveling off as a steady state is approached, with approximately 50% of the gas remaining in the chamber at the end of the first phase of absorption (Andersen et al., 1980; Filser and Bolt, 1979). A second phase of absorption followed, showing proportional first-order decline in chamber levels of *trans*-1,2-DCE at low concentrations (20−30 ppm) and slower, constant (zero-order) decline at higher concentrations (1,000−10,000 ppm), suggesting saturation of *trans*-1,2-DCE metabolism at the higher concentrations. No studies quantifying the rate or extent of *trans*-1,2-DCE uptake following oral or dermal exposure were located.

Distribution

No studies have been identified that investigated the tissue distribution of *trans*-1,2-DCE in the body. Tissue-air partition coefficients determined for rats in vitro were 8.96 for liver, 3.52 for muscle, and 148 for fat (Gargas et al., 1988), suggesting that *trans*-1,2-DCE in the blood will be distributed to the liver and will accumulate preferentially in fat.

Metabolism

Studies both in vitro and in vivo indicate that metabolism of *trans*-1,2-DCE is initiated upon the binding of *trans*-1,2-DCE to the active site of hepatic microsomal cytochrome P450s (CYP450s) (Costa and Ivanetich, 1982). Upon activation, presumably by CYP2E1 (in hepatic tissue), *trans*-1,2-DCE is metabolized to an unstable epoxide intermediate that rearranges to form 2,2-dichloracetaldehyde, which is enzymatically converted to dichloroacetic acid (DCA) and 2,2-dichloroethanol acid by alcohol dehydrogenase (Nakajima, 1997; Costa and Ivanetich, 1984; Bonse et al., 1975). DCA appears to be the primary metabolite, with only trace amounts of 2,2-dichloroethanol and 2,2-dichloracetaldehyde formed (Costa and Ivanetich, 1984). The rate and total amount of *trans*-1,2-DCE metabolites produced appear to be slower and less than the *cis*- isomer. Although CYP2E1 is likely the primary CYP450 responsible for *trans*-1,2-DCE metabolism, other CYP450s may also be involved. In vitro inhibition studies by Costa and Ivanetich (1982) indicated that metyrapone, a specific inhibitor of CYP3A4, was able to suppress *trans*-1,2-DCE metabolism, while phenobarbital, an inducer of CYPs, including CYP34A, increased *trans*-1,2-DCE metabolism. Studies indicate that both *cis*- and *trans*-1,2-DCE (or their metabolites) are capable of suicide inhibition, with *trans*-1,2-DCE 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; Freundt and Macholz, 1978, 1972). The turnover velocity (V_{max}) of *trans*-1,2-DCE was determined to be

2.4 mg/hour-kg by Filser and Bolt (1979), 3.4 mg/hour-kg by Andersen et al. (1980), and 3 mg/hour-kg by Gargas et al. (1988). In a later study, Gargas et al. (1990) compensated for enzyme inhibition and resynthesis and determined the V_{max} value to be 2.49 mg/hour-kg.

Excretion

Data on excretion of *trans*-1,2-DCE are limited. The metabolite DCA is ultimately broken down into carbon dioxide or further metabolized by oxidative dichlorination to produce glyoxylate (Costa and Ivanetich, 1984, 1982). Glyoxylate can further undergo oxidation to oxylate, which is either excreted in urine or reduced to glycolic acid, followed by transamination to glycine with subsequent formyl group transfer to form serine [see the IRIS *Toxicological Review for Dichloroacetic Acid* (U.S. EPA, 2003)]. Trace amounts of dichloroethanol are expected to be ultimately exhaled.

Physiologically Based Pharmacokinetic Models

Pharmacokinetic modeling of *trans*-1,2-DCE has been performed in several studies (Lilly et al., 1998; Barton et al., 1995; Gargas et al., 1990; Andersen et al., 1980; Filser and Bolt, 1979). A four-compartment physiologically based pharmacokinetic (PBPK) model (fat, slowly and rapidly perfused tissues, and liver) linked by the arterial blood supply with the chemical entering the pulmonary circulation via the lungs, developed by Lilly et al. (1998), was the first model to quantitatively describe the mechanisms of both suicide inhibition of CYP2E1 along with its resynthesis. The model, based on a model for styrene (Ramsey and Andersen, 1984), was created using kinetic constants from Gargas et al. (1988) and partition coefficients from Gargas et al. (1989). This model approximates experimentally obtained animal data, but because of the lack of human data on CYP2E1 inhibition and/or resynthesis, neither validation nor calibration of the model for allometric scaling to humans is possible without introducing considerable uncertainty (Lilly et al., 1998). More recently, Peyret and Krishnan (2012) attempted to develop quantitative property-property relationship (QPPR) models from available animal data to estimate intrinsic clearance of 26 different volatile organic compounds (VOCs), including *trans*-1,2-DCE, for future incorporation into human PBPK models and simulation of blood concentration profiles associated with inhalation exposures. The results of their experiments indicate medium confidence in using the *trans*-1,2-DCE QPPR in a human inhalation PBPK model to evaluate areas under the curve (AUCs) (Peyret and Krishnan, 2012).

Mode-of-Action/Mechanistic Studies

Studies in vivo and in vitro indicate that *trans*-1,2-DCE suppresses select liver and lung CYP450s by binding to the heme moiety of CYP450. This leads to both suicide inhibition of *trans*-1,2-DCE metabolism and the metabolic inhibition of xenobiotics and other mixed function oxidase substrates (U.S. EPA, 2008; Nakahama et al., 2000; Hanioka et al., 1998; Mathews et al., 1998; Barton et al., 1995; Freundt and Macholz, 1978, 1972). The development of this hypothesis followed observations of significant increases in hexobarbital sleeping time and zoxazolamine paralysis times in rats exposed to *trans*-1,2-DCE vapors, in which *trans*-1,2-DCE was thought to be interfering with the oxidative metabolism of hexobarbital and zoxazolamine (Freundt and Macholz, 1978). Further experimentation led the study authors to conclude that *trans*-1,2-DCE was competing for the Type 1 binding site of CYP450. In a later study, Barton et al. (1995) showed that pre-exposure of rats to 40 ppm *trans*-1,2-DCE for 1.5 hours resulted in marked inhibition of TCE and vinyl chloride metabolism by competitive inhibition.

Numerous studies have been done to identify the specific CYP450s inhibited by *trans*-1,2-DCE, based on altered protein levels or activity. It seems that the effects on CYP450s are likely dependent upon exposure route and may also be strain specific and tissue dependent. For example, in hepatic microsomes extracted from Wistar rats injected with 500 mg/kg of *trans*-1,2-DCE, CYP3A was suppressed but not CYP2E1 (Nakahama et al., 2000). A similar study in Wistar rats also found no differences in CYP2E1 protein levels in liver microsomes after injection of ~727 mg/kg for 4 consecutive days (Hanioka et al., 1998). In male F344 rats, however, injection of 100 mg/kg of *trans*-1,2-DCE resulted in marked inhibition of hepatic CYP2E1, with no effect on CYP3A (Mathews et al., 1998). At least three other studies indicate hepatic CYP2E1 as a major target of *trans*-1,2-DCE inhibition in F344 and S-D rats following in vivo exposures to *trans*-1,2-DCE vapors (Lilly et al., 1998; Barton et al., 1995).

Organ specificities have also been observed. When comparing the effects on CYP450s from liver and lung microsomes from rats injected i.p. with 500 mg/kg *trans*-1,2-DCE, CYP2B and CYP2E1 were suppressed in the lung, but not in the liver (Nakahama et al., 2000). In the same study, ethoxyresorufin *O*-deethylase (EROD) and erythromycin *N*-demethylase significantly decreased in liver microsomes; in lung, specific decreases in pentoxyresorufin *O*-dealkylase (PROD) were observed (Nakahama et al., 2000). In mice, however, PROD significantly increased in liver microsomes at i.p. doses ≥213 mg/kg, indicating CYP2B1 induction (Paolini et al., 1994; Paolini et al., 1992).

Hanioka et al. (1998) evaluated CYP450 protein content as well as CYP450-dependent monooxygenase activities in liver microsomes from both male and female Wistar rats injected with ~727 mg/kg *trans*-1,2-DCE consecutively for 4 days, identifying possible sex differences. In males, the protein content of the male-specific CYP2C11/6 was significantly reduced. Decreases in testosterone 2α-hydroxylase (T2AH) activity (37% decreased) and increases in EROD and 7-methoxyresorufin *O*-demethylase (MROD) activities were also observed in males only.

Other in vivo studies in rats have evaluated the effects of *trans*-1,2-DCE on liver or lung enzyme activities. Treatment with *trans*-1,2-DCE had no significant effects on the activities of liver alcohol dehydrogenase or mitochondrial or microsomal aldehyde dehydrogenases 5 hours following dosing with *trans*-1,2-DCE (100 mg/kg i.p.) (Mathews et al., 1998); no significant effects on liver glucose-6-phosphatase, ALP, or tyrosine transaminase in Holtzman rats following gavage administration of 400 or 1,500 mg/kg *trans*-1,2-DCE (Jenkins et al., 1972); and no significant increases in hepatic lipid hydroperoxides in male F344 rats after an i.p. dose of 100 mg/kg (Mathews et al., 1997). In mice, *p*-nitrophenol hydroxylase activities increased after injection of 1,089 mg/kg *trans*-1,2-DCE (Paolini et al., 1992), and in a 90-day oral toxicity study, alanine hydroxylase activity was decreased in female mice at all doses tested (23, 224, and 452 mg/kg-day) (Barnes et al., 1985).

DERIVATION OF PROVISIONAL VALUES

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The database of potentially relevant studies for deriving provisional reference values for *trans*-1,2-DCE is limited. No repeated-exposure inhalation studies on *trans*-1,2-DCE in humans have been identified. Available animal inhalation studies include a subchronic study in rats exposed for up to 16 weeks (Freundt et al., 1977), an unpublished non-peer-reviewed 90-day study conducted by DuPont (Kelly, 1998), and a published peer-reviewed developmental toxicity study in rats (Hurtt et al., 1993; Haskell Laboratories, 1988). No chronic inhalation studies have been identified.

Freundt et al. (1977) observed increased incidences of lung and liver lesions (pulmonary capillary hyperemia and distension of the alveolar septum and fatty accumulation in liver lobules and Kupffer cells) at 793 mg/m^3 in rats exposed for up to 16 weeks. The lung lesions were similarly observed after i.p. and oral exposures, suggesting that the effects may be systemic. However, the precise mechanism of *trans*-1,2-DCE-induced lung lesions is unknown and a potential effect due to airway exposure could not be ruled out. Therefore, HECs were estimated for both extrarespiratory and airway exposure pulmonary effects (HEC_{ER} of 189 mg/m^3 and HEC_{PU} of 2,500 mg/m^3, respectively). The estimated HEC_{ER} of 189 mg/m^3 was ultimately selected for all lesions because it is more sensitive. Furthermore, Freundt et al. (1977) had several important limitations. These included the use of a single exposure concentration, which precludes evaluation of exposure concentration-response relationships, small sample sizes (six rats/group) that provide low statistical power to detect effects, testing of a single sex, and a study design that did not include evaluating other relevant endpoints (e.g., organ-weight data or clinical chemistry evaluations). Additionally, there is uncertainty in the lung and liver lesions reported by Freundt et al. (1977) given that no histopathological changes in the lung or the liver or any other supportive evidence of liver or respiratory toxicity were observed in rats from the 90-day inhalation study by Kelly (1998) at higher exposure concentrations (790−16,000 mg/m^3). Note that the Freundt et al. (1977) and the Kelly (1998) studies used different staining methodologies for histopathology. Thus, it is not possible to determine whether such differences could have contributed to the discrepancies in the histopathological findings, particularly with respect to the liver lesions [Freundt et al. (1977) used both H & E and a lipid stain (scarlet red) and observed fat accumulation in the liver, while Kelly (1998) used only H & E staining and reported no effects]. Overall, the Freundt et al. (1977) study was considered to be inadequate for deriving a provisional reference concentration (p-RfC) because of the outstanding deficiencies in study design and methodology outlined previously.

Decreases in WBC and lymphocyte counts were reported in rats with statistically significant changes occurring only in males (decreased WBC and lymphocytes at 45 days and decreased WBC at 90 days) at the highest exposure concentration (16,000 mg/m^3 or an HEC_{ER} of 2,800 mg/m^3) (Kelly, 1998). Furthermore, trend test results were generally statistically significant supporting concentration-related decreases in WBC and lymphocyte counts in both males and females (see Table B-3). When considering that alterations in circulating WBC and lymphocytes showed consistency in the directionality and magnitude of effects across sexes and sampling time points, the results suggest potential treatment-related effects on the immune system. Histopathological evaluations of immune system organs (thymus, bone marrow, and spleen) did not provide corroborative evidence of immunotoxicity, but more direct measures of

immune function were not included in the study (Kelly, 1998). The immune system is a sensitive target for *trans*-1,2-DCE via the oral route, and suppression of humoral immunity in mice (i.e., decreased AFC in response to sRBC challenge; see summary of Oral Toxicity Studies for further details) was used to derive an oral RfD for this chemical (U.S. EPA, 2010). The supportive evidence of humoral immunosuppression in mice after oral administration increases confidence in the observed immune-related hematological response from the Kelly (1998) study.

The developmental study (Hurtt et al., 1993; Haskell Laboratories, 1988) reported increased ocular irritation (i.e., lacrimation) in dams at ≥7,930 mg/m^3 (HEC_{ER}: 1,980 mg/m^3) and other clinical signs (brown periocular staining, lethargy, and salivation) and mild effects on maternal body weights (significant reductions in body-weight gain and food consumption but not mean body weights) occurred at ≥23,800 mg/m^3 (HEC_{ER}: ≥5,950 mg/m^3). Fetal effects, including significant reductions in body weight and nonsignificant increases in the incidence of hydrocephalus, were observed at the highest concentration (47,580 mg/m^3 [HEC_{ER}: 11,890 mg/m^3]). However, confounding effects with overt maternal toxicity and the lack of significant findings for other developmental endpoints evaluated in the study by Hurtt et al. (1993) and Haskell Laboratories (1988) (i.e., external, visceral, and skeletal malformations) suggest that *trans*-1,2-DCE is not a potent developmental toxicant. Similarly, evidence from reproductive/developmental studies in mice and rats exposed to a mixture of *cis*- and *trans*-1,2-DCE following oral administration demonstrated a lack of developmental toxicity, with maternal toxicity occurring only at high doses (≥5,778 mg/kg-day) (NTP, 1991a, b).

In summary, the inhalation toxicity database for *trans*-1,2-DCE in experimental animals showed alterations in WBC and lymphocyte counts in rats after a 90-day exposure reflective of potential immune-related effects (Kelly, 1998) and clinical signs of maternal toxicity related to the irritant effects of this compound from a developmental rat study with gestational exposure (GDs 7−16) (Hurtt et al., 1993; Haskell Laboratories, 1988). The studies by Kelly (1998) and Hurtt et al. (1993)/Haskell Laboratories (1988) were adequate for dose-response analysis because they included multiple concentrations, evaluated relevant endpoints, and identified sensitive effects at similar concentrations (HEC_{ER} of 2,800 mg/m^3 for Kelly (1998) and HEC_{ER}: 1,980 mg/m^3 for Hurtt et al. (1993) and Haskell Laboratories (1988); therefore, these studies were considered further for benchmark concentration (BMC) modeling for potential derivation of p-RfC values.

Derivation of a Subchronic and Chronic Provisional Reference Concentration

To provide a basis for comparing potential points of departure (PODs) and critical effects for deriving p-RfCs for *trans*-1,2-DCE, data sets for the most sensitive endpoints from the subchronic rat study by Kelly (1998) and the developmental rat study by Hurtt et al. (1993) and Haskell Laboratories (1988) were evaluated via Benchmark Dose Software (BMDS, Version 3.1). Based on consistencies in the directionality and magnitude of the responses, the decreases in WBC and lymphocytes in both males and females from the Kelly (1998) study were modeled via BMDS and results from the longer sampling time point were preferred (90 days). The increased lacrimation in dams from the Hurtt et al. (1993) and Haskell Laboratories (1988) study was significant at all exposure levels but responses were high even at the lowest exposure group (54% at HEC_{ER}: 1,980 mg/m^3). Based on the limited information in this data set to inform the model fit at the low-dose region, BMDS modeling was not attempted and the corresponding LOAEL of 1,980 mg/m^3 was selected as a candidate POD for this endpoint. Increased brown periocular staining and alopecia in dams showed a concentration-response gradient and,

therefore, were considered amenable for BMDS modeling (Hurtt et al., 1993; Haskell Laboratories, 1988). Other clinical signs in maternal animals (lethargy, salivation, and wet perinasal hair) occurred mostly in the high-dose group and were not modeled via BMDS. The developmental effects (reduced fetal body weight and hydrocephalus) in the Hurtt et al. (1993) and Haskell Laboratories (1988) study were excluded from potential POD derivation because they were only observed at the highest concentration tested (HEC_{ER}: 11,890 mg/m^3) and the interpretation of the results is confounded by the overt maternal toxicity reported at lower exposure concentrations ($HEC_{ER} \geq$ 1,980 mg/m^3) and the lack of additional supportive evidence of developmental toxicity.

All available continuous and dichotomous-variable models in the BMDS were fit to the data sets (see Table C-1) from the studies by Kelly (1998), Hurtt et al. (1993) and Haskell Laboratories (1988). Appendix C contains details of the modeling results for these data sets. The HEC, in mg/m^3, was used as the dose metric. The benchmark response (BMR) for the alterations in WBC and lymphocyte counts was 1 standard deviation (SD) change from control means because no information is available regarding the change in response that would be considered biologically significant. Incidence data for periocular staining and alopecia were modeled using a standard BMR of 10% extra risk for dichotomous data. One or more of the models provided adequate fit for each data set except decreased WBC and lymphocytes in female rats. Candidate PODs, including the benchmark concentration lower confidence limits (BMCLs) from the selected models, are presented in Table 5. Candidate PODs that were not successfully evaluated via BMDS analysis, are presented as NOAELs and LOAELs.

The benchmark concentration lower confidence limit 1 SD ($BMCL_{1SD}$) (HEC) of 109 mg/m^3 for decreased lymphocyte counts in males at Day 90 from the subchronic-duration rat study (Kelly, 1998) is the lowest candidate POD in the available inhalation toxicity database for *trans*-1,2-DCE. Additionally, the lowest dose tested (LOAEL [HEC] of 1,980 mg/m^3) in the Hurtt et al. (1993) and Haskell Laboratories (1988) study was identified as the candidate POD for increased lacrimation in dams after gestational exposure (GDs 7−16). The study by Kelly (1998) is considered more appropriate for deriving subchronic and chronic p-RfCs than the Hurtt et al. (1993) and Haskell Laboratories (1988) study because of its longer exposure duration (90 days vs. 10 days). Also, the estimated $BMCL_{1SD}$ for immune-related effects from the Kelly (1998) study is at least an order of magnitude lower than the LOAEL for increased lacrimation in Hurtt et al. (1993) and Haskell Laboratories (1988), and no evidence of ocular irritation or other clinical signs were found in the 90-day study at lower exposure concentrations (HEC: ≥140 mg/m^3) (Kelly, 1998). Furthermore, the observed maternal effects in the developmental study are related to irritant effects and other clinical signs of systemic toxicity and not associated with reproductive/developmental function [fetal effects were only observed at the highest concentration (HEC_{ER}: 11,890 mg/m^3) in the presence of overt maternal toxicity (Hurtt et al., 1993; Haskell Laboratories, 1988)]. In summary, Kelly (1998) is selected as the principal study because it identified the most sensitive POD and was adequate in experimental design and protocol. However, because the study is not peer reviewed, screening-level p-RfC values are derived for *trans*-1,2-DCE in Appendix A, in lieu of p-RfC values.

Table 5. Candidate PODs in Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) for Deriving p-RfCs[a]

Endpoint	NOAEL (HEC) (mg/m^3)	LOAEL (HEC) (mg/m^3)	BMCL (HEC) (mg/m^3)	POD (HEC) (mg/m^3)
Kelly (1998), 90-d study				
WBC counts in males (D 90)[b]	710	2,800	133	133 ($BMCL_{1SD}$)
WBC counts in females (D 90)[b]	710	2,800	DUB (No models provided adequate fit to data)	710 (NOAEL)
Lymphocyte counts in males (D 90)[b, c]	**710**	**2,800**	**109**	**109 ($BMCL_{1SD}$)**
Lymphocyte counts in females (D 90)[b]	710[c]	2,800	DUB (No models provided adequate fit to data)	710 (NOAEL)
Hurtt et al. (1993); Haskell Laboratories (1988), developmental study from GDs 7–16				
Lacrimation	NDr	1,980	DUB (Limited information in data set to inform model fit at the low-dose region)	1,980 (LOAEL)
Periocular stain (brown)	1,980	5,950	1,110	1,110 ($BMCL_{10}$)
Alopecia	1,980	5,950	2,190	2,190 ($BMCL_{10}$)

[a]Modeling results are described in more detail in Appendix C.
[b]NOAEL/LOAEL determinations are based on consistent evidence (both in directionality and magnitude) of WBC and lymphocyte changes observed across sexes and exposure durations at the highest concentration, which was associated with statistically significant changes in males (decreased WBC and lymphocyte counts at 45 days and decreased WBC counts at 90 days). Furthermore, trend test results were generally statistically significant supporting concentration-related decreases in WBC and lymphocyte counts in both males and females (see Table B-3).
[c]Chosen as the critical effect for deriving p-RfCs.

BMCL = benchmark concentration lower confidence limit; BMDS = Benchmark Dose Software; DUB = data unamenable to BMDS; GD = gestation day; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; WBC = white blood cell.

Screening p-RfCs are summarized in Table 6 and described in Appendix A.

Table 6. Summary of Noncancer Inhalation Reference Values for *trans*-1,2-DCE (CASRN 156-60-5)

Toxicity Type (unit)	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	300	Kelly (1998)
Screening chronic p-RfC (mg/m^3)	Rat/M	Decreased lymphocyte counts	4×10^{-2}	$BMCL_{1SD}$	109	3,000	Kelly (1998)

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; M = male; POD = point of departure; p-RfC = provisional reference concentration; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; UF_C = composite uncertainty factor.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional reference concentrations (p-RfCs) for *trans*-1,2-dichloroethylene (*trans*-1,2-DCE). However, 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.

DERIVATION OF SCREENING PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

As discussed in the main body of the report, Kelly (1998) was an adequately designed subchronic study that evaluated a number of endpoints following exposure to three concentrations of *trans*-1,2-DCE. This study was chosen as the principle study and the corresponding 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. The observed leukopenia in rats (decreased white blood cell [WBC] and lymphocyte counts) was determined to be treatment related and suggests potential effects on the immune system. The critical effects for deriving a chronic oral reference dose (RfD) were based on altered immune function in mice (U.S. EPA, 2010), which provide additional evidence to suggest that *trans*-1,2-DCE targets the immune system. The Kelly (1998) study used whole-body inhalation exposure for compound administration; therefore, additional exposure through the gastrointestinal tract due to grooming is possible. This potential source of uncertainty cannot be quantified based on the available information. As a conservative estimate, the identified critical effects are assumed to be mostly due to inhalation exposure.

Derivation of Screening Subchronic Provisional Reference Concentration

The screening subchronic p-RfC is derived 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.

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

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfC for *trans*-1,2-DCE.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfC for *trans*-1,2-DCE (CASRN 156-60-5)

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_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation database consists of a subchronic study that tested only a single exposure level and limited endpoints (Freundt et al., 1977), a comprehensive, but non-peer-reviewed subchronic study (Kelly, 1998), and a developmental toxicity study (Hurtt et al., 1993; Haskell Laboratories, 1988), all in rats. However, none of the inhalation exposure studies included immune function assays, which are considered to be most sensitive for evaluating immunotoxicity (Luster et al., 1992). The lack of these assays in the database represents a major source of uncertainty. Indeed, the selected critical effect (decreased lymphocyte counts) provides suggestive evidence of immunotoxicity and the oral RfD for *trans*-1,2-DCE was based on suppression of humoral immunity in mice (U.S. EPA, 2010). Additionally, there are no multigenerational reproductive toxicity studies for this chemical.
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_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 = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfD = oral reference dose; *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 Screening Chronic Provisional Reference Concentration

In the absence of available chronic inhalation studies on *trans*-1,2-DCE, the POD from the subchronic study by Kelly (1998) was used to derive a screening chronic p-RfC. The screening chronic p-RfC is derived by applying a UF_C of 3,000 (reflecting a UF_A of 3, a UF_H of 10, a UF_D of 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.

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= \text{POD (HEC)} \div UF_C \\ &= 109\ \text{mg/m}^3 \div 3{,}000 \\ &= \mathbf{4 \times 10^{-2}\ mg/m^3} \end{aligned}$$

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

Table A-2. Uncertainty Factors for the Screening Chronic p-RfC for *trans*-1,2-DCE (CASRN 156-60-5)

UF	Value	Justification
UF_A	3	A UFA 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_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation database consists of a subchronic study that tested only a single exposure level (Freundt et al., 1977), a comprehensive, but non-peer-reviewed subchronic study (Kelly, 1998), and a developmental toxicity study (Hurtt et al., 1993; Haskell Laboratories, 1988), all in rats. However, none of the inhalation exposure studies included immune function assays, which are considered to be most sensitive for evaluating immunotoxicity (Luster et al., 1992). The lack of these assays in the database represents a major source of uncertainty. Indeed, the selected critical effect (decreased lymphocyte counts) provides suggestive evidence of immunotoxicity and the oral RfD for *trans*-1,2-DCE was based on suppression of humoral immunity in mice (U.S. EPA, 2010). Additionally, there are no multigenerational reproductive toxicity studies for this chemical.
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_L	1	A UF_L of 1 is applied 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 = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfD = oral reference dose; *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. DATA TABLES

Table B-1. Human Exposure to *trans*-1,2-DCE (CASRN 156-60-5) Vapors[a]

Concentration (mg/m^3)	Exposure Time (min)	Effect[b]
1,090	5	No effect
3,270	10	Slight dizziness after 5 min
3,770	5	Slight burning of eyes
3,960	30	Dizziness after 10 min; slight burning of eyes
4,758	10	Dizziness after 5 min; drowsiness; slight burning of eyes
6,740	5	Dizziness after 3 min; slight burning of eyes; "intracranial pressure"; nausea that persisted for a half an hour after exposure
8,723	5	Severe dizziness after 5 min; "intracranial pressure"; nausea that persisted for half an hour after exposure

[a]Lehmann and Schmidt-Kehl as cited in U.S. EPA (2008).
[b]Effects were self-reported.

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

Table B-2. Incidence of Lesions in Female Wistar Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors[a]

Exposure Duration and Concentration [HEC_{ER}][b] in mg/m^3	Fat Accumulation in Liver Lobule	Fat Accumulation in Kupffer Cells	Capillary Hyperemia and Alveolar Septum Distension in the Lung
1 wk			
0	0/6 (0%) [NA][c]	0/6 (0%) [NA]	1/6 (17%) [+]
793 [189]	2/6 (33%) [+]	2/6 (33%) [+]	6/6* (100%) [+]
2 wk			
0	0/6 (0%) [NA]	0/6 (0%) [NA]	2/6 (33%) [+]
793 [189]	4/6 (67%) [+]	4/6 (67%) [+]	6/6 (100%) [+]
8 wk			
0	0/6 (0%) [NA]	1/6 (17%) [++]	0/6 (0%) [NA]
793 [189]	3/6 (50%) [+]	3/6 (50%) [++]	6/6* (100%) [+][d]
16 wk			
0	2/6 (33%) [+]	2/6 (33%) [+]	0/6 (0%) [NA]
793 [189]	5/6 (83%) [+(2), ++(3)]	5/6 (83%) [+]	6/6* (100%) [+][d]

[a]Freundt et al. (1977).
[b]Although the study authors considered the lung lesions systemic in nature based on similar observations after i.p. and oral exposure routes, the potential contribution of airway exposure cannot be ruled out [see study summary for Kelly (1998) in the "Animal Studies" section for more details]. Therefore, the vapor concentration of 793 mg/m^3 was converted to HECs for both extrarespiratory (HEC_{ER} of 189 mg/m^3) and airway exposure pulmonary effects (HEC_{PU} of 2,500 mg/m^3). The HEC_{ER} was ultimately selected for all lesions because it is more sensitive.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence) [severity, graded as + = slight change or ++ = severe change].
[d]Three rats exhibited severe pneumonic infiltration.
*Significantly different from control by two-tailed Fisher's exact test ($p < 0.05$), as conducted for this review.

ER = extrarespiratory; HEC = human equivalent concentration; NA = not applicable; PU = pulmonary effects; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Table B-3. Select Hematological Results in Male and Female Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day, 5 Days/Week for 90 Days[a]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	790 [140]	4,000 [710]	16,000 [2,800]
Male				
Hemoglobin (g/dL)				
D 45	16.1 ± 0.7[b, c]	15.6 ± 0.5 (−3%)	15.3 ± 0.4* (−5%)	15.4 ± 0.7* (−4%)
D 90	15.8 ± 0.6	15.4 ± 0.5 (−3%)	15.9 ± 0.6 (+1%)	15.8 ± 0.4 (0%)
Hematocrit (%)				
D 45	47 ± 3	45 ± 2 (−4%)	44 ± 2* (−6%)	44 ± 2* (−6%)
D 90	47 ± 2	45 ± 2 (−4%)	46 ± 2 (−2%)	47 ± 2 (0%)
WBC (× 10^3/µL)				
D 45	17.2 ± 2.3[#]	15.0 ± 2.3 (−13%)	16.5 ± 4.1 (−4%)	13.9 ± 1.6* (−19%)
D 90	15.7 ± 2.0[#]	13.6 ± 2.5 (−13%)	13.6 ± 3.4 (−13%)	12.6 ± 1.8 (−20%)
Lymphocytes (/µL)				
D 45	13,953 ± 2,321[#]	12,187 ± 2,293 (−13%)	13,766 ± 3,455 (−1%)	10,451 ± 900* (−25%)
D 90	12,901 ± 1,961[#]	10,670 ± 2,189 (−17%)	10,706 ± 2,766 (−17%)	9,597 ± 1,230* (−26%)
Monocytes (/µL)				
D 45	1,689 ± 585	1,221 ± 570 (−28%)	1,367 ± 754 (−19%)	2,020 ± 913 (+19%)
D 90	1,449 ± 443	1,455 ± 515 (+0.4%)	1,269 ± 494 (−12%)	1,441 ± 620 (−0.6%)
Female				
Hemoglobin (g/dL)				
D 45	15.2 ± 1.0	15.0 ± 0.2 (−1%)	15.0 ± 0.7 (−1%)	14.8 ± 0.6 (−3%)
D 90	15.3 ± 0.8	15.0 ± 0.6 (−2%)	15.1 ± 0.9 (−1%)	15.3 ± 0.5 (0%)
Hematocrit (%)				
D 45	44 ± 3	44 ± 1 (0%)	44 ± 2 (0%)	43 ± 2 (−2%)
D 90	46 ± 2	46 ± 2 (0%)	46 ± 2 (0%)	46 ± 2 (0%)
WBC (× 10^3/µL)				
D 45	15.5 ± 4.9[#]	13.5 ± 2.7 (−13%)	13.2 ± 3.3 (−15%)	12.1 ± 2.2 (−22%)
D 90	11.7 ± 4.5	10.1 ± 0.9 (−14%)	9.0 ± 2.3 (−23%)	9.6 ± 2.1 (−18%)

Table B-3. Select Hematological Results in Male and Female Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day, 5 Days/Week for 90 Days[a]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	790 [140]	4,000 [710]	16,000 [2,800]
Lymphocytes (/µL)				
D 45	13,295 ± 4,389	11,508 ± 2,792 (−13%)	11,244 ± 2,880 (−15%)	10,516 ± 1,989 (−21%)
D 90	10,239 ± 4,147[#]	8,337 ± 892 (−19%)	7,705 ± 2,147 (−25%)	7,948 ± 1,943 (−22%)
Monocytes (/µL)				
D 45	1,204 ± 534	801 ± 299 (−33%)	927 ± 622 (−23%)	606 ± 273* (−50%)
D 90	627 ± 372	792 ± 378 (+26%)	519 ± 341 (−17%)	700 ± 475 (+12%)

[a]Kelly (1998).
[b]Data are mean ± SD for 10 rats/group.
[c]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by Dunnett's multiple comparison test ($p < 0.05$), as reported by the study author.
[#]Statistically significant trend according to ordinary one-way ANOVA test for linear trend performed 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).

ANOVA = analysis of variance; ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; WBC = white blood cell.

Table B-4. Select Serum Biochemistry Results in Male and Female Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day, 5 Days/Week for 90 Days[a]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	790 [140]	4,000 [710]	16,000 [2,800]
Male				
ALP (U/L)				
D 45	124 ± 27[b, c]	103 ± 20 (−17%)	122 ± 17 (−2%)	106 ± 20 (−15%)
D 90	90 ± 22	76 ± 10 (−16%)	89 ± 10 (−1%)	81 ± 17 (−10%)
ALT (U/L)				
D 45	43 ± 6	39 ± 7 (−9%)	38 ± 5 (−12%)	38 ± 7 (−12%)
D 90	44 ± 12	38 ± 7 (−14%)	71 ± 108 (+61%)	40 ± 6 (−9%)
AST (U/L)				
D 45	106 ± 29	83 ± 10 (−22%)	88 ± 13 (−17%)	97 ± 26 (−8)
D 90	103 ± 25	85 ± 20‡ (−17)	124 ± 98 (+20%)	96 ± 18 (−7%)
SDH (U/L)				
D 45	20.6 ± 4.4	16.6 ± 4.5 (−19%)	13.6 ± 3.6* (−34%)	15.4 ± 4.4* (−25%)
D 90	18.7 ± 4.3	14.1 ± 4.6‡ (−25%)	22.5 ± 25.5 (+20%)	14.9 ± 2.9 (−20%)
Albumin (g/dL)				
D 45	4.7 ± 0.1	4.5 ± 0.2* (−4%)	4.5 ± 0.2* (−4%)	4.4 ± 0.2* (−6%)
D 90	4.7 ± 0.2	4.6 ± 0.2 (−2%)	4.8 ± 0.3 (+2%)	4.8 ± 0.2 (+2%)
Glucose (mg/dL)				
D 45	90 ± 7	96 ± 5 (+7%)	97 ± 8 (+8%)	106 ± 14* (+18%)
D 90	98 ± 8	107 ± 12 (+9%)	112 ± 17 (+14%)	117 ± 12* (+19%)
Female				
ALP (U/L)				
D 45	58 ± 9	74 ± 12‡ (+28%)	70 ± 24 (+21%)	60 ± 9 (+3%)
D 90	38 ± 12	47 ± 8 (+24%)	46 ± 16 (+21%)	46 ± 8 (+21%)
ALT (U/L)				
D 45	39 ± 12	32 ± 5 (−18%)	37 ± 8 (−5%)	34 ± 3 (−13%)
D 90	35 ± 7	31 ± 5 (−11%)	37 ± 8 (+6%)	41 ± 23 (+17%)
AST (U/L)				
D 45	88 ± 17	86 ± 13 (−2%)	83 ± 10 (−6%)	78 ± 9 (−11%)
D 90	86 ± 19	78 ± 5 (−9%)	79 ± 16 (−8%)	88 ± 34 (+2%)
SDH (U/L)				
D 45	19.0 ± 4.0	15.3 ± 1.9* (−19%)	15.7 ± 2.3* (−17%)	13.0 ± 1.9* (−32%)
D 90	15.1 ± 3.5	14.1 ± 2.4 (−7%)	13.7 ± 3.4 (−9%)	15.1 ± 10.2 (0%)

Table B-4. Select Serum Biochemistry Results in Male and Female Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day, 5 Days/Week for 90 Days[a]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	**790 [140]**	**4,000 [710]**	**16,000 [2,800]**
Albumin (g/dL)				
D 45	5.6 ± 0.4	5.1 ± 0.2* (−9%)	5.7 ± 0.6 (+2%)	5.6 ± 0.4 (0%)
D 90	5.8 ± 0.5	5.5 ± 0.5 (−5%)	5.8 ± 0.6 (0%)	5.8 ± 0.3 (0%)
Glucose (mg/dL)				
D 45	97 ± 9	100 ± 11 (+3%)	102 ± 10 (+5%)	108 ± 8 (+11%)
D 90	103 ± 9	108 ± 8 (+5%)	114 ± 15 (+11%)	121 ± 15* (+17)

[a]Kelly (1998).
[b]Data are mean ± SD for 10 rats/group.
[c]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by Dunnett's multiple comparison test ($p < 0.05$), as reported by the study author.
‡Significantly different from control by Mann-Whitney U test ($p < 0.05$), as reported by the study author.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation; SDH = sorbitol dehydrogenase; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Table B-5. Select Organ Weights of Male and Female Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day, 5 Days/Week for 90 Days[a]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	790 [140]	4,000 [710]	16,000 [2,800]
Male				
Final body weight (g)	477.6 ± 50.2[b, c]	475.6 ± 40.3 (−0.4%)	454.8 ± 32.7 (−5%)	485.1 ± 52.2 (+2%)
Liver, absolute (g)	12.886 ± 1.857	13.451 ± 1.607 (+4%)	13.267 ± 1.516 (+3%)	13.652 ± 2.003 (+6%)
Liver, relative (% BW)	2.693 ± 0.187	2.824 ± 0.179 (+5%)	2.914 ± 0.201 (+8%)	2.808 ± 0.191 (+4%)
Kidney, absolute (g)	3.463 ± 0.325	3.618 ± 0.391 (+4%)	3.518 ± 0.239 (+2%)	3.626 ± 0.256 (+5%)
Kidney, relative (% BW)	0.728 ± 0.071	0.761 ± 0.06 (+5%)	0.775 ± 0.048 (+6)	0.752 ± 0.059 (+3%)
Adrenals, absolute (g)	0.059 ± 0.007	0.063 ± 0.008 (+7%)	0.052 ± 0.007 (−12%)	0.056 ± 0.01 (−5%)
Adrenals, relative (% BW)	0.012 ± 0.002	0.013 ± 0.002 (+8%)	0.012 ± 0.001 (0%)	0.011 ± 0.002 (−8%)
Female				
Final body weight (g)	267.8 ± 28.9	271.2 ± 21.1 (+1%)	272.6 ± 23 (+2%)	274.2 ± 21.1 (+2%)
Liver, absolute (g)	7.677 ± 0.0985	7.925 ± 1.158 (+3%)	8.195 ± 0.771 (+7%)	8.312 ± 0.825 (+8%)
Liver, relative (% BW)	2.877 ± 0.342	2.918 ± 0.297 (+1%)	3.014 ± 0.275 (+5%)	3.043 ± 0.324 (+6%)
Kidney, absolute (g)	1.976 ± 0.296	1.963 ± 0.216 (−0.7%)	2.109 ± 0.203 (+7%)	2.077 ± 0.159 (+5%)
Kidney, relative (% BW)	0.737 ± 0.057	0.724 ± 0.051 (−2%)	0.775 ± 0.067 (+5%)	0.76 ± 0.067 (+3%)
Adrenals, absolute (g)	0.065 ± 0.009	0.066 ± 0.009 (+2%)	0.07 ± 0.007 (+8%)	0.065 ± 0.016 (0%)
Adrenals, relative (% BW)	0.024 ± 0.003	0.024 ± 0.003 (0%)	0.026 ± 0.004 (+8%)	0.024 ± 0.005 (0%)

[a]Kelly (1998).
[b]Data are mean ± SD for 10 rats/group.
[c]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by Dunnett's multiple comparison test ($p < 0.05$), as reported by the study author.

BW = body weight; ER = extrarespiratory; HEC = human equivalent concentration; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Table B-6. Select Clinical Signs of Female Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day during GDs 7−16[a, b]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	**7,930 [1,980]**	**23,800 [5,950]**	**47,580 [11,890]**
GDs 7−16				
Alopecia	1/24 (4%)[c]	2/24 (8%)	9/24* (38%)	19/24* (79%)
Lacrimation	0/24 (0%)	13/24* (54%)	22/24* (92%)	24/24* (100%)
Lethargy	0/24 (0%)	0/24 (0%)	0/24 (0%)	10/24* (42%)
Salivation	0/24 (0%)	0/24 (0%)	2/24 (8%)	17/24* (71%)
Periocular stain (brown)	1/24 (4%)	3/24 (13%)	18/24* (75%)	22/24* (92%)
Wet perinasal hair	0/24 (0%)	0/24 (0%)	1/24 (4%)	10/24* (42%)
GDs 17−22				
Alopecia	1/24 (4%)	6/24 (25%)	7/24* (29%)	11/24* (46%)

[a]Hurtt et al. (1993); Haskell Laboratories (1988).
[b]Observations in home cage outside of exposure period.
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control by Fisher's exact test ($p < 0.05$), conducted for this review.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration;
trans-1,2-DCE = *trans*-1,2-dichloroethylene.

Table B-7. Mean Body Weights and Body-Weight Change of Maternal Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day during GDs 7−16[a]

GDs	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	**7,930 [1,980]**	**23,800 [5,950]**	**47,580 [11,890]**
	(*n* = 22)	(*n* = 24)	(*n* = 24)	(*n* = 23)[b]
Mean body weights (g)				
GD 1	271.5 ± 18.4[c, d]	270.3 ± 15.04 (−0.4%)	271.4 ± 17.22 (0%)	270.2 ± 14.22 (−0.5%)
GD 7 (exposure start)	306.3 ± 21.28	304.4 ± 18.64 (−0.6%)	307.1 ± 18.18 (+0.3%)	302.1 ± 17.1 (−1%)
GD 9	310.6 ± 19.87	309.9 ± 19.72 (−0.2%)	309.5 ± 18.88 (−0.4%)	298.1 ± 15.75 (−4%)
GD 11	318.1 ± 22.29	318.5 ± 19.6 (+0.1%)	317.1 ± 20.39 (−0.3%)	304.3 ± 13.29 (−4%)
GD 13	331.2 ± 23.24	329 ± 20.77 (−0.7%)	325.1 ± 21.48 (−2%)	313.2 ± 14.75 (−5%)
GD 15	342.4 ± 23.91	338 ± 22.65 (−1%)	334.5 ± 19.36 (−2%)	323.1 ± 15.69 (−6%)
GD 17 (exposure end)	356.3 ± 24.85	352.2 ± 25.2 (−1%)	350.4 ± 20.57 (−2%)	336.1 ± 18.15 (−6%)
GD 22	442.4 ± 30.55	439.9 ± 26.52 (−0.6%)	442.1 ± 23.69 (−0.1%)	422.4 ± 25.34 (−5%)
Mean body-weight change (g)				
GDs 1−7	34.8 ± 7.24	34.1 ± 7.04 (−2%)	35.8 ± 6.61 (+3%)	32.4 ± 11.14 (−7%)
GDs 7−9 (exposure start)	4.4 ± 10.13‡	5.5 ± 4.75 (+25%)	2.4 ± 5.97 (−45%)	−4.9 ± 10.59* (−211%)
GDs 9−11	7.5 ± 7.88	8.6 ± 5.07 (+15%)	7.6 ± 6.18 (+1%)	6.2 ± 6.31 (−17%)
GDs 11−13	13.1 ± 6.55‡	10.6 ± 5.69 (−19%)	8 ± 7.53* (−39%)	8.9 ± 4.6* (−32%)
GDs 13−15	11.2 ± 2.82	9 ± 4.97 (−20%)	9.5 ± 6.66 (−15%)	9.9 ± 5.34 (−12%)
GDs 15−17 (exposure end)	13.8 ± 4.06	14.2 ± 5.82 (+3%)	15.9 ± 6.11 (+15%)	13 ± 5.89 (−6%)
GDs 7−17 (total exposure period)	50 ± 12.73‡	47.8 ± 12.26 (−4%)	43.3 ± 10.91 (−13%)	33.4 ± 14.59* (−33%)
GDs 17−22 (postexposure)	86.1 ± 11.29	87.7 ± 8.37 (+2%)	91.7 ± 9.94 (+7%)	86.3 ± 11.42 (+0.2%)
Final BW (without products of conception)	345.3	341.2 (−1%)	343.5 (−1%)	333.2 (−4%)

[a]Hurtt et al. (1993); Haskell Laboratories (1988).
[b]Weight for one animal was not recorded on GD 7 (*n* = 22).
[c]Data are mean ± SD.
[d]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.
‡Significant trend by linear combination of dose ranks from ANOVA ($p < 0.05$), as reported by the study authors.

ANOVA = analysis of variance; BW = body weight; ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Table B-8. Mean Feed Consumption of Maternal Crl:CD (SD) BR Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day during GDs 7−16[a]

GDs	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	**7,930 [1,980]**	**23,800 [5,950]**	**47,580 [11,890]**
	(*n* = 22)	(*n* = 24)	(*n* = 24)	(*n* = 23)
GDs 1−7	22.0 ± 3.04[b, c]	21.3 ± 2.24 (−3%)	22.3 ± 2.09 (+1%)	22.6 ± 2.46 (+3%)
GDs 7−9 (exposure start)	21.7 ± 5.34‡	20.7 ± 3.09 (−5%)	19.4 ± 2.52 (−11%)	16.2 ± 3.37* (−25%)
GDs 9−11	23.2 ± 3.58‡	21.5 ± 3.42 (−7%)	19.1 ± 2.97* (−18%)	18 ± 3.95* (−22%)
GDs 11−13	23.3 ± 4.83‡	21.9 ± 3.14 (−6%)	20.7 ± 3.01* (−11%)	20.2 ± 2.45* (−13%)
GDs 13−15	24.9 ± 2.66‡	22.3 ± 3.04* (−10%)	21.2 ± 2.67* (−15%)	21.7 ± 2.76* (−13%)
GDs 15−17 (exposure end)	25.7 ± 2.6‡	24.1 ± 3.5 (−6%)	23.6 ± 2.27* (−8%)	23.7 ± 2.88 (−8%)
GDs 7−17 (total exposure period)	23.7 ± 2.85‡	22.1 ± 2.71 (−7%)	20.8 ± 1.82* (−12%)	20 ± 2.39* (−16%)
GDs 7−22 (post exposure)	28.0 ± 2.44	27.5 ± 2.51 (−2%)	28.6 ± 2.5 (+2%)	28.9 ± 3.16 (+3%)

[a]Hurtt et al. (1993); Haskell Laboratories (1988).
[b]Data are mean ± SD in units of g feed/day.
[c]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from control by Dunnett's Test ($p < 0.05$), as reported by the study authors.
‡Significant trend by linear combination of dose ranks from ANOVA ($p < 0.05$), as reported by the study authors.

ANOVA = analysis of variance; ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Table B-9. Select Reproductive and Fetal Outcomes Following Maternal Crl:CD (SD) BR Rat Exposure to *trans*-1,2-DCE (CASRN 156-60-5) Vapors for 6 Hours/Day during GDs 7−16[a]

Endpoint	Exposure Concentration [HEC_{ER}] in mg/m^3			
	0	**7,930 [1,980]**	**23,800 [5,950]**	**47,580 [11,890]**
Number pregnant	22	24	24	24
Number of litters	22	24	24	23[b]
Mean number per litter				
Live fetuses (total)	15.3 ± 0.55[c, d]	15.0 ± 0.49 (−2%)	15.3 ± 0.44 (0%)	14.3 ± 0.49 (−7%)
Resorptions				
Total	0.3 ± 0.12‡	0.6 ± 0.20 (+100%)	0.8 ± 0.16* (+167%)	1.1 ± 0.27* (+267%)
Early	0.3 ± 0.12‡	0.6 ± 0.19 (+100%)	0.8 ± 0.16* (+167%)	1.1 ± 0.27* (+267%)
Late	0.0 ± 0.00	0.0 ± 0.04	0.0 ± 0.04	0.0 ± 0.00
Mean fetal weight (g) per litter				
Total	4.97 ± 0.08‡	5.13 ± 0.07 (+3%)	5.01 ± 0.06 (+0.8%)	4.76 ± 0.09* (−4%)
Male	5.05	5.27 (+4%)	5.19 (+3%)	4.96 (−2%)
Female	4.88‡	5.00 (+2%)	4.86 (−0.04%)	4.59* (−6%)

[a]Hurtt et al. (1993); Haskell Laboratories (1988).
[b]One animal delivered on Study Day 18 with term fetuses and the animals were removed from the study.
[c]Data are mean ± SE. No SE values were provided for some data sets.
[d]Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.
*Significantly different from controls by Mann-Whitney U test ($p < 0.05$), as reported by the study authors.
‡Significant trend by Jonckheere's test, as reported by the study authors.

ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; SE = standard error; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

APPENDIX C. BENCHMARK CONCENTRATION MODELING RESULTS

Benchmark concentration (BMC) modeling is conducted with U.S. EPA's Benchmark Dose Software (BMDS, Version 3.1). All continuous models available within the software are fit using a default benchmark response (BMR) of 1 standard deviation (SD) relative risk (RR) unless a biologically determined BMR is available (e.g., BMR 10% relative deviation [RD] for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b). For the decreased white blood cell (WBC) and lymphocyte counts, a standard BMR of 1 SD change from the control means was attempted. All available dichotomous-variable models in the BMDS were fit to the incidence data on brown periocular stain and alopecia using a BMR of 10% extra risk typically used for dichotomous data sets.

An adequate fit is judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected (*p*-value < 0.1), the model is run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark concentration lower confidence limit (BMCL) is selected if the BMCL estimates from different models vary >threefold; otherwise, the BMCL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential point of departure (POD) from which to derive the provisional reference concentration (p-RfC).

In addition, in the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve. Thus, if lack of fit is due to characteristics of the dose-response data for high doses, then the *Benchmark Dose Technical Guidance* (U.S. EPA, 2012b) document allows for data to be adjusted by eliminating the high-dose group. Because the focus of BMC analysis is on the low-dose regions of the response curve, elimination of the high-dose group is deemed reasonable.

BMC MODELING TO IDENTIFY POTENTIAL POINTS OF DEPARTURE FOR THE DERIVATION OF PROVISIONAL REFERENCE CONCENTRATIONS

The selected data sets from the subchronic study by Kelly (1998) and the developmental study by Hurtt et al. (1993) and Haskell Laboratories (1988) were used to determine potential PODs for the p-RfCs for *trans*-1,2-DCE, using BMC analysis. Table C-1 shows the data that were modeled. Summaries of modeling approaches and results (see Tables C-2 to C-7 and Figures C-1 to C-4) for each data set follow.

Table C-1. Selected Data Sets in Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation

Reference/Endpoint	Exposure Concentration [HEC_{ER}][a] in mg/m^3			
Kelly (1998), Crl:CD (SD) BR Rats, 90 D[b]				
	0	**790 [140]**	**4,000 [710]**	**16,000 [2,800]**
Number of animals	10	10	10	10
WBC in males (D 90)	15.7 ± 2.0[#]	13.6 ± 2.5 (−13%)	13.6 ± 3.4 (−13%)	12.6 ± 1.8 (−20%)
WBC in females (D 90)	11.7 ± 4.5	10.1 ± 0.9 (−14%)	9.0 ± 2.3 (−23%)	9.6 ± 2.1 (−18%)
Lymphocytes in males (D 90)	12,901 ± 1,961[#]	10,670 ± 2,189 (−17%)	10,706 ± 2,766 (−17%)	9,597 ± 1,230* (−26%)
Lymphocytes in females (D 90)	10,239 ± 4,147[#]	8,337 ± 892 (−19%)	7,705 ± 2,147 (−25%)	7,948 ± 1,943 (−22%)
Hurtt et al. (1993); Haskell Laboratories (1988), Crl:CD (SD) BR Rats, GDs 7−16[c]				
	0	**7,930 [1,980]**	**23,800 [5,950]**	**47,580 [11,890]**
Periocular stain (brown)	1/24 (4%)	3/24 (13%)	18/24‡ (75%)	22/24‡ (92%)
Alopecia	1/24 (4%)	2/24 (8%)	9/24‡ (38%)	19/24‡ (79%)

[a]HEC calculated by treating *trans*-1,2-DCE as a Category 3 gas and using the following equation from U.S. EPA (1994) methodology: HEC_{ER} = exposure concentration (mg/m^3) × (hours/day exposed ÷ 24 hours) × (days/week exposed ÷ 7 days) × ratio of blood-gas partition coefficient (animal:human), using a default coefficient of 1 because the rat blood-air coefficient of 9.58 is greater than the human blood-air coefficient of 6.04 as indicated by Gargas et al. (1989).
[b]WBC (× 10^3/µL) and lymphocyte (/µL) numbers are expressed as mean ± SD (% change relative to control).
[c]Values denote number of animals showing changes ÷ total number of animals examined (% incidence).
*Significantly different from control by Dunnett's multiple comparison test ($p < 0.05$), as reported by the study authors.
‡Significantly different from control by Fisher's exact test ($p < 0.05$), conducted for this review.
[#]Statistically significant trend according to ordinary one-way ANOVA test for linear trend performed 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).

ANOVA = analysis of variance; ER = extrarespiratory; GD = gestation day; HEC = human equivalent concentration; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene; WBC = white blood cell.

Model Predictions for Decreased WBC Counts in Male Rats Exposed to *trans*-1,2-DCE via Inhalation for 90 Days (Kelly, 1998)

The procedure outlined above for continuous data was applied to the data set for decreased WBC counts in male rats after exposure for 90 days (Kelly, 1998). Table C-2 and Figure C-1 summarize the BMC modeling results. The constant variance models provided adequate fit to the variance data (variance p-value > 0.1), and adequate fit to the means was provided by several of the included models (means p-value > 0.1). The BMCLs for models providing an adequate fit differed by >threefold, thus the model with the lowest BMCL was selected (Exponential 5). The $BMCL_{1SD}$ of 133 mg/m^3 from the Exponential model 5 was selected for decreased WBC counts in males.

Table C-2. Modeling Results for Decreased WBC Counts in Male Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation for 90 Days[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
Constant variance							
Exponential (Model 2)[e]	0.04099776	0.174513339	0.156401211	0.212559996	192.3945021	3,275.314951	1,719.70436
Exponential (Model 3)[e]	0.04099776	0.174513339	0.156401221	0.212487866	192.394502	3,275.332975	1,719.682637
Exponential (Model 4)[e]	0.04099776	0.174513339	0.05407706	0.212621957	194.3941595	3,275.539589	0
Exponential (Model 5)[e, f]	**0.04099776**	**0.174513339**	**0.543286877**	**0.802073003**	**189.9040762**	**425.1746178**	**133.2237321**
Hill[e]	0.04099776	0.174513339	0.413399464	−0.169460913	191.3528436	358.1910446	0
Polynomial (2-degree)[g]	0.04099776	0.174513339	0.151267381	0.192437023	192.4612532	3,293.272638	1,844.258957
Polynomial (3-degree)[g]	0.04099776	0.174513339	0.151267382	0.192474079	192.4612532	3,293.221903	1,844.234034
Power[e]	0.04099776	0.174513339	0.151267382	0.192462701	192.4612532	3,293.237904	1,844.266277
Linear[g]	0.04099776	0.174513339	0.151267382	0.19247013	192.4612532	3,293.229914	1,844.265035

[a]Kelly (1998).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at dose closest to BMC.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

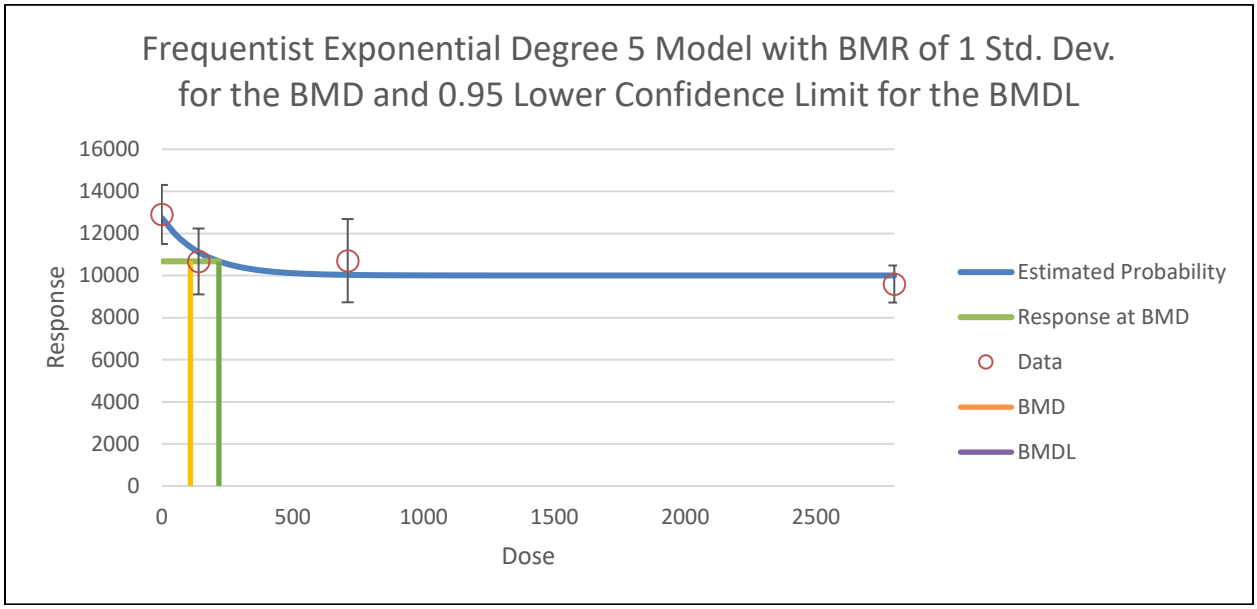

Figure C-1. Exponential 5 Model for Decreased WBC Count in Male Rats Exposed to *trans*-1,2-DCE via Inhalation for 90 Days (Kelly, 1998)

Model Predictions for Decreased WBC Counts in Female Rats Exposed to *trans*-1,2-DCE via Inhalation for 90 Days (Kelly, 1998)

The procedure outlined above for continuous data was applied to the data set for decreased WBC counts in female rats after exposure for 90 days (Kelly, 1998). Table C-3 summarizes the BMC modeling results. The constant variance model did not provide adequate fit to the variance data (variance p-value < 0.1). The nonconstant variance provided adequate fit to the variance data (variance p-value > 0.1); however, none of the models provided adequate fit to the means (means p-value < 0.1) and the data were deemed unsuitable for BMC modeling.

Table C-3. Modeling Results for Decreased WBC Counts in Female Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation for 90 Days[a, b]

Model	Test for Significant Difference *p*-Value[c]	Variance *p*-Value[d]	Means *p*-Value[d]	Scaled Residuals for Dose Group[e]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
Nonconstant variance							
Exponential (Model 2)[f]	0.00011423	0.131208618	0.000247266	198.0448327	9,096.561337	3,372.825057	0.364016312
Exponential (Model 3)[f]	0.00011423	0.131208618	0.000247266	198.0448307	9,093.465137	3,372.812265	0.36349989
Exponential (Model 4)[f]	0.00011423	0.131208618	0.005889908	191.1028924	−9,999	0	−9,999
Exponential (Model 5)[f]	0.00011423	0.131208618	0.005889908	191.1028924	−9,999	0	−9,999
Hill[f]	0.00011423	0.131208618	NA	190.8585656	−9,999	0	−9,999
Polynomial (2-degree)[g]	0.00011423	0.131208618	<0.0001	200.079418	9,717.429352	3,405.475347	0.220999848
Polynomial (3-degree)[g]	0.00011423	0.131208618	<0.0001	200.079418	9,717.431021	3,368.072497	0.220999463
Power[f]	0.00011423	0.131208618	<0.0001	200.079418	9,717.42973	3,405.478856	0.221000229
Linear[g]	0.00011423	0.131208618	<0.0001	200.079418	9,717.434692	3,405.477219	0.220998999

[a]Kelly (1998).
[b]No model was selected. Neither the constant nor nonconstant variance models provide adequate fit to the variance data.
[c]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[d]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[e]Scaled residuals at dose closest to BMC.
[f]Power restricted to ≥1.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration.; BMCL = benchmark concentration lower confidence limit; NA = not applicable; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Model Predictions for Decreased Lymphocyte Counts in Male Rats Exposed to *trans*-1,2-DCE via Inhalation for 90 Days (Kelly, 1998)

The procedure outlined above for continuous data was applied to the data set for decreased lymphocyte counts in male rats after exposure for 90 days (Kelly, 1998). Table C-4 and Figure C-2 summarize the BMC modeling results. The constant variance models provided adequate fit to the variance data (variance *p*-value > 0.1), and adequate fit to the means was only provided by the Exponential model 5 (means *p*-value > 0.1). Upon inspection of the scaled residuals and graph of the model fit, the Exponential model 5 was determined to be adequate, and the corresponding benchmark concentration lower confidence limit 1 standard deviation ($BMCL_{1SD}$) of 109 mg/m^3 was selected for decreased lymphocyte counts in males.

Table C-4. Modeling Results for Decreased Lymphocyte Counts in Male Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation for 90 Days[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals for Dose Group[d]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
Constant variance							
Exponential (Model 2)[e]	<0.0001	0.107225219	0.059803913	0.257761593	733.2726356	2,578.585425	1,459.112969
Exponential (Model 3)[e]	<0.0001	0.107225219	0.059805795	0.258908641	733.2725726	2,574.03955	1,458.239514
Exponential (Model 4)[e]	<0.0001	0.107225219	0.017632017	0.259208791	735.2716134	2,573.14188	0
Exponential (Model 5)[e, f]	**<0.0001**	**0.107225219**	**0.358034978**	**−0.679011939**	**729.6935164**	**217.8391027**	**108.924072**
Hill[e]	<0.0001	0.107225219	0.043072427	0.240974366	733.7318245	1,361.55955	0
Polynomial (2-degree)[g]	<0.0001	0.107225219	0.055914165	0.226726414	733.4071423	2,660.956421	1,626.462393
Polynomial (3-degree)[g]	<0.0001	0.107225219	0.055914165	0.226726439	733.4071423	2,660.956401	1,957.435435
Power[e]	<0.0001	0.107225219	0.055914165	0.226726772	733.4071423	2,660.956125	2,237.571419
Linear[g]	<0.0001	0.107225219	0.055914165	0.226726165	733.4071423	2,660.956614	1,625.856447

[a]Kelly (1998).
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at dose closest to BMC.
[e]Power restricted to ≥1.
[f]Selected model. Lowest AIC among models that provided an adequate fit.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = benchmark concentration lower confidence limit; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

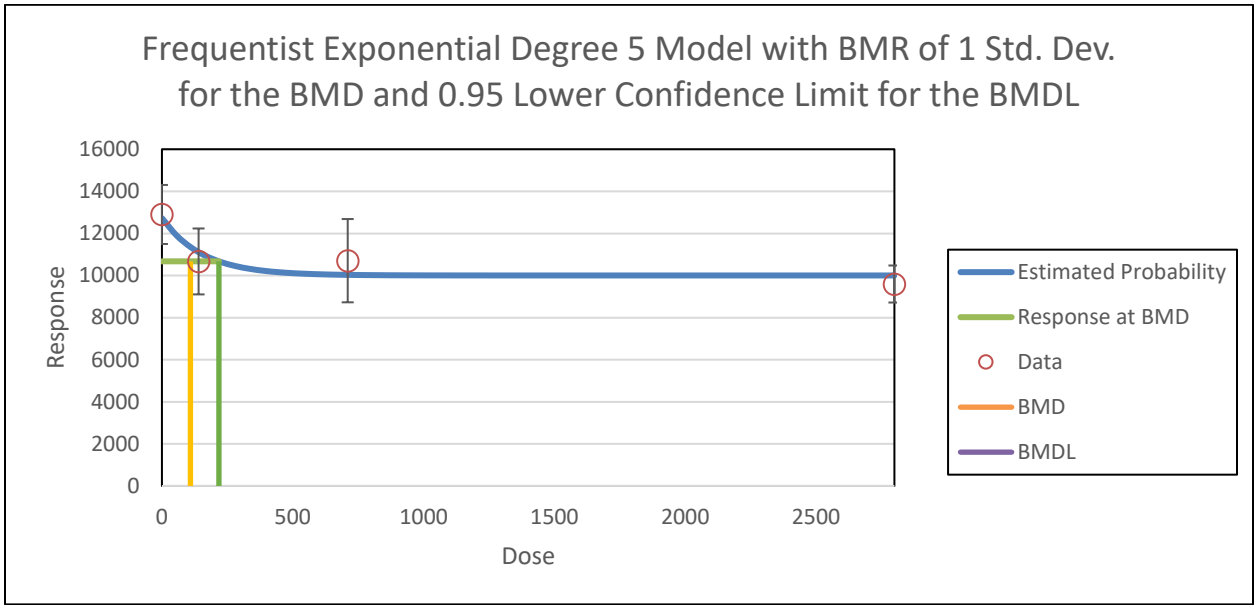

Figure C-2. Exponential 5 Model for Decreased Lymphocyte Count in Male Rats Exposed to *trans*-1,2-DCE via Inhalation for 90 Days (Kelly, 1998)

Model Predictions for Decreased Lymphocyte Counts in Female Rats Exposed to *trans*-1,2-DCE via Inhalation for 90 Days (Kelly, 1998)

The procedure outlined above for continuous data was applied to the data set for decreased lymphocyte counts in female rats after exposure for 90 days (Kelly, 1998). Table C-5 summarizes the BMC modeling results. Neither the constant nor nonconstant variance models provided adequate fit to the variance data; thus, these data were not suitable for BMC modeling.

Table C-5. Modeling Results for Decreased Lymphocyte Counts in Female Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation for 90 Days[a, b]

Model	Test for Significant Difference *p*-Value[c]	Variance *p*-Value[d]	Means *p*-Value[d]	Scaled Residuals for Dose Group[e]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
Nonconstant variance							
Exponential (Model 2)[f]	<0.0001	0.00012026	0.00065345	0.624862974	745.2710264	5,917.520848	2,873.291436
Exponential (Model 3)[f]	<0.0001	0.00012026	0.00066347	0.610130098	745.2389072	5,632.4976	2,885.591336
Exponential (Model 4)[f]	<0.0001	0.00012026	0.0460978	−9,999	736.1013398	−9,999	0
Exponential (Model 5)[f]	<0.0001	0.00012026	0.00018839	0.621633978	747.2594968	5,854.674263	0
Hill[f]	<0.0001	0.00012026	0.06328607	−9,999	735.5546089	−9,999	0
Polynomial (2-degree)[g]	<0.0001	0.00012026	<0.0001	0.161572813	749.8609773	5,177.931382	2,804.542348
Polynomial (3-degree)[g]	<0.0001	0.0001202	NA	0.170169868	751.9382154	4,891.075414	2,783.326222
Power[f]	<0.0001	0.00012026	0.00023688	0.068864515	746.8014459	9,221.601015	3,150.012054
Linear[g]	<0.0001	0.00012026	0.00023587	0.297479128	746.810005	6,910.44751	3,146.779327

[a]Kelly (1998).
[b]No model was selected. Neither the constant nor nonconstant variance models provide adequate fit to the variance data.
[c]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[d]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[e]Scaled residuals at dose closest to BMC.
[f]Power restricted to ≥1.
[g]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration.; BMCL = benchmark concentration lower confidence limit; NA = not applicable; SD = standard deviation; *trans*-1,2-DCE = *trans*-1,2-dichloroethylene.

Model Predictions for Increased Brown Periocular Stain in Female Rats Exposed to *trans*-1,2-DCE via Inhalation during GDs 7−16 (Hurtt et al., 1993; Haskell Laboratories, 1988)

The procedure outlined above for dichotomous data was applied to the data set for increased periocular stain in dams exposed during GDs 7−16 (Hurtt et al., 1993; Haskell Laboratories, 1988). Table C-6 and Figure C-3 summarize the BMC modeling results. The Gamma, Log-Logistic, Weibull, and Log-Probit models provided adequate fit to the data (*p*-value > 0.1). BMCLs for models providing adequate fit were sufficiently close (i.e., differed by <threefold), so the model with the lowest AIC was selected (Log-Logistic). For increased brown periocular stain in dams, the $BMCL_{10}$ of 1,110 mg/m^3 from the Log-Logistic model was selected.

Table C-6. Modeling Results for Increased Brown Periocular Stain in Female Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation during GDs 7−16[a]

Model	*p*-Value[b]	Scaled Residuals for Dose Group	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	0.184718398	−0.549497506	74.88282537	1,683.403683	787.047734
Log-Logistic[d, e]	**0.494576234**	**−0.261788671**	**73.6106529**	**1,902.032036**	**1,109.478648**
Multistage Degree 3[f]	0.071849056	−0.874916989	76.422566	1,301.926215	559.2344192
Multistage Degree 2[f]	0.071848167	−0.874908763	76.422566	1,301.9172	561.0782643
Multistage Degree 1[f]	0.070439209	0.373579745	77.2565984	589.5022218	445.0414877
Weibull[c]	0.118212597	−0.842944016	75.66260339	1,406.540549	659.9499894
Dichotomous Hill	NA	−0.26167165	75.61065282	1,902.010142	1,109.463555
Logistic	0.070529966	−0.593068777	75.56893074	1,851.111014	1,354.408947
Log-Probit	0.408300783	−0.307020107	73.8289546	1,886.376152	1,139.58615
Probit	0.052822609	−0.687415537	76.6322265	1,756.879374	1,319.509329

[a]Hurtt et al. (1993); Haskell Laboratories (1988).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMC_{10} = benchmark concentration 10% extra risk; $BMCL_{10}$ = 95% benchmark concentration lower confidence limit; NA = not applicable;
trans-1,2-DCE = *trans*-1,2-dichloroethylene.

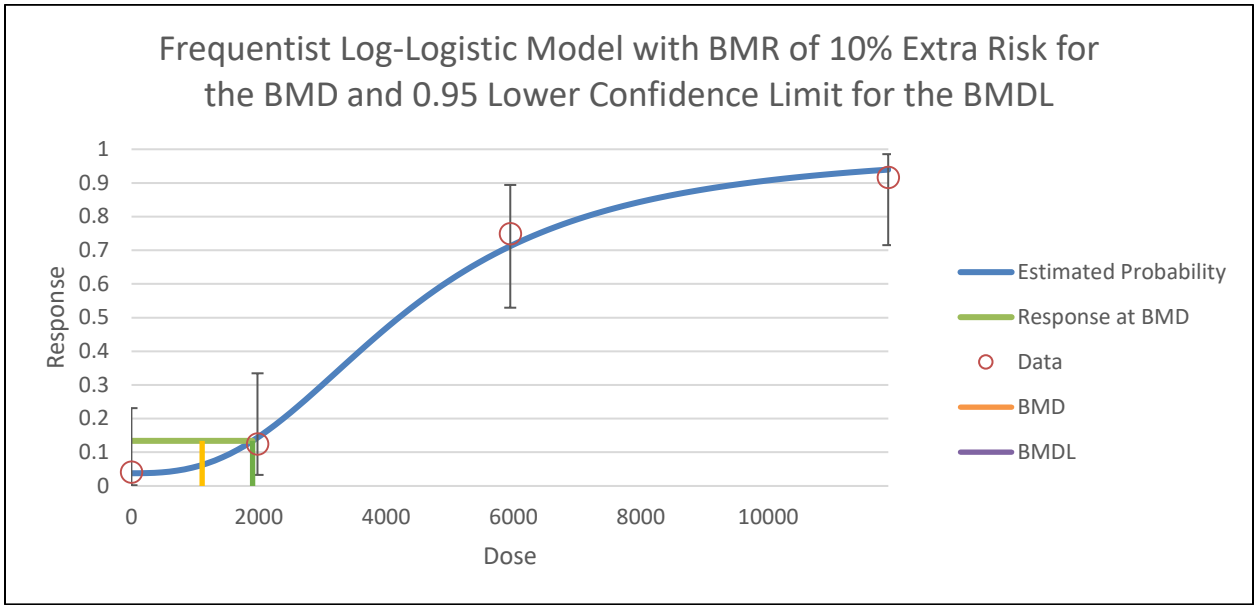

Figure C-3. Log-Logistic Model for Increased Brown Periocular Stain in Female Rats Exposed to *trans*-1,2-DCE via Inhalation during GDs 7−16 (Hurtt et al., 1993; Haskell Laboratories, 1988)

Model Predictions for Increased Alopecia in Female Rats Exposed to *trans*-1,2-DCE via Inhalation during GDs 7−16 (Hurtt et al., 1993; Haskell Laboratories, 1988)

The procedure outlined above for dichotomous data was applied to the data set for increased alopecia in dams exposed during GDs 7−16 (Hurtt et al., 1993; Haskell Laboratories, 1988). Table C-7 and Figure C-4 summarize the BMC modeling results. All the models except for the Dichotomous Hill model provided adequate fit to the data (*p*-value > 0.1). BMCLs for models providing adequate fit were sufficiently close (i.e., differed by <threefold), so the model with the lowest AIC was selected (Probit). For increased alopecia in dams, the $BMCL_{10}$ of 2,190 mg/m^3 from the Probit model was selected.

Table C-7. Modeling Results for Increased Alopecia in Female Rats Exposed to *trans*-1,2-DCE (CASRN 156-60-5) via Inhalation during GDs 7−16[a]

Model	*p*-Value[b]	Scaled Residuals for Dose Group	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	0.921367419	0.064672437	84.41024679	3,030.480486	1,433.482044
Log-Logistic[d]	0.80997918	0.17231264	84.45781504	3,254.420006	1,639.029337
Multistage Degree 3[e]	0.845827707	−0.105411411	84.43841885	2,899.724333	1,193.819337
Multistage Degree 2[e]	0.84582769	−0.105410319	84.43841885	2,899.727464	1,268.742054
Multistage Degree 1[e]	0.14761207	−1.337609512	86.69714827	1,133.452408	829.2720096
Weibull[c]	0.893517079	−0.095298473	84.41858031	2,867.341123	1,388.839563
Dichotomous Hill	NA	0.172318998	86.45781505	3,254.436469	1,639.040203
Logistic	0.797850772	−0.284385158	82.85193042	3,125.441581	2,342.789334
Log-Probit	0.672689738	0.298111572	84.57696201	3,336.901383	1,686.21612
Probit[f]	**0.874570178**	**−0.272100733**	**82.66926811**	**2,893.266258**	**2,193.910583**

[a]Hurtt et al. (1993); Haskell Laboratories (1988).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model.

AIC = Akaike's information criterion; BMC_{10} = benchmark concentration 10% extra risk; $BMCL_{10}$ = 95% benchmark concentration lower confidence limit; NA = not applicable;
trans-1,2-DCE = *trans*-1,2-dichloroethylene.

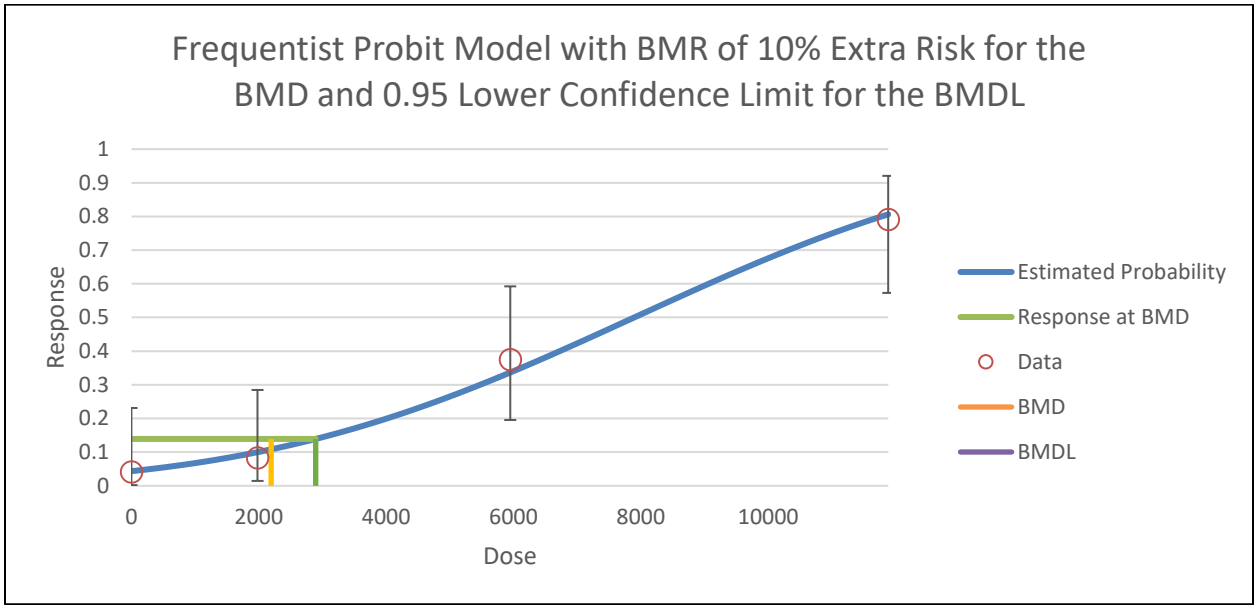

Figure C-4. Probit Model for Increased Alopecia in Female Rats Exposed to *trans*-1,2-DCE via Inhalation during GDs 7−16 (Hurtt et al., 1993; Haskell Laboratories, 1988)

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