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Draft Human Health Hazard Assessment for 1,2-Dichloroethane

Technical Support Document for the Draft Risk Evaluation

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KEY ABBREVIATIONS AND ACRONYMS

ADME	Absorption, distribution, metabolism, and elimination
AF	Assessment factor
ALT	Alanine transaminase
AMTIC	Ambient Monitoring Technology Information Center
AST	Aspartate aminotransferase (AST)
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	Bioaccumulation factor
BALF	Bronchioalveolar lavage fluid
BCF	Bioconcentration factor
BMC	Benchmark concentration
BMD	Benchmark dose
BMR	Benchmark response
BUN	Blood urea nitrogen
CASRN	Chemical Abstracts Service Registry Number
ChV	Chronic value
CSF	Cancer slope factor
CWA	Clean Water Act
EPA	Environmental Protection Agency
GD	Gestation day
GSH	Glutathione
GST	Glutathione-S-transferase
HC05	Hazardous concentration for 5 percent of species
HEC	Human Equivalent Concentration
HED	Human Equivalent Dose
HERO	Health and Environmental Research Online (Database)
IRIS	Integrated Risk Information System
IUR	Inhalation unit risk
LCx	Lethal concentration at which (x) percent of test organisms die
LDH	Lactate dehydrogenase
LDx	Lethal dose at which (x) percent of test organisms die
LOD	Limit of detection
LOAEL	Lowest-adverse-effect-level
MOE	Margin of exposure
NATA	National Scale Air-Toxics Assessment
ND	Non-detect
NEI	National Emissions Inventory
NOAEL	No-adverse-effect-level
NTP	National Toxicology Program
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation and Development
OPPT	Office of Pollution Prevention and Toxics
PBPK	Physiologically-based pharmacokinetic

PECO	Population, exposure, comparator, and outcome
PESS	Potentially exposed or susceptible subpopulations
POD	Point of departure
SD	Sprague-Dawley (rat)
SR	Systematic review
SSD	Species sensitivity distribution
TLV	Threshold limit value
TRI	Toxics Release Inventory
TRV	Toxicity reference value
TSCA	Toxic Substances Control Act
TWA	Time-weighted average
UF	Uncertainty Factor
U.S.	United States
WOSE	Weight of scientific evidence

SUMMARY

This technical support document for 1,2-dichloroethane describes the non-cancer and cancer hazards associated with exposure to 1,2-dichloroethane and identifies the points of departure (PODs) to be used to estimate risks from 1,2-dichloroethane exposures in the draft risk evaluation of 1,2-dichloroethane.

The Existing Chemicals Risk Evaluation Division (ECRAD) has received input from senior scientists and technical experts from EPA's OCSPP and across the Agency. Specifically, ECRAD has received input from the OCSPP Senior Science Advisors, OCSPP's Science Policy Council, and through the intra-agency review process. The areas of analysis contained in this draft 1,2-dichloroethane human health hazard assessment technical support document reflect some of the revisions received throughout the review process and during scientific deliberations; however, there are some significant aspects of the development of this draft 1,2-dichloroethane human health hazard assessment for which there is not agreement between ECRAD and senior scientists and technical experts. In accordance with EPA's Scientific Integrity Policy (https://www.epa.gov/scientific-integrity/epas-scientific-integrity-policy), the areas of scientific disagreement are described in relevant charge questions and are intended to guide the scientific peer review by the TSCA Science Advisory Committee on Chemicals (SACC). EPA is requesting the SACC provide input on these science issues—including the differences of scientific opinion—which relate specifically to 1,2-dichloroethane (and the concurrently released draft 1,1-dichloroethane risk evaluation) but also more broadly in the application of risk assessment practices and use of existing EPA and internally accepted guidance documents.

EPA evaluated the reasonably available information for human health hazards and identified hazard PODs for adverse effects following acute, short-term/subchronic, and chronic exposures. These PODs represent the potential for greater biological susceptibility across subpopulations. The most biologically relevant and sensitive PODs for non-cancer for 1,2-dichloroethane from among the human health hazards identified—along with the corresponding Human Equivalent Dose (HED), the Human Equivalent Concentration (HEC), and the total combined uncertainty factors (UF) for each route and exposure duration—are summarized below (Table ES-1). The lack of adequate non-cancer data by the dermal route for 1,2-dichloroethane required route-to-route extrapolation from oral PODs. The following summarizes the key points of this section of the draft risk evaluation.

The most biologically relevant and sensitive PODs for cancer effects for 1,2-dichloroethane from among the human health hazards identified—along with the corresponding cancer slope factor (CSF), dermal slope factor, inhalation unit risk (IUR), and drinking water unit risk—are also summarized below (Table ES-2).

EPA identified kidney toxicity, immunotoxicity, and neurotoxicity as the most sensitive critical human health hazard outcomes associated with 1,2-dichloroethane. These hazard outcome categories received *likely* evidence integration conclusions, and sensitive health effects were identified for these hazard outcomes. In the draft risk evaluation, renal toxicity forms the basis of the POD used for acute oral exposure scenarios and immunotoxicity is the basis of the POD used for both short-term and chronic oral exposure scenarios. Neurotoxicity is the basis of the POD used for acute inhalation exposure and reproductive effects is the basis for short-term/subchronic and chronic inhalation exposure scenarios. Additionally, hazard identification and evidence integration of other toxicity outcomes are also outlined to emphasize the systematic review process applied to identify potential POD with within the 1,2-dichloroethane database.

EPA is proposing a POD of 153 mg/kg-day (HED of 19.9 mg/kg-day) to estimate non-cancer risks from oral exposure to 1,2-dichlorethane for acute durations of exposure in the draft risk evaluation for 1,1-dichloroethane. The proposed POD was derived based on benchmark dose modeling of increased kidney weight in male mice (*i.e.*, the only sex tested). Increased blood urea nitrogen levels support the kidney findings as both parameters were dose-responsive. The POD of 153 mg/kg-day is the 90 percent lower confidence limit of the BMD associated with a benchmark response (BMR) of 10 percent. As presented in Section 6.1.2 and Table 6-1, additional acute duration studies of 1,2-dichlorethane provide similar, although less sensitive, candidate PODs, which further support EPA's proposal to use the selected HED of 19.9 mg/kg-day for increased kidney weight. The Agency has performed ¾ body weight scaling to yield the HED of 19.9 mg/kg-day and is applying the animal to human extrapolation factor (*i.e.*, interspecies extrapolation; UF_A) of 3× and a within human variability extrapolation factor (*i.e.*, intraspecies extrapolation; UF_H) of 10×. Thus, a total UF of 30× is applied for use as the benchmark margin of exposure (MOE). Based on the strengths, limitations, and uncertainties discussed Section 6.4.1, **EPA has robust overall confidence in the proposed POD based on increased kidney weight for use in characterizing risk from exposure to 1,2-dichloroethane for acute oral exposure scenarios**.

EPA is proposing a POD of 48.9 mg/m^3 (HEC of 10.14 ppm) to estimate non-cancer risks from inhalation to 1,2-dichloroethane for acute durations of exposure in the draft risk evaluation for 1,1-dichloroethane. The proposed POD was derived based on benchmark dose modeling of degeneration with necrosis of the olfactory (nasal) mucosa in male and female mice. The POD of 48.9 mg/m^3 is the 90 percent lower confidence limit of the BMD associated with a BMR of 10 percent. As presented in Section 6.1.2 and Table 6-2, additional acute duration studies of 1,2-dichloroethane provide similar, although less sensitive, candidate PODs, which further support EPA's proposal to use the selected POD of 48.9 mg/m^3 for degeneration with necrosis of the olfactory (nasal) mucosa. The Agency is applying the animal to human extrapolation factor (*i.e.*, interspecies extrapolation; UF_A) of 3× and a within human variability extrapolation factor (*i.e.*, intraspecies extrapolation; UF_H) of 10×. Thus, a total UF of 30× is applied for use as the benchmark MOE. Based on the strengths, limitations, and uncertainties discussed in Section 6.4.1, **EPA has robust overall confidence in the proposed POD based on degeneration with necrosis of the olfactory (nasal) mucosa for use in characterizing risk from exposure to 1,2-dichloroethane for acute inhalation exposure scenarios**.

EPA is proposing an adjusted lowest-observed-adverse effect level ($LOAEL_{adj}$) of 4.89 mg/kg-day (HED of 0.890 mg/kg-day) from a high quality 14-day gavage study in male mice based on suppression of immune response (antibody forming cells [AFCs] in the spleen) to estimate non-cancer risks from oral exposure to 1,2-dichloroethane for short-term/chronic durations of exposure in the draft risk evaluation of 1,1-dichloroethane. The study also demonstrated decreased leukocyte counts to support immunosuppression. As presented in Sections 6.1.3 and 6.1.4 and Table 6-3 and Table 6-5, additional short-term/chronic duration studies of 1,2-dichloroethane provide similar, although less sensitive, candidate PODs, which further support EPA's proposal to use the selected POD of 4.89 mg/kg-day for suppression of immune response (AFCs in the spleen). The Agency has performed ¾ body weight scaling to yield the HED of 0.890 mg/kg-day and is applying the animal to human extrapolation factor (*i.e.*, interspecies extrapolation; UF_A) of 3×, a within human variability extrapolation factor (*i.e.*, intraspecies extrapolation; UF_H) of 10× and a LOAEL to extrapolate a no-observed-adverse-effect-level (NOAEL) factor (*i.e.*, UF_L) of 3×. The use of a duration adjustment factor (*i.e.*, short-term study to long-term risk assessment, UF_S) of 10× was applied for the chronic duration, specifically. Thus, a total uncertainty factor (UF) of 100× is applied for use as the benchmark MOE for the short-term duration and 1000× chronic duration, respectively. Based on the strengths, limitations, and uncertainties discussed in Section 6.4.1, **EPA has robust overall confidence in the proposed POD based on**

suppression of immune response for use in characterizing risk from exposure to 1,2-dichloroethane for short-term/chronic oral exposure scenarios.

EPA is proposing a POD of 21.2 mg/m^3 (HEC of 22.0 ppm) to estimate non-cancer risks from inhalation to 1,2-dichloroethane for short-term/chronic durations of exposure in the draft risk evaluation for 1,1-dichloroethane. The proposed POD was derived based on benchmark dose modeling of decreased sperm concentration in male mice after a whole body, 4-week exposure. The POD of 21.2 mg/m^3 is the 95 percent lower confidence limit of the BMD associated with a BMR of 5 percent due to a biological significance and relevance at this level in humans.

As presented in Sections 6.1.3 and 6.1.4, as well as Table 6-4 and Table 6-6, additional short-term duration studies of 1,2-dichloroethane provide less sensitive, candidate PODs, which further support EPA's proposal to use the selected POD of 21.2 mg/m^3 for decreased sperm concentration. The Agency is applying the animal to human extrapolation factor (*i.e.*, interspecies extrapolation; UFA) of 3× and a within human variability extrapolation factor (*i.e.*, intraspecies extrapolation; UFH) of 10×. The use of a duration adjustment factor (*i.e.*, short-term study to long-term risk assessment, UFS) of 10× was applied for the chronic duration, specifically. Thus, a total UF of 30× is applied for use as the benchmark MOE for the short-term duration and 300× chronic duration, respectively. Based on the strengths, limitations, and uncertainties discussed Section 6.4.1, **EPA has robust overall confidence in the proposed POD based on decreased sperm concentration for use in characterizing risk from exposure to 1,2-dichloroethane for short-term/chronic inhalation exposure scenarios**.

No data were available for the dermal route identified based on systematic review that were suitable for deriving route-specific PODs. Therefore, EPA used the acute, short-term, and chronic oral PODs to evaluate risks from dermal exposure to 1,2-dichloroethane.

Systematic review identified two high-quality 1,2-dichloroethane cancer studies for cancer dose-response. The oral cancer studies in mice performed by NTP (1978) on 1,2-dichloroethane resulted in tumor types or pre-cancerous lesions (*i.e.*, hepatocellular carcinomas, endometrial polyps, hemangiosarcomas, and mammary gland tumors). Therefore, EPA is proposing a CSF of 0.062 per mg/kg-day for the oral/dermal exposure routes to 1,2-dichloroethane based on hepatocellular carcinomas in male mice for both continuous (*i.e.*, general population) and worker (occupational) scenarios. In addition, EPA is proposing a drinking water (DW) unit risk of 1.8×10^{-6} per µg/L based on an extrapolation from the oral gavage data and further discussed in Section 6.3.1.

The 1,2-dichloroethane inhalation cancer study by Nagano et al. (2006) is the basis for the inhalation unit risk (IHR) as this study identified similar tumors as observed in the 1,2-dichloroethane oral cancer study. EPA is therefore proposing an IUR of 7.1×10^{-6} per µg/m^3 and 2×10^{-6} per µg/m^3 for the inhalation exposure route to 1,2-dichloroethane based on a combined tumor model (mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas) for the continuous and worker scenarios, respectively (see Section 6.3.1).

Based on the strengths, limitations, and uncertainties discussed in Section 6.4.1, **EPA has robust overall confidence in the proposed CSF and IUR based on hepatocellular carcinomas and a combined tumor model (mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas), respectively.**

Table ES-1. Non-cancer HECs and HEDs Used to Estimate Risks

Exposure Scenario	Target Organ System	Species	Duration	POD (mg/kg-day)	Effect	Worker HEC (mg/m^3) [ppm]	Continuous HEC (mg/m^3) [ppm]	Worker HED (mg/kg-day)	Continuous HED (mg/kg-day)	Benchmark MOE	Reference
Acute – Oral	Renal	Mice (male)	Single dose via oral gavage	$BMDL_{10}$ = 153 mg/kg-day BMD = 270 mg/kg	Increased kidney weight	N/A	N/A	19.9	19.9	UF_A [a] = 3 UF_H = 10 *Total UF = 30*	Storer et al. (1984)
Acute – Inhalation	Neurological	Rats (males and females combined)	8-hours (whole body to vapor)	BMC_{10} = 48.9 mg/m^3 [12.1 ppm]	Degeneration with necrosis of the olfactory mucosa	(41.1 mg/m^3) [10.14 ppm]	(9.78 mg/m^3) [2.42 ppm]	N/A	N/A	UF_A = 3 UF_H = 10 *Total UF = 30*	Dow Chemical (2006b)
Short-term and Chronic – Oral	Immune System	Mice (male)	14-days via oral gavage	$LOAEL_{adj}$ = 4.89 mg/kg	Suppression of immune response (AFCs/ spleen)	N/A	N/A	0.890	0.636	*Short-term:* UF_A = 3 UF_H = 10 UF_L = 3 *Total UF = 100* *Chronic:* UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 10 *Total UF = 1,000*	Munson et al. (1982)
Short-term and Chronic – Inhalation	Reproductive	Mice (male)	4-weeks (6 hours/day for 7 days/week whole body to vapor)	$BMCL_5$ = 21.2 mg/m^3 [5.2 ppm]	Decreases in sperm concentration	(89.0 mg/m^3) [22.0 ppm]	(21.2 mg/m^3) [5.2 ppm]	N/A	N/A	*Short-term:* UF_A = 3 UF_H = 10 *Total UF = 30* *Chronic:* UF_A = 3 UF_H = 10 UF_S = 10 *Total UF = 300*	Zhang et al. (2017)

Exposure Scenario	Target Organ System	Species	Duration	POD (mg/kg-day)	Effect	Worker HEC (mg/m^3) [ppm]	Continuous HEC (mg/m^3) [ppm]	Worker HED (mg/kg-day)	Continuous HED (mg/kg-day)	Benchmark MOE	Reference

HEC = human equivalent concentration; HED = human equivalent dose; MOE = margin of exposure; NOAEL = no-observed-adverse-effect level; POD = point of departure; SD = Sprague-Dawley; UF = uncertainty factor

[a] EPA used allometric body weight scaling to the three-quarters (¾) power to derive the HED. Consistent with EPA Guidance U.S. EPA (2011b), the UF_A was reduced from 10 to 3.

Table ES-2. Cancer PODs for 1,2-Dichloroethane Lifetime Exposure Scenarios

Exposure Assumption [a]	Oral Slope Factor [b]	Dermal Slope Factor [b]	Inhalation Unit Risk [c]	Drinking Water Unit Risk [d]	Extra Cancer Risk Benchmark
Continuous Exposure	0.062 per mg/kg/day	0.062 per mg/kg/day	7.1E−06 (per µg/m^3) 2.9E−02 (per ppm)	1.8E–06 per ug/L	1E−06 (general population)
Worker	0.062 per mg/kg/day	0.062 per mg/kg/day	2.4E−06 (per µg/m^3) 9.5E−03 (per ppm)	1.8E–06 per ug/L	1E−04 (occupational)

[a] Cancer slope factor and unit risk will be derived based on continuous exposure scenarios. Due to the exposure averaging time adjustments incorporated into lifetime exposure estimates, separate cancer hazard values for occupational scenarios are not required.

[b] The oral CSF for male mice based on hepatocellular carcinomas in male mice was 6.2×10^{-2} (per mg/kg-bw/day) in a study by NTP (1978). Due to scarcity of data, route-to-route extrapolation from the oral slope factor is used for the dermal route.

[c] Cancer inhalation PODs from 1,2-dichloroethane based on combined tumor model (mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas in female rats) Nagano et al. (2006)

[d] Therefore, the oral CSF for 1,2-dichloroethane from the reliable NTP mouse cancer study NTP (1978) was selected for use in assessment of cancer risks associated with exposure to 1,2-dichloroethane. This mouse CSF was used to calculate a drinking water unit risk of 1.8 E–06 per ug/L using a drinking water intake of 2 L/day and body weight of 70 kg.

1 INTRODUCTION

Following publication of the *Final Scope of the Risk Evaluation for 1,2-Dichloroethane CASRN 107-06-2* (U.S. EPA, 2020), one of the next steps in the Toxic Substances Control Act (TSCA) risk evaluation process is to identify and characterize the human health hazards of 1,2-dichloroethane and conduct a dose-response assessment to determine the points of departure (PODs) to be used to estimate risks from 1,2-dichloroethane exposures. This technical support document for 1,2-dichloroethane summarizes the non-cancer and cancer hazards associated with exposure to 1,2-dichloroethane and identifies the PODs to be used to estimate risks from 1,2-dichloroethane exposures.

1.1 Approach and Methodology

To identify and integrate human epidemiologic data and animal data into the draft 1,2-Dichloroethane Risk Evaluation, EPA first reviewed existing assessments of 1,2-dichloroethane conducted by regulatory and authoritative agencies such as ATSDR (2022), as well as several systematic reviews of studies of 1,2-dichloroethane published by U.S. EPA Integrated Risk Information System (IRIS) programU.S. EPA (1987b) and U.S. EPA Provisional Peer-Reviewed Toxicity Values U.S. EPA (2010). A summary and evaluation of the toxicity values identified from these assessments are provided in Appendix E.

EPA used the general approach described in Figure 1-1 to evaluate and extract evidence for 1,2-dichloroethane human health hazard and dose-response information. This approach is based on the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021) (hereafter referred to as the 2021 Draft Systematic Review Protocol), updates to the systematic review processes presented in the *Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Protocol* (U.S. EPA, 2024b) (hereafter referred to as the 1,1-Dichloroethane Systematic Review Protocol) and the *Framework for Human Health Risk Assessment to Inform Decision Making* (U.S. EPA, 2014).

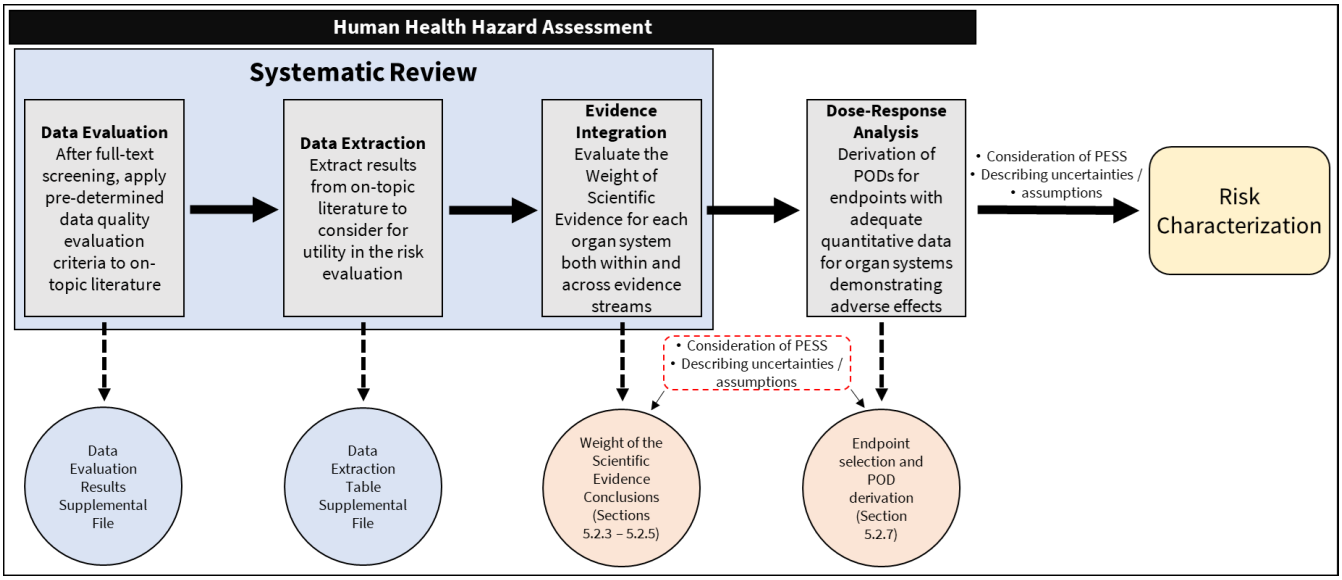

Figure 1-1. EPA Approach to Hazard Identification, Evidence Integration, and Dose-Response Analysis for Human Health Hazard

1.1.1 Identification and Evaluation of 1,2-Dichloroethane Hazard Data

For the human health hazard assessment, EPA used a systematic review (SR) approach described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021), to identify relevant studies of acceptable data quality and integrate the pertinent data while evaluating the weight of scientific evidence. For identified hazards and endpoints with weight of scientific evidence supporting an adverse outcome, studies were considered for dose-response analysis. The 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) describes the general process of evidence evaluation and integration, with relevant updates to the process presented in the 1,1-dichloroethane Systematic Review Protocol (U.S. EPA, 2024b).

For **data quality evaluation**, EPA systematically reviewed literature studies for 1,2-dichloroethane first by reviewing screened titles and abstracts and then full texts for relevancy using population, exposure, comparator, and outcome (PECO) screening criteria. Studies that met the PECO criteria were evaluated for data quality using pre-established metrics as specified in the 1,2-Dichloroethane Systematic Review Protocol (U.S. EPA, 2024b). Studies (based on the specified metrics) received overall data quality determinations of either Uninformative, Low, Medium, or High. The results and details of the data quality evaluation for 1,2-dichloroethane human health hazard are included in the *Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Supplemental File: Data Quality Evaluation Information for Human Health Hazard Epidemiology* (U.S. EPA, 2024e). This supplemental file is hereafter referred to as the 1,1-Dichloroethane Data Quality Evaluation Information for Human Health Hazard Epidemiology. The results and details of the data quality evaluation for 1,2-dichloroethane animal toxicity studies are included in the *Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Supplemental File: Data Quality Evaluation Information for Human Health Hazard Animal Toxicology* (U.S. EPA, 2024d). This supplemental file is hereafter referred to as 1,1-Dichloroethane Data Quality Evaluation Information for Human Health Hazard Animal Toxicology (U.S. EPA, 2024d) or OPPT SR review (U.S. EPA, 2024d).

Following data quality evaluation, EPA completed data extraction of the toxicological information from each on topic study that met the PECO criteria. This data extraction included studies of all data quality determinations including "uninformative." The results of data extraction for human and animal for 1,2-dichloroethane toxicity studies are reported in the *Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Supplemental File: Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology* (U.S. EPA, 2024c). This supplemental file is hereafter referred to as the 1,1-Dichloroethane Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology.

1.1.2 Summary and Structure of the Draft Human Health Hazard Assessment

EPA completed a hazard identification and evidence integration for 1,2-dichloroethane based on a review and evaluation of the results of the SR process including data quality evaluation and data extraction. The hazard identification and evidence integration completed for 1,2-dichloroethane are provided in Section 2 for toxicokinetics, Section 3 for non-cancer human and animal study data (stratified by organ system), Section 4 genotoxicity and evidence integration, Section 5 for cancer and evidence integration, Section 6 for dose-response assessment, Section 7 for potentially exposed or susceptible subpopulations, and Section 8 for PODs for non-cancer and cancer human health hazard endpoints.

2 TOXICOKINETICS

This section provides a summary on the absorption, distribution, metabolism, and elimination (ADME) data available for 1,2-dichloroethane.

2.1 Oral Route

Case reports and experimental animal studies were identified that provided useful data in evaluating absorption, distribution, metabolism, and excretion (ADME) of 1,2-dichloroethane for the oral route. Human studies were not identified specifically regarding the absorption of 1,2-dichloroethane following oral exposure, however, based on case studies that demonstrate the toxic effects (such as death) due to intentional(Yodaiken and Babcock, 1973; Lochhead and Close, 1951) or accidental(Hueper and Smith, 1935) ingestion, it can be inferred that 1,2-dichloroethane is rapidly absorbed into systemic circulation. With a K_{ow} of 1.48, 1,2-dichloroethane is lipophilic and is anticipated to traverse mucosal membranes within the gastrointestinal tract via passive diffusion (ATSDR, 2022). Experimental animal studies further support this conclusion.

Oral absorption is rapid and complete according to Reitz et al. (1982)and Spreafico et al. (1980) as cited in ATSDR (2022). In rats given a single gavage dose of 150 mg/kg of 1,2-dichloroethane in corn oil, peak blood concentrations were reached within 15 minutes and approximately 94 percent of the administered dose was absorbed within 48 hours Reitz et al. (1982). Spreafico et al. (1980) also demonstrated rapid oral absorption, with peak blood levels occurring between 30 and 60 minutes in rats given gavage doses of 25, 50, or 150 mg/kg of 1,2-dichloroethane in corn oil. Additionally, it is to be noted that at 3.3 minutes and 6.4 minutes, half of the 25 and 150 mg/kg doses were absorbed, respectively. This further emphasizes the rapid oral absorption of 1,2-dichloroethane. Examination of the peak blood level curves at the different doses shows a linear curve up to 50 mg/kg 1,2-dichloroethane and a decrease in steepness of the curve at 100 mg/kg, suggesting a relative saturation of oral absorption at doses exceeding 100 mg/kg. Additionally, in a study by Withey et al. (1983), rats given a single gavage dose of 100 mg/kg of 1,2-dichloroethane in corn oil or water, peak blood concentrations (C_{max}) were approximately 4-fold higher and the time to reach C_{max} was 3-fold faster following administration in water compared to corn oil, thus implicating the choice of the vehicle in affecting absorption rates. Similar findings regarding the rate of absorption were observed in rats given doses of 43 mg/kg/day in water or 150 mg/kg/day in corn oil via oral gavage with C_{max} values of 15 or 30 minutes in water and corn oil, respectively (Dow Chemical, 2006a). Based on these data from animal studies and the available, though limited, human evidence exposure to 1,2-dichloroethane via drinking water may be of concern to human health.

Distribution, based on experimental animal studies was also identified to be rapid following gavage dosing, with concentrations peaking first in the liver at 6 to 7 minutes, followed by lung at 10 to 20 minutes and adipose tissue at 20 to 60 minutes (MCA, 1979). Tissue levels were dose-dependent and the highest peak tissue concentration at any dose was detected in fat. Similar mean peak tissue levels in liver and lung were seen following 11 daily doses of 50 mg/kg, indicating that bioaccumulation does not occur in these tissues with multiple doses. Bioaccumulation in adipose tissue is suggested by higher peak adipose tissue levels after 11 gavage doses compared to a single gavage dose (Table 2-1).

Table 2-1. Tissue Levels and Time to Peak Tissue Level in Rats Exposed to 1,2-Dichloroethane by Gavage in Corn Oil

Organ/Peak Concentration/Time to Peak Concentration		Dose (mg/kg)			
		25 (Single)	50 (Single)	50 (11 Oral Doses)	150 (Single)
Liver	µg/g	30.02 ± 3.29	55.00 ± 4.12	53.12 ± 3.87	92.10 ± 7.58
	Minutes	6	6	6	7.5
Lung	µg/g	2.92 ± 0.38	7.20 ± 0.39	7.19 ± 0.59	8.31 ± 1.27
	Minutes	10	20	15	20
Adipose	µg/g	110.67 ± 6.98	148.92 ± 20.75	161.69 ± 9.93	259.88 ± 25.03
	Minutes	20	60	40	40
Source: (MCA, 1979)					

In pregnant rats exposed to a single dose of 160 mg/kg radiolabeled [^{14}C]-1,2-dichloroethane on gestation day (GD) 12, the highest tissue concentrations were found in the liver and intestine after 48 hours (radiolabel was also detected in the stomach, kidney, and ovary) Payan et al. (1995) as cited in ATSDR (2022). Distribution across the placenta was also demonstrated by detection of the radiolabeled 1,2-dichloroethane in the developing fetus within 1 hour; the maximum concentration was detected 4 hours after exposure Payan et al. (1995) as cited in ATSDR (2022). Administration of 160 mg/kg ^{14}C-1,2-dichloroethane on GD 18 showed a greater degree of accumulation in the developing fetuses and the placenta Payan et al. (1995) as cited in ATSDR (2022).

No human studies on the metabolism of 1,2-dichloroethane were located via the oral route, so the primary metabolic pathways for 1,2-dichloroethane was elucidated from *in vitro* studies and *in vivo* studies in rats and mice that include cytochrome P450 (CYP) oxidation and glutathione (GSH) conjugation (Figure 2-1) (IPCS, 1995). Metabolism by CYP results in an unstable gem-chlorohydrin that releases hydrochloric acid, resulting in the formation of 2-chloroacetaldehyde. 2-Chloroacetaldehyde is oxidized to form chloroacetic acid or reduced to form 2-chloroethanol, and these metabolites are conjugated with GSH and excreted in the urine (IPCS, 1995). Metabolism via glutathione-S-transferase results in formation of S-(2-chloroethyl)-glutathione, which rearranges to form a reactive episulfonium ion. The episulfonium ion can form adducts with protein, DNA or RNA or interact further with GSH to produce water soluble metabolites that are excreted in the urine (Figure 2-1) (IPCS, 1995). As depicted in Figure 2-1, 1,2-dichloroethane is directly reactive and forms chloroaldehydes, which can form persistent DNA cross-links (OECD, 2015).

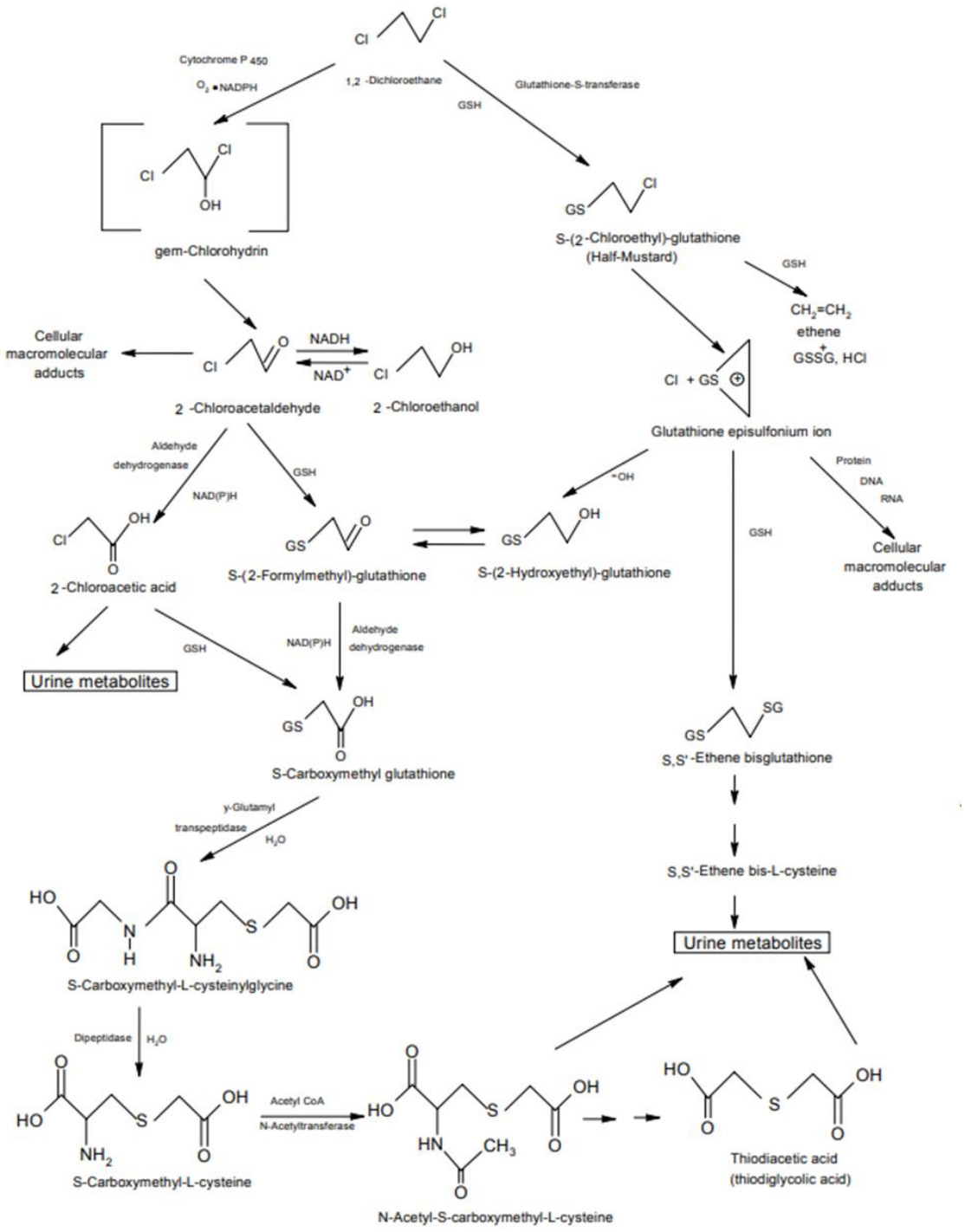

Figure 2-1. Proposed Metabolic Scheme for 1,2-Dichloroethane (IPCS, 1995)

In male rats exposed to a single oral dose of 150 mg/kg [^{14}C]-1,2-dichloroethane, 60 percent of the administered dose was detected as urinary metabolites and 29 percent was released unchanged in expired air, suggesting that metabolic saturation occurred at this dose (Reitz et al., 1982). Although urinary metabolites were not characterized in this study, a decrease in hepatic non-protein sulfhydryl content suggests that the glutathione (GSH) conjugation pathway was involved.

Animal studies were useful in demonstrating the elimination of 1,2-dichloroethane as being rapid following oral exposure, primarily via urinary excretion of water-soluble metabolites and exhalation of

unchanged compound or CO_2 (Payan et al., 1995; Mitoma et al., 1985; Reitz et al., 1982) as cited in ATSDR (2022). In rats given a single gavage dose of 150 mg/kg [^{14}C]-1,2-dichloroethane, elimination was 96 percent complete within 48 hours, with 60 percent of the radiolabel excreted as urinary metabolites (70 percent thiodiacetic acid, 26–28 percent thiodiacetic acid sulfoxide), 29 percent exhaled as unchanged 1,2-dichloroethane, 5 percent exhaled as CO_2, and the remaining 6 percent recovered in feces, carcass, and cage washes (Reitz et al., 1982). The elimination kinetics were described as biphasic with an initial elimination half-life (t½) of 90 minutes, followed by a t½ of approximately 20 to 30 minutes when blood levels were 5 to 10 µg/mL (Reitz et al., 1982).

In a study by Mitoma et al. (1985), rats and mice given gavage doses of 100 and 150 mg/kg [^{14}C]-1,2-dichloroethane, respectively, following pretreatment with unlabeled 1,2-dichloroethane 5 days/week for 4 weeks, resulted in a recovery of radiolabel in excreta (urine and feces) at 69.5 percent in rats and 81.9 percent in mice after 48 hours. Exhalation of the radiolabeled/non-radiolabeled 1,2-dichloroethane compounds and CO_2 accounted for 11.5 and 8.2 percent, respectively, in rats and 7.7 and 18.2 percent, respectively, in mice. The recovery of radiolabel in the carcass was 7 percent of the administered dose in rats and 2.4 percent of administered dose in mice (Mitoma et al., 1985).

The excretion of thioglycolic acid and other thioether metabolites were measured in rat urine 24 hours after gavage administration of 0.25, 0.5, 2.02, 4.04, or 8.08 mmol/kg (25, 50, 200, 400, or 800 mg/kg) [^{14}C]-1,2-dichloroethane (Payan et al., 1993). The total concentration of urinary metabolites increased linearly with administered doses between 25 and 400 mg/kg; however, the percentage of the administered dose excreted in the urine decreased with increasing dose level, likely due to metabolic saturation and ranging from 63 to 7.4 percent (Payan et al., 1993).

2.2 Inhalation Route

Case reports and experimental animal studies were identified that provided useful data in evaluating absorption, distribution, metabolism, and excretion (ADME) of 1,2-dichlorethane for the inhalation route. As 1,2-dichloroethane possesses a high vapor pressure of 79 mmHg at 20°C and a high blood/air partition coefficient estimated to be 19.5 ± 0.7 in humans and 30.4 ± 1.2 in F344 rats the absorption of 1,2-dichloroethane may be attributed to passive diffusion across the alveolar membranes (Gargas et al., 1989). This has been demonstrated by the presence of 1,2-dichloroethane in the breast milk of nursing women exposed to 15.6 ppm (63 mg/m^3)of 1,2-dichloroethane in workplace air (with concurrent dermal exposure) (Urusova, 1953). A fatal case report by Nouchi et al. (1984)identified a poisoning due to exposure to 1,2-dichloroethane in an enclosed space for 30 minutes. Although the air concentrations were not measured in this incidence, it can be inferred that the absorption of 1,2-dichloroethane occurred rapidly thus providing support for absorption through the lungs. This rapid absorption by inhalation has also been supported in animal studies. In studies by Reitz et al. (1982); Reitz et al. (1980) peak blood levels approached a steady-state of 8 µg/mL within 1 to 2 hours after a 6 hour inhalation exposure to 150 ppm (607 mg/m^3)of 1,2-dichloroethane. Furthermore, exposure to 50 ppm (202 mg/m^3) of 1,2-dichloroethane in a study by Spreafico et al. (1980) also identified similar peak blood levels. An inhalation exposure of 250 ppm 1,2-dichloroethane in the same study by Spreafico et al. (1980) and in Dow Chemical (2006a), however, did not reach a steady state until 3 hours post-exposure. In rats exposed to 150 ppm (607 mg/m^3) ^{14}C-1,2-dichloroethane for 6 hours, approximately 93 percent absorption occurred, based on recovery of radiolabel in urine and feces and as CO_2 in expired air by 48 hours Reitz et al. (1982).

Distribution, based on reports in humans indicated that 1,2-dichloroethane was detected in the breath (14.3 ppm/58 mg/m^3) and breast milk (0.54–0.64 mg percent [per 100 mL]) of nursing mothers 1 hour after leaving an occupational facility with exposure concentrations of 15.6 ppm (63 mg/m^3)1,2-

dichloroethane Urusova (1953) as cited in ATSDR (2022). It needs to be noted that this measurement suggests a rapid distribution of 1,2-dichloroethane, yet these data can be attributed to prior exposures prior to the sampling. Various animal studies have been identified that demonstrate the distribution profile of 1,2-dichloroethane further. In a study in rats following a 6-hour inhalation exposure to 50 or 250 ppm (202 or 1011 mg/m^3) 1,2-dichloroethane, it was observed that 1,2-dichloroethane was readily distributed in various tissue in a concentration-dependent manner Spreafico et al. (1980). Additionally, among the tissues evaluated by Spreafico et al. (1980), peak tissue levels in liver and lung were lower than concentrations in blood, but adipose tissue levels were 8 to 9 times higher than blood levels Spreafico et al. (1980)(see Table 2-2). Furthermore, the distribution equilibrium occurred within 2 hours and 3 hours of the 50 ppm and 250 ppm (202 and 1011 mg/m^3) exposures, respectively.

Table 2-2. Tissue Levels and Time to Peak Tissue Level in Rats Exposed by Inhalation to 1,2-Dichloroethane for 6 Hours

Organ/Peak Concentration/ Time to Peak Concentration		Concentration (ppm)	
		50	250
Blood	µg/g	1.37 ± 0.11	31.29 ± 1.19
	Hours	6	6
Liver	µg/g	1.14 ± 0.17	22.49 ± 1.12
	Hours	4	6
Lung	µg/g	0.42 ± 0.05	14.47 ± 1.12
	Hours	4	3
Adipose	µg/g	11.08 ± 0.77	273.32 ± 12.46
	Hours	4	6
Source: Spreafico et al. (1980) as cited in ATSDR (2022)			

A similar study in male rats exposed to 160 ppm (648 mg/m^3) 1,2-dichloroethane for 6 hours showed the highest tissue levels of 1,2-dichloroethane in abdominal fat Take et al. (2013).

As indicated in Section 2.1, due to no human studies on the metabolism of 1,2-dichloroethane being available, the primary metabolic pathways for 1,2-dichloroethane via the inhalation route are also based on *in vitro* and *in vivo* studies in rats and mice. Thus, the proposed metabolic pathways for the oral route is also applicable to the inhalation route (see Figure 2-1). Additional studies also outline metabolism as near complete in rats exposed to 150 ppm (607 mg/m^3) of [^{14}C]-1,2-dichloroethane for 6 hours, with 84 percent of radiolabel excreted as urinary metabolites and 2 percent released as unchanged compound in expired air Reitz et al. (1982). Urinary metabolites were not characterized; however, a decrease in the hepatic non-protein sulfhydryl content suggest involvement of the GSH conjugation pathway. In a rat inhalation study comparing blood concentrations resulting from exposure to 50 or 250 ppm (202 and 1011 mg/m^3), peak blood levels of 1,2-dichloroethane were 22-fold higher at the higher concentration Spreafico et al. (1980). Taken together, these results suggest that metabolic saturation occurs at a concentration between 150 and 250 ppm (607 and 1011 mg/m^3) for 1,2-dichloroethane, corresponding to blood levels of 5 to 10 µg/mL (Reitz et al., 1982; Spreafico et al., 1980).

Urusova (1953) showed that 1,2-dichloroethane was detected in expired air of women occupationally exposed to 15.6 ppm (63 mg/m^3) by inhalation. Similar findings were noted in women exposed by dermal contact only in this study as well. In rats exposed via inhalation, elimination occurred by excretion of metabolites in urine and exhalation of unchanged compound or CO_2 (Reitz et al., 1982;

Spreafico et al., 1980). Following inhalation of 150 ppm (607 mg/m^3) [^{14}C]-1,2-dichloroethane for 6 hours, elimination from the blood was near complete by 48 hours, with 84 percent of the dose detected as urinary metabolites (70 percent thiodiacetic acid, 26–28 percent thiodiacetic acid sulfoxide), 2 percent excreted unchanged in feces, and 7 percent exhaled as CO_2 (Reitz et al., 1982). The elimination kinetics of 1,2-dichloroethane in rats were described as monophasic with t½ values of 12.7 and 22 minutes at inhalation concentrations of 25 and 250 ppm (100 to 1011 mg/m^3) 1,2-dichloroethane, respectively (Spreafico et al., 1980). Excretion was dose-dependent with the percentage exhaled as unchanged 1,2-dichloroethane increased at the highest concentration; elimination from adipose tissue was slower than elimination from blood, liver, or lungs (Spreafico et al., 1980).

In male mice exposed to 25, 87, or 185 ppm (100, 350, or 700 mg/m^3) 1,2-dichloroethane for 6 hours, elimination was rapid, with clearance of parent compound from the blood near complete within 1 hour after exposure (Zhong et al., 2022). In a 28-day study in male mice also exposed to 25, 87, or 185 ppm (100, 350, or 700 mg/m^3) for 6 hours/day, 5 days/week, 2-chloroacetic acid was detected as the primary metabolite in urine at concentrations of 300, 1,000, and 1,300 µg/L, respectively (Liang et al., 2021).

2.3 Dermal Route

As no studies were located regarding distribution following dermal exposure to 1,2-dichloroethane in animals and EPA was not able to identify neither human studies nor *in vivo* animal data that evaluated metabolism of 1,2-dichloroethane following exposure by the dermal route, case reports and animal studies did provide some useful information regarding the toxicokinetic profile of 1,2-dichloroethane via the dermal route regarding absorption, distribution (in humans) and elimination.

In the study by Urusova (1953), an increase in the presence of 1,2-dichloroethane was observed in the breast milk of nursing women due to concurrent dermal and inhalation exposure within the workplace with peak levels of 2.8 mg/100 mL within 1 hour. This observation by Urusova (1953) suggests that percutaneous absorption to contaminated water or directly to the 1,2-dichlorethane may be a key route to exposure in humans. Although the analytical methodology for this study were not provided in detail to allow for a thorough assessment, other *in vivo* animal studies have demonstrated that 1,2-dichloroethane is readily absorbed through the skin (Morgan et al., 1991; Jakobson et al., 1982; Tsuruta, 1975).

In guinea pigs dermally exposed to neat 1,2-dichloroethane, using a covered dermal cell on clipped intact skin, blood concentrations rose rapidly during the first 30 minutes and continued to increase over a 12-hour period (Jakobson et al., 1982). Tsuruta (1975) estimated a percutaneous absorption rate of 480 nmol/minute/cm^2 for 1,2-dichloroethane through the clipped, intact abdominal skin of mice following a 15-minute exposure using a closed dermal cell. Application of neat 1,2-dichloroethane to the shaved backs of rats using covered dermal cells resulted in approximately 50 percent absorption of the applied dose with the peak blood level measured at 24 hours (Morgan et al., 1991). Dermal absorption was faster and more complete for aqueous solutions of 1,2-dichloroethane, with peak blood levels measured within 1 to 2 hours and greater than 99 percent of the applied dose absorbed within the 24-hour exposure period (Morgan et al., 1991).

Additionally, 1,2-dichloroethane was detected in expired air of women occupationally exposed by dermal contact only (gas masks were worn to prevent inhalation) (Urusova, 1953).

2.4 Parenteral Routes, *In Vitro* Studies, and Physiologically-Based Pharmacokinetic (PBPK) Modeling Approach

2.4.1 Parenteral Routes

Although not identified as a key route of exposure to 1,2-dichloroethane, these studies can provide information regarding the toxicokinetic profile. In mice administered a single intravenous injection radiolabel 1,2-dichloroethane, high levels of radioactivity were identified in the nasal mucosa and tracheobronchial epithelium within 1 minute of injection that continued through the 4 day observation period of the study (Brittebo et al., 1989). Radioactivity to a lesser extent were found in the epithelia of the upper alimentary tract, the eyelid, vagina, liver, kidney, adrenal cortex, and submaxillary salivary gland (Brittebo et al., 1989). The localization of the radioactivity found in the study by Brittebo et al. (1989), was considered to be of non-volatile metabolites of 1,2-dichloroethane formed within those tissue rather than the parent chemical. In a study by Withey and Collins (1980), rats that were dosed with a single 15 mg/kg intravenous dose of 1,2-dichloroethane to investigate 1,2-dichloroethane kinetics identified fat is the preliminary distribution site as compared to the other tissues that were evaluated (brain, kidney, spleen, liver, lung, and heart).

2.4.2 Studies

As mentioned earlier, due to no human studies on the metabolism of 1,2-dichloroethane being identified, the primary metabolic pathways for 1,2-dichloroethane, were elucidated from *in vitro* studies and *in vivo* studies in rats and mice. This section aims to focus on the *in vitro* studies identified to illustrate the metabolic profile for 1,2-dichloroethane.

In vitro studies using rat and human liver microsomes have demonstrated that oxidative metabolism via CYP2E1 results in the formation of 2-chloroacetaldehyde by dechlorination of an unstable chlorohydrin molecule (Guengerich et al., 1991; Casciola and Ivanetich, 1984; McCall et al., 1983; Guengerich et al., 1980). GSH conjugation of 1,2-dichloroethane was demonstrated in primary rat hepatocytes resulting in the formation of S-(2-hydroxyethyl) glutathione, S-(carboxymethyl) glutathione, and S,S'-(1,2-ethanediyl)bis(glutathione), and GSH depletion was observed (Jean and Reed, 1992). The S-(carboxymethyl) glutathione metabolite likely results from conjugation of 2-chloroacetic acid with GSH (Johnson, 1967). This metabolite can be degraded to form glycine, glutamic acid, and S-carboxymethylcysteine, which may be oxidized to yield thiodiglycolic acid (see Figure 2-1) (IPCS, 1995). Metabolic rate constants were determined using rat liver microsomes and substrate concentrations between 50 µM and 1 mM (V_{max} = 0.24 nmol/minute per mg protein; K_m = 0.14 mM) (Salmon et al., 1981).

In vitro studies using skin from humans, pigs, and guinea pigs have reported apparent partition coefficients (K_p), steady-state flux (J_{ss}) values, and lag time estimates (*i.e.*, the time to achieve a steady-state concentration) (see Table 2-3). In human skin, 0.1 to 0.2 percent of the applied dose was absorbed over 24 hours, with the maximum flux occurring within 10 minutes of exposure (Gajjar and Kasting, 2014). Evaporation from the skin surface accounted for the majority of applied dose in this study. Specifically, it was determined that 0.21 percent of the lowest dermal administration of 7.9 mg/cm^2 and 0.13 percent of the highest dose of 63.1 mg/cm^2 was absorbed by the skin over a 24 hour period. The K_p and lag time values for 1,2-dichloroethane were similar for human and guinea pig skin (Frasch and Barbero, 2009); however, the dermal permeability rate was lower in pig skin (decreased K_p value; longer lag time) (Schenk et al., 2018). In guinea pig skin, the flux was lower in saturated aqueous solution compared to the undiluted test substance (Frasch et al., 2007). This result appears to differ from the *in*

vivo study using the shaved skin of rats, which showed a higher percent absorption for an aqueous solution of 1,2-dichloroethane compared to a neat application (Morgan et al., 1991).

Table 2-3. 1,2-Dichloroethane Partition Coefficients Steady State Estimates

Partition Coefficients (K_p) Steady-State Flux (J_{ss}) Estimates from *In Vitro* Dermal Absorption Studies					
Species	**Test Material(s)**	**K_p (cm/hour)**	**J_{ss} (µg/cm²-hour)**	**Lag Time (minutes)**	**Reference**
Human	Neat	ND	37–193[a]	ND	Gajjar and Kasting (2014)
Human Guinea pig	Neat Neat	0.259 0.259	ND ND	6 6	Frasch and Barbero (2009)
Pig	Neat	1.9E−03	1,360	30.7	Schenk et al. (2018)
Guinea pig	Neat Aqueous	ND ND	6,280[b] 1,076	ND ND	Frasch et al. (2007)

[a] Range of Jss values for applied doses of 7.9, 15.8, 31.5, or 63.1 mg/cm².
[b] Also reported a Jss value of 3,842 µg/cm²-hour from a different laboratory.
ND = not derived

Tissue:air partition coefficients calculated using a vial equilibration method and tissues obtained from male Fischer 344 rats suggest that 1,2-dichloroethane is preferentially distributed to highly perfused tissues and will accumulate in fat (see Table 2-4) (Dow Chemical, 2006a; Gargas and Andersen, 1989).

Table 2-4. 1,2-Dichloroethane Tissue:Air Partition Coefficients

Partition Coefficient							
Blood:Air	**Liver:Air**	**Muscle:Air**	**Fat:Air**	**Brain:Air**	**Kidney:Air**	**Testis:Air**	**Ovary:Air**
30.4 ± 1.2[a]	35.7 ± 1.6[a]	23.4 ± 1.4[a]	344 ± 5[a]	39.5 ± 2.89[b]	44.89 ± 6.77[b]	31.14 ± 7.98[b]	74.59 ± 9.82[b]

[a] Gargas and Andersen (1989).
[b] Dow Chemical (2006a).

2.4.3 Physiologically-Based Pharmacokinetic (PBPK) Modeling Approach

Two PBPK models were developed to describe the disposition of 1,2-dichloroethane. The D'Souza et al. (1988); D'Souza et al. (1987)model used five compartments (lung, liver, richly perfused tissues, slowly perfused tissues, and fat) and assumed that metabolism occurs only in the liver and lung. Metabolic pathways included a saturable oxidation pathway and GSH conjugation. This PBPK model, which was validated in rats and mice, predicted that inhalation produces less GSH-conjugate metabolites (measured as GSH depletion in the liver) than gavage exposure.

Sweeney et al. (2008)extended and updated the D'Souza et al. (1988); D'Souza et al. (1987) model by adding two gastrointestinal compartments, a compartment for the kidney, and an additional metabolism pathway for extrahepatic enzymes. Model parameter values that were revised included the oral absorption rate, time delay constant for GSH synthesis following depletion, and GSH levels in liver and lung tissue. Model predictions were compared to experimental rat data for intravenous, oral, and inhalation routes, and the model performed well for single and repeated exposure. Because the model has not been validated in humans, it is unclear whether this model would be useful for extrapolating between rats and humans (ATSDR, 2022).

2.5 Summary

Toxicokinetic data indicates that orally administered 1,2-dichloroethane is rapidly metabolized in the body with the primary metabolic pathways mediated by cytochrome P450 and glutathione conjugation.

Upon absorption via the oral and inhalation routes, 1,2-dichloroethane is readily distributed to various tissues, including breast milk, with the highest concentrations found in adipose tissue. Tissue distribution patterns of 1,2-dichloroethane revealed that absorption from the gastrointestinal tract is rapid with peak steady-state blood concentrations within one hour after oral exposure, 2-3 hours after inhalation exposure and 1-2 hours after dermal exposure (for aqueous solutions).

Metabolites of 1,2-dichloroethane via inhalation are rapidly excreted as illustrated by animal studies with almost complete elimination within 48 hours post-exposure primarily in urine in the form of the metabolites thiodiglycolic acid and thiodiglycolic acid sulfoxide (84 percent) and to a lesser extent in feces and expired air (7 percent as CO_2). Specifically for oral exposure, 1,2-dichloroethane is excreted via the urine and feces, however, a large percent (29 percent) is excreted unchanged in expired air.

3 NON-CANCER HAZARD IDENTIFICATION AND EVIDENCE INTEGRATION

The sections below describe adverse outcome and mechanistic data available as well as evidence integration conclusions for each human health hazard outcome observed in 1,2-dichloroethane toxicity studies. EPA identified very few epidemiological studies relevant to non-cancer endpoints. Therefore, evidence is primarily based on available laboratory animal toxicity studies—exclusively via the oral and inhalation routes.

The 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) describes the general process of evidence evaluation and integration, with relevant updates to the process presented in the 1,2-Dichloroethane Systematic Review Protocol (U.S. EPA, 2024b). Section 3.1 provides a detailed evaluation of the 1,2-dichloroethane hazard outcomes and evidence integration conclusions. The analyses are presented as a series of evidence integration tables in Appendix B for 1,2-dichloroethane (non-cancer) and Appendix C for 1,2-dichloroethane (cancer).

3.1 Critical Human Health Hazard Outcomes

The sections below focus on hazard identification and evidence integration of kidney toxicity, immunotoxicity, and neurotoxicity, which are the most sensitive critical human health hazard outcomes associated with 1,2-dichloroethane. These hazard outcome categories received *likely* evidence integration conclusions, and sensitive health effects were identified for these hazard outcomes. In the risk evaluation, renal toxicity forms the basis of the POD used for acute oral exposure scenarios and immunotoxicity is the basis of the POD used for short-term and chronic oral exposure scenarios. The 2022 ATSDR document for 1,2-dichloroethane confirmed that immunotoxicity is the most sensitive endpoint (ATSDR, 2022). Neurotoxicity is the basis of the POD used for acute inhalation exposure and reproductive effects is the basis for short-term/subchronic and chronic inhalation exposure scenarios. Due to a lack of adequate dermal studies, dermal hazard was based on route-to-route extrapolation from oral exposure. Additionally, hazard identification and evidence integration of other toxicity outcomes are also outlined to emphasize the integration of the identified health outcomes of 1,2-dichloroethane.

3.1.1 Renal Toxicity

Humans

EPA did not identify epidemiological studies that evaluated any potential renal hazards for 1,2-dichloroethane.

Laboratory Animals

A review of high and medium quality acute, subchronic, and chronic studies identified studies that indicated renal effects following 1,2-dichloroethane exposure.

Oral

B6C3F1 mice in the Storer et al. (1984) study that were administered a single oral gavage dose of 1,2-dichloroethane at 0, 100, 200, 300, 400, 500, or 600 mg/kg-bw resulted in kidney weights increased at 300 mg/kg-bw doses and greater. In support, L-iditol dehydrogenase (IDH, 9-fold increase) and blood urea nitrogen (BUN) indicated a trend increase at 200 mg/kg-bw and greater doses but was not statistically significant due to the low number of animals tested (N = 5).

In the Morel et al. (1999) acute single exposure oral gavage study in male Swiss OF1 mice treated with 0, 1,000, or 1,500 mg/kg-bw of 1,2-dichloroethane, a significant increase in damaged renal tubules (7.66

vs. 0.32 percent in controls) was seen only seen in the highest dose group with the lowest dose already above the limit dose.

In the subchronic 90 day (7 day/week for 13 weeks) oral gavage study by Daniel et al. (1994), male and female Sprague-Dawley rats treated with 0, 37.5, 75, or 150 mg/kg-bw/day of 1,2-dichloroethane resulted in increased relative kidney weights in both males and females (18 and 15 percent higher than controls, respectively) at the 75 and 150 mg/kg-bw/day.

The subchronic 90-day oral gavage study in Wistar rats by van Esch et al. (1977) dosed at 0, 10, 30 or 90 mg/kg-bw/day of 1,2-dichloroethane resulted in a significant increase in relative kidney weight of 17 and 16 percent higher than controls in males and females in the 90 mg/kg-bw/day, respectively.

In the subchronic study by NTP (1991), oral gavage of 1,2-dichloroethane at the dosages of 0, 30, 60, 120, 240 or 480 mg/kg-bw/day for 13 weeks in male F344 rats, resulted in significant increases in absolute kidney weights at 30, 60, and 120 mg/kg/day (9, 21 and 25 percent, respectively) and significant increases in relative kidney weights at 60 and 120 mg/kg-bw/day doses (15 and 26 percent, respectively). Female F344 rats dosed at 0, 18, 37, 75, 150, or 300 mg/kg/day at 5 days/week via oral gavage for 13 weeks caused significant increases in absolute kidney weights (12 and 23 percent) and relative kidney weights (10 and 21 percent) at 75 and 150 mg/kg-bw/day, respectively.

Inhalation

Storer et al. (1984) identified increased serum BUN (85 percent) and relative kidney weight (12 percent) in B6C3F1 male mice as compared to controls after a 4 hour exposure to 1,2-dichloroethnae vapor of 499 ppm (2,020 mg/m^3). Increased mortality at concentrations greater than 499 ppm precluded a more thorough evaluation of these effects in this study and subsequent dose-response analysis.

Mechanistic

EPA did not identify mechanistic studies that evaluated any potential renal hazards for 1,2-dichloroethane.

Evidence Integration Summary

There were no human epidemiological nor mechanistic studies available for 1,2-dichlorethane and therefore, there is *indeterminate* human evidence and mechanistic support to assess whether 1,2-dichloroethane can cause renal changes in humans. The evidence in animal studies for 1,2-dichloroethane is *moderate* based on several high- and medium-quality studies that found associations between 1,2-dichloroethane exposure and increased kidney weights, BUN, and/or renal tubular histopathology in rats (both sexes) and mice following inhalation, oral, dermal, and intraperitoneal injection exposures.

Overall, EPA concluded that evidence indicates that 1,2-dichloroethane likely causes renal effects under relevant exposure circumstances.

3.1.2 Immunological/Hematological

Humans

EPA did not identify epidemiological studies that evaluated any potential immunological/hematological hazards for 1,2-dichloroethane.

Laboratory Animals

A review of high- and medium-quality acute, subchronic, and chronic studies identified studies that indicated immunological/hematological effects following 1,2-dichloroethane exposure.

Oral

Munson et al. (1982)—a study in male CD-1 mice administered 1,2-dichloroethane by oral gavage for 14 days at doses of 0, 4.9, and 49 mg/kg-bw/day—resulted in decreased antibody-forming cells with immunosuppression at adverse 25 and 40 percent levels at the 4.9 and 49 mg/kg-bw/day dose groups, respectively. Suppression of cell-mediated immune responses were also indicated at both dosages. A decrease in leukocytes at approximately 30 percent was reported in the highest dosage group. No effects were observed regarding the organ weights of the liver, spleen, lungs, thymus, kidney, or brain. Additionally, hepatic clinical chemistry also remained unchanged. It is important to note that the ATSDR (2022) document concluded that the immune system was the most sensitive target, but it also considered this 14-day study in the acute duration category, so it was not utilized for the subchronic or chronic PODs.

Inhalation

In the study by Sherwood et al. (1987), female CD-1 mice exposed to 1,2 dichloroethane for 3 hours at 5.4 ppm (22 mg/m^3) resulted in mortality following streptococcal challenge but it is important to note that the inoculation with the bacteria was unlikely representative of a human equivalent immunological challenge. Male SD rats in the same study did not exhibit any effects to the streptococcal immunological challenge after exposures up to 200 ppm (801 mg/m^3). In addition, in Sherwood et al. (1987), identified no effects in female CD-1 mice or male SD rats due to streptococcal challenge after 1,2-dichloroethane inhalation exposure for 5 or 12 days in the mice or rats, respectively.

Mechanistic

EPA identified mechanistic studies that indicated potential immunological/hematological hazards for 1,2-dichloroethane. Immunosuppression is a recognized characteristic of carcinogens and tumors were reported for 1,2-dichloroethane in various studies. An *in vitro* study utilizing human Jurkat immune T cells indicated cytotoxicity by 1,2-dichloroethane and other similar chlorinated solvents such as trichloroethylene, perchloroethylene and dichloromethane McDermott and Heffron (2013). Human Jurkat T cell death at 5 and 10 percent responses occurred at concentrations of 157 and 379 micromolar, respectively. Importantly, these 1,2-dichloroethane cytotoxic concentrations are similar to milk levels in female workers (*i.e.*, 283 micromolar) and blood levels in rats (*i.e.*, 1.36 mM), both via dermal exposures (ATSDR, 2022); McDermott and Heffron (2013). That study also reported increases in reactive oxygen species and increased cellular calcium levels by 1,2-dichloroethane and other similar chlorinated solvents such as trichloroethylene, perchloroethylene and dichloromethane. Cell death caused by 1,2-dichloroethane and the other similar chlorinated solvents trichloroethylene, perchloroethylene and dichloromethane was, however, inhibited by the antioxidant N-acetylcysteine. Additionally, 1,2-dichloroethane possessing immunological/hematological effects is demonstrated in an *in vitro* study that identified reduced phagocytic activity of mouse peritoneal macrophages to 76 percent of control levels at a concentration of 200 mM (Utsumi et al., 1992). Cell-free and *in vitro* studies that investigated 1,2-dichloroethane effects on human erythrocyte glutathione-S-transferase (GST) by (Ansari et al., 1987) resulted in dose-related reductions in the GST enzymatic activity.

Evidence Integration Summary

There were no human epidemiological studies available for 1,2-dichloroethane and therefore, there is *indeterminate* human evidence to assess whether 1,2-dichloroethane may cause immunological/ hematological changes in humans. Limited mechanistic evidence based on *in vitro* data that showed reductions in macrophage phagocytic activity and erythrocyte GST activity after exposure to 1,2-dichloroethane was also considered to be *indeterminate*.

Available toxicological studies based on high-quality inhalation and gavage studies of immune function in mice indicated an association between 1,2-dichloroethane exposure and immunosuppression was observed. A more limited inhalation study in rats and a longer-term drinking water study in mice that was rated uninformative did not show any effects. Evidence from other studies showed only small effects on hematology and no effects on relevant organ weights or histopathology. Based on this information, evidence based on animal studies for 1,2-dichloroethane, suggests the immunological/ hematological effects as *slight*.

Overall, EPA concluded that robust weight of scientific evidence (WOSE) information indicates that 1,2-dichloroethane likely causes immune system suppression under relevant exposure conditions to both animals and humans. This conclusion is supported by multiple lines of evidence such as the cytotoxicity to human Jurkat T cells *in vitro* at relevant human tissue levels, the cell mediated immunosuppression in mice at the lowest-observable-adverse-effect level (LOAEL) of 4.89 mg/kg/day, decreased leukocytes count in mice. In support, the 1,2-dichloroethane ATSDR (2022) authoritative document concluded that "the immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice."

3.1.3 Neurological/Behavioral

Humans

Chlorinated aliphatic solvents are known to cause central nervous system depression, and respiratory tract and dermal irritation in humans (ATSDR, 2015). Case reports of human exposure to 1,2-dichloroethane by inhalation or ingestion indicated clinical signs of neurotoxicity (dizziness, tremors, paralysis, coma) as well as histopathology changes in the brain at autopsy (ATSDR, 2022). Workers exposed to 1,2-dichloroethane for extended periods were shown to develop cerebral edema and toxic encephalopathy (ATSDR, 2022). A single study of Russian aircraft manufacturing workers noted decreased visual-motor reaction and decreased upper extremity motor function, as well as increased reaction making errors in workers exposed to 1,2-dichloroethane compared to those that were not, however the results were only described qualitatively and no statistical analyses were conducted, and the study was determined to be uninformative by systematic review (Kozik, 1957).

Laboratory Animals

A review of high and medium quality acute, subchronic, and chronic studies identified studies that indicated neurological/behavioral effects following 1,2-dichloroethane exposure.

Oral

Male and female F344/N rats in the (NTP, 1991) study administered 1,2-dichloroethane at dosages of 0, 30, 60, 120, 240, or 480 mg/kg/day (males) and 0, 18, 37, 75, 150, or 300 mg/kg/day (females) in corn oil via gavage, 5 days/week for 13 weeks in the resulted in death in all males in the 240 and 480 mg/kg/day groups and 9/10 of the females in the 300 mg/kg/day group, respectively, with the identified presence of necrosis in the cerebellum at the highest dose group. In addition, clinical signs observed in the 240 and 300 mg/kg/day groups of male and female rats included tremors and abnormal posture.

Inhalation

Male SD rats exposed to 1.5 hours of 1,2-dichloroethane in Zhou et al. (2016) were shown to develop histological changes in the brain as denoted by edema at 975.9 ppm (3,950 mg/m^3).

Neurotoxicity and histological changes in the brains of SD rats exposed to 1,2-dichloroethane for 12 hours was seen in a study by Qin-li et al. (2010) at a LOAEL of 5,000 mg/m^3 as indicated by abnormal behavior and edema, however, details regarding the histological severity of edema were not provided.

In the acute Dow Chemical (2006b) inhalation study, histological changes and injury were identified in the olfactory mucosa of F344/DUCRL rats exposed for 4 or 8 hours to 1,2-dichlorethane vapor at 100 and 200 ppm (405 and 809 mg/m^3), respectively. The effect on the olfactory mucosa is also considered neurological as this tissue is neuroepithelial in nature.

Mechanistic

EPA identified mechanistic studies that suggest 1,2-dichloroethane can result in brain edema due to a downregulation of tight junction proteins (occludin and ZO-1) and mRNA, increase of free calcium, decreased ATP content, and decrease ATPase activity in the brains of mice after an exposure of to 296 ppm (1,200 mg/m^3) for 3.5 hours/day for 3 days (Wang et al., 2018a; Wang et al., 2014).

Evidence Integration Summary

Case reports document clinical signs of neurotoxicity and brain histopathology changes in humans exposed to 1,2-dichloroethane by inhalation or ingestion as well as the ability of 1,2-dichloroethane to downregulate tight junction proteins and energy production while also upregulating aquaporin and matrix metalloproteinase in the brains of exposed mice. Based on these human epidemiological and mechanistic data available for 1,2-dichloroethane, the evidence is *slight* for an association between 1,2-dichloroethane and adverse neurological effects. Several high- and medium-quality studies using rats exposed to 1,2-dichloroethane by inhalation or gavage or mice exposed by intraperitoneal injection showed the occurrence of neurobehavioral changes, clinical signs of neurotoxicity, or changes in brain histopathology. Therefore, EPA determined that the animal evidence for adverse neurological/behavioral effects based on these data are *moderate* for the association between 1,2-dichloroethane and adverse neurological/behavioral effects.

Overall, EPA concluded that evidence indicates that to 1,2-dichloroethane likely causes neurological/ behavioral effects under relevant exposure circumstances.

3.1.4 Reproductive/Developmental

Humans

EPA did not locate adequate human epidemiology studies for 1,2-dichloroethane that could be utilized for a non-cancer dose response analysis and the overall non-cancer, 1,2-dichloroethane epidemiology literature is considered indeterminate for non-cancer health effects. The Brender et al. (2014) study found associations between any exposure to 1,2-dichloroethane and neural tube defects and spina bifida; however, exposure was estimated based on maternal residential proximity to industrial point sources of emissions rather than using a measured level of exposure. Additionally, two studies of 1,2-dichloroethane presence in drinking water and congenital anomalies found a relationship between 1,2-dichloroethane detection and major cardiac defects in newborns, but the same relationship was not significant when comparing odds of major cardiac defects between newborns with 1,2-dichloroethane water concentrations above 1 ppb vs. equal to or below 1 ppb (Bove, 1996; Bove et al., 1995).

Laboratory Animals

A review of high and medium quality acute, subchronic, and chronic studies identified studies that indicated reproductive/developmental effects following 1,2-dichloroethane exposure.

Oral

Sprague-Dawley dams that were administered 1,2-dichloroethane by gavage at doses of 0, 1.2, 1.6, 2.0, and 2.4 mmol/kg (corresponding to 0, 120, 160, 200, and 240 mg/kg-bw/day in the Payan et al. (1995) study during gestation day (GD) 6 to GD 21 resulted in increases in non-implantations and resorptions. The increases in non-implants and resorptions are difficult to interpret given the significant maternal toxicity (decreases in maternal body weight gain) observed at corresponding doses (30 and 49 percent at 200 and 240 mg/kg/day, respectively), and because there was no effect on the number of live fetuses per litter despite changes in non-surviving implants/litter and resorption sites/litter.

Inhalation

Rao et al. (1980), a reproductive/developmental study in pregnant SD rats exposed to 1,2-dichloroethane vapor at 0, 100, or 300 ppm (0, 405, 1214 mg/m^3) or during GD 6 to 15, identified a significant decrease in bilobed thoracic centra incidences. However, due to increased incidence in maternal mortality a dose-response evaluation could not be performed on this effect. Additionally, a multi-generational evaluation by Rao et al. (1980) also identified decreased body weight of F1B male weanlings as a result of exposure to 150 ppm (613 mg/m^3) for 6 hours/day for 7 weeks *in utero*.

Exposure to pregnant SD rats to 1,2-dichloroethane in Payan et al. (1995) indicated a significant decrease in pregnancy rate at 250 ppm (1,000 mg/m^3); however, this effect was not seen at the highest concentration of 300 ppm (1,200 mg/m^3).

Zhang et al. (2017), a reproductive study that evaluated the effects of 1,2-dichloroethane on male Swiss mice following a 4-week exposure period, resulted in changes in sperm morphology and concentration along with decreased seminiferous tubules and the height of germinal epithelium at 25 ppm (102 mg/m^3).

Mechanistic

Male mice treated with 86 ppm or 173 ppm (350 or 700 mg/m^3) of 1,2-dichlorethane for 4 weeks resulted in an inhibition of the cyclic adenosine monophosphate (cAMP)-response element binding (CREB) protein and the cAMP-response element modulator (CREM), subsequently inducing apoptosis, and resulting in reproductive toxicity in male mice as indicated by a decrease in sperm concentration of greater than 25 percent (4.65 ± 0.52 vs. 3.30 ± 0.57 M/g) in the control vs. 700 mg/m^3 treated animals, respectively (Zhang et al., 2017).

Evidence Integration Summary

In high- and medium-quality studies, associations were observed between 1,2-dichloroethane exposure and various birth defects (neural tube defects including spina bifida and heart defects of different types). However, the effect sizes were small with associations that were weak and, in some cases, based on very low group sizes. Results of the two available epidemiological studies were also not consistent (neural tube defects/spina bifida in one study but not the other; different types of cardiac defects in the two studies) and both studies were limited in various ways, including incomplete data on neural tube defects, potential exposure misclassification, questionable temporality, and co-exposures to other chemicals that were also associated with the same defects. Based on these evaluations, the evidence of reproductive/developmental effects due to 1,2-dichloroethane was considered *indeterminate* for these effects.

In high-quality studies, mice exposed to 1,2-dichloroethane by inhalation or intraperitoneal injection, but not by drinking water, exhibited effects on testicular pathology and sperm parameters. Most of the data in rats indicated no effect on the testes (or other reproductive organs); however, sperm parameters were not evaluated in rats. Thus, the evidence for effects on the male reproductive tract was considered *moderate*. Evidence was considered *moderate* based on inhalation studies in rats, oral studies in rats and mice, and a dermal study in mice that all indicated no effects of 1,2-dichloroethane on female reproductive organ weights or histopathology. With regard to developmental effects, a high-quality study on 1,2-dichlorethane indicated sterility in male mice exposed by intraperitoneal injection. In addition, evidence for effects on weanling pup body weight after 1,2-dchloroethane inhalation exposure was considered weak and inconsistent. Thus, evidence was considered *slight* for developmental effects due to 1,2-dichloroethane.

Mechanistic evidence for reproductive/developmental effects based on inhibition of CREM/CREB signaling and the occurrence of apoptosis in testes of male mice exposed to 1,2-dichloroethane *in vivo* to support observed effects on testes pathology, sperm morphology, and fertility in this species was considered *moderate*.

Overall, EPA concluded that the evidence indicates that 1,2-dichloroethane likely causes effects on male reproductive structure and/or function under relevant exposure conditions. The nature of the effect chosen for calculating risks—changes in sperm morphology and concentration identified by Zhang et al. (2017)—is considered adverse, and the fertility of human males is known to be sensitive to changes in sperm numbers and quality (U.S. EPA, 1996). The evidence is, however, inadequate to determine whether 1,2-dichloroethane may cause effects on the developing organism and there is no evidence that 1,2-dichloroethane causes effects on female reproductive structure and/or function.

3.1.5 Hepatic

Humans

A single study of liver damage markers in the blood of vinyl chloride workers showed abnormal levels of aspartate aminotransferase (AST) and alanine transaminase (ALT) in the moderate 1,2-dichloroethane exposure intensity group compared with the low 1,2-dichloroethane exposure intensity group; however, all participants were also exposed to low levels of vinyl chloride monomer, which may also affect liver enzyme levels (Cheng et al., 1999).

Laboratory Animals

A review of high and medium quality acute, subchronic, and chronic studies identified studies that indicated hepatic effects following 1,2-dichloroethane exposure.

Oral

In Cottalasso et al. (2002), a single gavage of 628 mg/kg-bw of 1,2-dichloroethane in female SD rats after 16 hours of fasting resulted in increased ALT, AST, and lactate dehydrogenase (LDH) at 45, 44, and 67 percent as compared to controls, respectively. Histological examination also identified moderate steatosis.

In the 10-day oral gavage study by Daniel et al. (1994), male and female SD rats administered 0, 10, 30, 100, or 300 mg/kg-bw/day of 1,2-dichloroethane exhibited significantly increased relative liver weights (14 percent relative to controls) and serum cholesterol levels in male rats alone at 100 mg/kg-bw/day.

The short-term, 10-day oral gavage study in Wistar rats by van Esch et al. (1977) dosed at 0, 3, 10, 30, 100, or 300 mg/kg-bw/day 1,2-dichloroethane resulted in death of all animals in the 300 mg/kg-bw/day, which upon subsequent histological evaluation showed extensive liver vacuolization and lipid droplets.

In the subchronic, 90-day (7 day/week for 13 weeks) oral gavage study by Daniel et al. (1994), male and female SD rats treated with 0, 37.5, 75, or 150 mg/kg-bw/day of 1,2-dichloroethane resulted in a 20 percent increase in relative liver weights in only male rats at 75 mg/kg-bw/day.

The subchronic, 90-day oral gavage study in male Wistar rats by van Esch et al. (1977) dosed at 0, 10, 30, 90 mg/kg-bw/day resulted in a significantly increase in relative liver weight of 13 percent higher than controls in females at the highest dose. However, this change was not accompanied by any changes in serum enzymes or liver histopathology.

Inhalation

Exposure to 1,2-dichloroethane for 4 hours at 499 ppm (2,020 mg/m^3) via inhalation in Storer et al. (1984) identified increased serum ALT (2-fold) and SDH (11-fold) in B6C3F1 male mice as compared to controls.

Absolute and relative liver weights in male Swiss mice at greater than or equal to 10 percent as compared to controls was indicated in a 6 hours/day for 28 days study by Zeng et al. (2018) at a concentration of 89.83 ppm (364 mg/m^3) of 1,2-dichloroethane.

IRFMN (1978), in a chronic 12-month study in both male and female SD rats, resulted in an increase of ALT and LDH in both sexes when exposed to 50 ppm (200 mg/m^3) of 1,2-dichloroethane.

Mechanistic

In the study by Storer et al. (1984), B6C3F1 mice were administered a single dose of 1,2-dichloroethane at 100, 200, 300, or 400 mg/kg via oral gavage in corn oil or to 100, 150, 200, or 300 mg/kg by intraperitoneal injection and euthanized 4 hours later. It was identified that a statistically significant increase in DNA damage in hepatic nuclei was present in all dose groups via oral administration and at doses greater or equal to 150 mg/kg via intraperitoneal injection, as characterized by single-strand breaks, when compared to controls.

Evidence Integration Summary

There were no adequate human epidemiological studies available for 1,2-dichloroethane; therefore, there is *indeterminate* human evidence to assess whether 1,2-dichloroethane may cause hepatic changes in humans. The only human epidemiological study was considered inadequate due to confounding associated with co-exposure to vinyl chloride. Limited *in vitro* data indicate that 1,2-dichloroethane may increase DNA damage, cause oxidative stress, or impair glucose and/or lipid metabolism in mice and in rat hepatocytes and liver slices; however, this information suggests that overall mechanistic evidence for hepatic effects is *indeterminate*. Several high- and medium-quality studies in rats and mice found associations between 1,2-dichloroethane exposure and increased liver weights, serum enzymes, or histopathology changes following inhalation, oral, and intraperitoneal injection exposures. Based on these studies, EPA determined that the animal evidence for adverse effects on the liver are *moderate* for the association between 1,2-dichloroethane and adverse hepatic effects.

Overall, EPA concluded that evidence suggests, but is not sufficient to conclude, 1,2-dichloroethane can cause hepatic toxicity under relevant exposure circumstances.

3.1.6 Nutritional/Metabolic

Humans

EPA did not identify epidemiological studies that evaluated any potential nutritional/metabolic hazards for 1,2-dichloroethane.

Laboratory Animals

A review of high- and medium-quality acute, subchronic, and chronic studies identified studies that indicated nutritional/metabolic effects following 1,2-dichloroethane exposure.

Oral

In the study by Payan et al. (1995), pregnant SD rats exposed to 1,2-dichloroethane via oral gavage exhibited a decrease in absolute maternal body weight during GD 6 to 21 relative to controls. The short-term NTP (1978), preliminary, dose-range finding study in male and female Osborne-Mendel rats gavaged with 0, 40, 63, 100, 150 or 251 mg/kg-bw/day of 1,2-dichloroethane for 5 days/week for 6 weeks suggested body weight effects during exposure. However, due to the lack of quantitative data provided in the study report, a thorough evaluation of the data could not be performed.

Inhalation

Male and female albino guinea pigs were exposed, whole body, to 1,2-dichloroethane vapor concentrations of 100, 200, and 400 ppm (405, 809, or 1619 mg/m^3) for 246 days (at 200 ppm/809 mg/m^3) and up to 212 days (at 100 ppm/405 mg/m^3) by (Spencer et al., 1951) that demonstrated, statistically significant reductions in final body weights were observed in males (16 percent) and females (9 percent), compared with air-only controls at 200 ppm (809 mg/m^3).

Mechanistic

EPA did not identify mechanistic studies that evaluated any potential nutritional/metabolic hazards for 1,2-dichloroethane.

Evidence Integration Summary

Because there were no human epidemiological or mechanistic studies available for 1,2-dichloroethane, there is *indeterminate* human evidence and mechanistic support to assess whether 1,2-dichloroethane can cause nutritional/metabolic changes in humans. The evidence is considered *slight* for animal studies for 1,2-dichloroethane based on decreased body weight as reported in mice and guinea pigs exposed by inhalation and rats and mice exposed orally to 1,2-dichloroethane in high- and medium-quality studies. In addition, several high- and medium-quality studies in a few species via various routes of exposure reported no effect on body weight, sometimes at lower exposure levels or shorter exposure durations to 1,2-dichloroethane.

Overall, EPA concluded that 1,2-dichloroethane may cause nutritional/ metabolic effects under relevant exposure conditions.

3.1.7 Respiratory

Humans

EPA did not identify epidemiological studies that evaluated any potential respiratory hazards for 1,2-dichloroethane.

Laboratory Animals

A review of high- and medium-quality acute, subchronic, and chronic studies identified that demonstrate respiratory effects following 1,2-dichloroethane exposure.

Oral

In the study by Salovsky et al. (2002), a single oral dose of 136 mg/kg-bw 1,2-dichloroethane in male Wistar rats resulted in increased total number of cells in the bronchioalveolar lavage fluid (BALF) at 30 days after dosing. Non-inflammatory histological changes such as cyanosis, interstitial edema, vacuolar changes, desquamative changes, atelectasis, and alveolar macrophage proliferation were also seen in the lungs. Inflammatory histological such as macrophage proliferation that was mixed with a small number of neutrophils and eosinophils) occurred in the peribronchial (mild degree on GD 5 and mild-moderate on GDs 15 and 30), interstitial (mild-moderate on GDs 5 and 30 and moderate on GD 15), and interbronchial (mild on GD 1 and mild-moderate on GD 5) regions. These histological data were only presented qualitatively.

Inhalation

In the acute Dow Chemical (2006b) inhalation study, histological changes and injury were identified in the olfactory mucosa of F344/DUCRL rats exposed for 4 or 8 hours to 1,2-dichloroethane vapor at 100 and 200 ppm (405 and 809 mg/m^3), respectively.

Mechanistic

EPA did not identify mechanistic studies that evaluated any potential respiratory hazards for 1,2-dichloroethane.

Evidence Integration Summary

Because there no human epidemiological or mechanistic studies are available for 1,2-dichloroethane, there is *indeterminate* human evidence and mechanistic support to assess whether 1,2-dichloroethane can cause respiratory tract changes in humans. In a high-quality study, an association between 1,2-dichloroethane inhalation exposure and nasal lesions was observed in rats exposed to concentrations greater or equal to 435 mg/m^3 (≥107.5 ppm). Although one medium-quality study reported lung lesions in rats after a single gavage dose, high- and medium- quality studies of longer duration and higher doses, as well as a high-quality study of acute inhalation exposure, did not show effects of 1,2-dichloroethane on lower respiratory tract tissues of rats. Based on this, evidence from animal studies was considered *slight to moderate*.

Overall, EPA concluded that the evidence suggests, but is not sufficient to conclude, that 1,2-dichloroethane can cause lower respiratory tract effects under relevant exposure conditions.

3.1.8 Mortality

Humans

EPA identified two limited retrospective cohort studies that found no increase in mortality of workers from either petrochemical or herbicide manufacturing plants with presumed exposure to 1,2-dichloroethane relative to the general United States population (BASF, 2005; Teta et al., 1991).

Laboratory Animals

A review of high-and medium-quality acute, subchronic, and chronic studies identified studies that indicated mortality following 1,2-dichloroethane exposure.

Oral

The short-term, 10 day oral gavage study in male Wistar rats by van Esch et al. (1977) dosed at 0, 3, 10, 30, 100, or 300 mg/kg-bw/day 1,2-dichloroethane resulted in death of all animals in the 300 mg/kg-bw/day exposure group.

Inhalation

In the study by Francovitch et al. (1986), male CD-1 mice treated with 1,2-dichloroethane for 4 hours via inhalation resulted in a dose-related increase in mortality beginning at a concentration of 1,000 ppm (4,050 mg/m^3).

Male SD rats exposed via inhalation to 1,2-dichloroethane for 7 hours/day for 5 days/weeks resulted in the occurrence of mortality starting at 304 ppm (1,230 mg/m^3) (Igwe et al., 1986b).

Female SD rats exposed to 300 ppm (1,210 mg/m^3) 1,2-dichloroethane resulted in increased incidences in mortality in dams when exposed for 10 days during GDs 6 to 15 (Rao et al., 1980). Additionally, in Rao et al. (1980), New Zealand white rabbits treated with 1,2-dichloroethane for 7 hours/day during the 13 days of GD 6 to 18 also showed increased incidences of maternal mortality beginning at the exposure concentration of 100 ppm (405 mg/m^3).

In the study by Payan et al. (1995), female SD rats treated with 1,2-dichloroethane resulted in increased incidence of maternal death at a LOAEL of 329 ppm (1,330 mg/m^3).

Mechanistic

EPA did not identify mechanistic studies that evaluated any potential mortality hazards for 1,2-dichloroethane.

Evidence Integration Summary

Limited epidemiological data show no increase in mortality among workers with presumed exposure to 1,2-dichloroethane but are insufficient to draw any broader conclusions. Therefore, there is *indeterminate* human evidence to assess whether 1,2-dichloroethane may cause mortality in humans. Because there are no mechanistic studies available for 1,2-dichloroethane, there is *indeterminate* mechanistic support to assess whether 1,2-dichloroethane may cause mortality in humans. The evidence is considered *robust* with regard to animal studies of 1,2-dichloroethane as treatment-related increases in the incidence of mortality were observed in several animal species exposed to 1,2-dichloroethane via inhalation, oral, or dermal exposure for acute, short-term/intermediate, or chronic durations in multiple studies.

Overall, EPA concluded that the evidence indicates that 1,2-dichloroethane may cause death under relevant exposure circumstances and lethal levels have been identified in animal studies.

4 GENOTOXICITY HAZARD IDENTIFICATION AND EVIDENCE INTEGRATION

1,2-Dichloroethane is considered a "probable human carcinogen" (U.S. EPA, 1987b) based on evidence of tumorigenicity in animal studies, including significant increases in tumors of the mammary gland (robust evidence), lung (moderate evidence), liver (slight-to-moderate evidence), circulatory system (slight evidence) and other tissues (indeterminate evidence) in male and/or female rats and/or mice by oral, inhalation, and/or dermal exposure (see Appendix C). The occurrence of tumors in multiple tissues and treated groups is suggestive of a genotoxic mode of action, and most data relating to mode of action for 1,2-dichloroethane carcinogenicity are assays for genetic toxicity. Recent comprehensive reviews (ATSDR, 2022; Gwinn et al., 2011) were used to develop an overview of genotoxicity data for 1,2-dichloroethane and the role of metabolism, which is presented below. Potential nongenotoxic modes of action for rat mammary tumors were investigated in one study (Lebaron et al., 2021). Brief discussions of the information (both genotoxic and non-genotoxic mechanisms) that pertain to specific tumor sites associated with 1,2-dichloroethane exposure (mammary gland, lung, liver, and circulatory system) follow the general genotoxicity discussion.

Genotoxicity Overview

Evidence from *in vivo* studies using multiple animal species and routes of exposure and *in vitro* studies using multiple test systems indicates that 1,2-dichloroethane and/or its metabolites can induce mutations, chromosomal aberrations, DNA damage, and DNA adducts in certain test systems. The available data show that biotransformation of 1,2-dichloroethane to reactive metabolites via a major CYP450-mediated oxidative pathway and a minor glutathione conjugation pathway contributes to the observed effects. There are species-, sex-, tissue-, and dose-related differences in the interactions between 1,2-dichloroethane and/or its metabolites and DNA.

Evidence that 1,2-dichloroethane induces gene mutation is based largely on *in vitro* studies. Reverse mutation studies in *Salmonella typhimurium* were predominantly positive, especially with metabolic activation (ATSDR, 2022; Gwinn et al., 2011). Mutagenicity was seen more consistently in *Salmonella* strains that detect base-pair substitutions (*e.g.*, TA1535) than those that detect frameshift mutations (*e.g.*, TA97) (ATSDR, 2022; Gwinn et al., 2011). Mutations at the HGPRT locus were increased in Chinese hamster ovary (CHO) cells in the presence of metabolic activation, both when 1,2-dichloroethane was incorporated in media (Tan and Hsie, 1981) and when cells were exposed to 1,2-dichloroethane as a vapor in a closed system (Zamora et al., 1983). There are limited gene mutation data from *in vivo* studies. Oral and inhalation studies assessing various types of mutations in *Drosophila* were generally positive, but many of the studies were limited by lack of methodological details and/or the use of a single exposure level (ATSDR, 2022; Gwinn et al., 2011). A single study of *lacZ* mutations in the liver and testis of Muta^{TM} mice showed no increase in the mutation frequency after exposure to 1,2-dichloroethane by oral or intraperitoneal administration at doses up to 150 or 280 mg/kg-bw, respectively (Hachiya and Motohashi, 2000).

In vivo rodent studies showing clastogenic effects, DNA damage, and DNA adducts in the mammary gland, lung, liver, and circulatory system tissues are discussed in the subsections below on potential mechanisms for carcinogenicity in these tissues. A small number of *in vivo* studies of genotoxicity endpoints in other tissue types showed evidence of DNA damage (Comet assay) in mouse kidney, bladder, and brain (Sasaki et al., 1998); and DNA binding or DNA adducts in mouse and rat stomach, forestomach, and kidney (Watanabe et al., 2007; Hellman and Brandt, 1986; Inskeep et al., 1986; Prodi et al., 1986; Arfellini et al., 1984) after exposure by intraperitoneal injection.

Role of Metabolism

Available data are not sufficient to determine whether metabolism of 1,2-dichloroethane is a necessary first step in its genotoxic action. *In vitro* studies in bacteria have shown that exogenous metabolic activation is either required for, or increases the mutagenic activity of, 1,2-dichloroethane (ATSDR, 2022; Gwinn et al., 2011). In contrast, experiments in human lymphocytes cultured *in vitro* with 1,2-dichloroethane showed increased micronucleus formation in the absence of S9, but not in the presence of S9 (Tafazoli et al., 1998).

Evidence suggests that metabolism of 1,2-dichloroethane, especially via the glutathione pathway, does lead to increased genotoxicity. Crespi et al. (1985) compared the genotoxicity of 1,2-dichloroethane in human cell lines with differing metabolic capacities. Crespi et al. (1985) observed 25-fold higher HGPRT mutation frequencies in AHH-1 compared with TK6 human lymphoblastoid cells. The study authors measured 5-fold greater glutathione-S-transferase activity in the AHH-1 cells than the TK6 cells, suggesting that the glutathione metabolic pathway increased the frequency of mutations induced by 1,2-dichloroethane.

Several studies have inhibited or stimulated enzymes to elucidate the relative importance of the CYP450 and glutathione pathways in 1,2-dichloroethane genotoxicity. In Ames assays, supplementation of the media with glutathione or glutathione-S-transferase increases the mutagenicity of 1,2-dichloroethane (ATSDR, 2022; Gwinn et al., 2011). *Drosophila melanogaster* pretreated with buthionine sulfoximine (BSO, an inhibitor of glutathione synthesis) before inhalation exposure to 1,2-dichloroethane exhibited reduced mutations (measured using somatic mutation and recombination tests [SMARTs]) compared with those that were not pretreated (Romert et al., 1990). Pretreatment of fruit flies with an inducer of glutathione-S-transferase (phenobarbital) significantly increased mutation frequency (Romert et al., 1990). In support of these findings, Chroust et al. (2001) observed increased mutagenicity in transgenic fruit flies expressing human glutathione-S-transferase (A1 subunit), an effect that was mitigated by pretreatment with BSO.

Inhibition of CYP450 metabolism has been shown to potentiate DNA damage and increase DNA binding from exposure to 1,2-dichloroethane. In rats exposed to piperonyl butoxide in addition to 1,2-dichloroethane (via intraperitoneal injection), increased levels of hepatic DNA damage (measured with alkaline DNA unwinding assay) were seen in comparison to the levels in rats treated with 1,2-dichloroethane alone (Storer and Conolly, 1985). Similarly, increased DNA binding in the liver, kidney, spleen, and testes was observed in rats exposed to 1,2-dichloroethane by inhalation with concurrent dietary exposure to the CYP450 inhibitor disulfiram (relative to 1,2-dichloroethane exposure alone) (Igwe et al., 1986a).

Mammary Gland Cancer Mechanisms

Lebaron et al. (2021) conducted *in vivo* experiments to assess potential mechanisms of rodent mammary tumors induced by 1,2-dichloroethane. The study authors exposed female F344 rats by inhalation to 0 or 200 ppm (809 mg/m^3) 1,2-dichloroethane for 6 hours/day on at least 28 consecutive days. At sacrifice, blood samples were obtained for assessment of serum prolactin, and mammary tissues were collected for histopathology and assays of epithelial cell proliferation (Ki-67 immunohistochemistry), DNA damage (Comet assay), and levels of glutathione, reduced glutathione, and oxidized glutathione. There was no difference between exposed and control groups for any of these endpoints, nor was there an effect of exposure on 8-oxo-2'-deoxyguanosine (8-OHdG) adduct levels, a marker of oxidative DNA damage. Exposure to 1,2-dichloroethane did, however, induce a significant increase in S-(2-N7-guanylethyl) glutathione DNA adducts, as also found in the liver in this and other studies. *In vitro* studies have shown these adducts to be mutagenic (Gwinn et al., 2011). Lebaron et al. (2021), however, argue that *in vivo*

evidence does not support this conclusion and that these adducts should be considered biomarkers of exposure, rather than mutagenic adducts.

No other data on potential mechanisms were located. The DNA adducts in mammary tissue resulting from 1,2-dichloroethane exposure *in vivo* could plausibly be related to subsequent formation of mammary tumors, although the role of these adducts in carcinogenicity of 1,2-dichloroethane has not been conclusively demonstrated.

Lung Cancer Mechanisms

Studies relevant to carcinogenic mechanisms of 1,2-dichloroethane-induced lung cancers are limited to measurements of DNA damage in the lung of mice exposed by intraperitoneal injection (Sasaki et al., 1998) and quantification of DNA adducts in the lungs of rats and mice also exposed by intraperitoneal injection (Baertsch et al., 1991; Prodi et al., 1988). Increased DNA damage (measured by alkaline single cell gel [SCG] assay and compared with measurement at time 0) was observed in the lungs of mice when measured 3 or 24 hours after dosing with 200 mg/kg 1,2-dichloroethane (Sasaki et al., 1998). DNA binding in the lungs of female rats was observed after 12 hours of inhalation exposure to ^{14}C-1,2-dichloroethane (Baertsch et al., 1991). Prodi et al. (1988) observed higher binding of ^{14}C-1,2-dichloroethane to DNA in the lungs of mice compared with rats, consistent with the susceptibility of mice, but not rats, to 1,2-dichloroethane-induced lung tumors (Nagano et al., 2006). Experiments on binding of radiolabeled 1,2-dichloroethane to calf thymus DNA in the presence of microsomes and/or or cytosol from mouse and rat lung indicated binding in the presence of lung-derived microsomes (containing CYP450), but not cytosol (containing glutathione-S-transferase) (Prodi et al., 1988).

In an *in vitro* experiment, Matsuoka et al. (1998) observed dose-related increases in chromosomal aberrations in Chinese hamster lung fibroblast (CHL) cells when incubated with 1,2-dichloroethane in the presence of S9. In the absence of S9, the results were judged to be equivocal (Matsuoka et al., 1998).

No other data on potential mechanisms were located. The observed genotoxic effects and DNA binding/adduct formation in lung tissue following 1,2-dichloroethane exposure *in vitro* and *in vivo* could plausibly be related to subsequent formation of lung tumors, although a direct connection between these events and 1,2-dichloroethane-induced lung carcinogenesis has not been conclusively demonstrated.

Liver Cancer Mechanisms

One study evaluated potential mutations in the livers of animals exposed to 1,2-dichloroethane. Hachiya and Motohashi (2000) measured the frequency of hepatic tissue *lacZ* mutations in the Muta^{TM} Mouse model 14 and 28 days after single gavage doses up to 150 mg/kg-bw or after repeated intraperitoneal injections resulting in cumulative doses up to 280 mg/kg-bw. No increase in mutation frequency was observed in the liver in any of the experiments.

When measured 3 and 24 hours after mice were exposed to 1,2-dichloroethane by intraperitoneal injection, an increase in DNA damage in the liver was detected by alkaline SGC assay (when compared to levels seen at time 0) (Sasaki et al., 1998). Significant decreases in the percentage of double-stranded DNA were observed in mice given single intraperitoneal doses of 300 mg/kg (Taningher et al., 1991) or 2 and 3 mmol/kg (200 and 300 mg/kg) (Storer and Conolly, 1983). Storer et al. (1984) assessed route differences in DNA damage in the livers of mice exposed by gavage (100–400 mg/kg), intraperitoneal injection (100-300 mg/kg), and inhalation (4 hours at 150–2,000 ppm/607–8095 mg/m^3). The fraction of double stranded DNA was significantly decreased in a dose-related fashion at all doses (≥100 mg/kg) after gavage administration, at doses greater than or equal to 150 mg/kg after intraperitoneal injection, and at concentrations greater than or equal to 1,000 ppm 4047 mg/m^3) after inhalation exposure. While

the lower doses producing DNA damage by oral and intraperitoneal exposure did not produce systemic effects in parallel groups of similarly-treated mice, all concentrations producing DNA damage by inhalation exposure were lethal to the similarly exposed mice (Storer et al., 1984). In a study comparing alkylation of hepatic DNA in rats and mice exposed to 1,2-dichloroethane by intraperitoneal injection, higher levels of alkylation were observed in mice compared with rats (at least 40-fold higher in the first 30 minutes after dosing) (Banerjee, 1988).

Binding of 1,2-dichloroethane or its metabolites to hepatic DNA of rats and mice exposed *in vivo* has been demonstrated in a number of studies (Lebaron et al., 2021; Watanabe et al., 2007; Baertsch et al., 1991; Prodi et al., 1988; Inskeep et al., 1986). Available data show sex-, species-, and dose-related differences in adduct levels. For example, an early study that compared DNA adduct levels in the livers of male rats and mice exposed to 1,2-dichloroethane by intraperitoneal injection (127 µCi/kg) showed higher binding in mouse compared to rat (Prodi et al., 1988). In contrast, in hepatic tissue from male and female mice and male rats exposed by intraperitoneal administration of a much lower dose of 1,2-dichloroethane (21 µCi/kg, corresponding to 5 mg/kg), the highest levels of adducts were in female mice (57 fmol/mg DNA), followed by male rats (46 fmol/mg DNA) and male mice (29 fmol/mg DNA) (Watanabe et al., 2007). In rats exposed by inhalation (50 ppm/202 mg/m^3) for 2 years and then given a single oral dose of radiolabeled 1,2-dichloroethane, no exposure-related difference in DNA adduct levels was detected (Cheever et al., 1990). Notably, this exposure level also failed to induce an increase in tumors at any site.

DNA adducts from the glutathione metabolic pathway have been demonstrated to occur in the livers of laboratory rodents exposed *in vivo*. In mice and rats administered 5 mg/kg 1,2-dichloroethane by intraperitoneal injection, the primary adduct was S-(2-N7-guanylethyl) glutathione (Watanabe et al., 2007). Similarly, in rats given 150 mg/kg ^{14}C-1,2-dichloroethane by intraperitoneal injection and sacrificed 8 hours later, prominent adducts in the liver were identified by high-performance liquid chromatography (HPLC) as S-[2-(N7-guanyl) ethyl]glutathione and S-[2-(N7-guanyl)ethyl]cysteinylglycine (Inskeep et al., 1986). Also, after 28 days of inhalation exposure to 200 ppm (809 mg/m^3) 1,2-dichloroethane, a significant increase in S-(2-N7-guanylethyl) glutathione DNA adducts was detected in the livers of female rats (Lebaron et al., 2021). As discussed above for mammary tumors, there is some uncertainty as to the toxicological significance of these adducts. While *in vitro* studies have shown these adducts to be mutagenic (Gwinn et al., 2011), Lebaron et al. (2021) argue that *in vivo* evidence does not support this conclusion and that these adducts should be considered biomarkers of exposure, rather than mutagenic adducts.

One study was located presenting *in vitro* data pertaining to the genotoxicity of 1,2-dichloroethane in the liver. In this study, 1,2-dichloroethane induced DNA repair in both rat and mouse primary hepatocytes (Milman et al., 1988).

No other data on potential mechanisms were located. The observed DNA damage and DNA binding/adduct formation in liver tissue following exposure to 1,2-dichloroethane *in vitro* and *in vivo* could plausibly be related to subsequent formation of liver tumors, although a direct connection between these events and 1,2-dichloroethane-induced liver carcinogenesis has not been conclusively demonstrated.

Circulatory System Cancer Mechanisms

Data pertaining to mechanisms of circulatory system cancers induced by 1,2-dichloroethane consist of genotoxicity studies, including one *in vivo* study in rats (Lone et al., 2016), three *in vivo* studies in mice (Witt et al., 2000; Sasaki et al., 1998; Giri and Que Hee, 1988), and three *in vitro* experiments in human

lymphoblastoid cells or lymphocytes (Tafazoli et al., 1998; Doherty et al., 1996; Crespi et al., 1985). Rats exposed by intraperitoneal injection to doses of 80.7, 161.4, or 242.1 mg/kg-bw exhibited statistically significant, dose-related increases in the incidences of chromosomal aberrations and micronuclei in bone marrow, as well as DNA damage (measured by alkaline comet assay) in blood cells (Lone et al., 2016). In mice exposed by intraperitoneal injection, significant increases in sister chromatid exchange frequencies (Giri and Que Hee, 1988) and DNA damage (Sasaki et al., 1998) were observed in bone marrow. However, 90 days of drinking water exposure to 1,2-dichloroethane (up to 8000 mg/L) did not increase the frequency of micronuclei in mice (Witt et al., 2000). A study of workers exposed to 1,2-dichloroethane and vinyl chloride showed increased sister chromatid exchanges in the blood of those exposed to moderate levels of 1,2-dichloroethane with low levels of vinyl chloride exposure (Cheng et al., 2000).

Several *in vitro* genotoxicity experiments were conducted in cells of the circulatory system. Increases in mutations (measured using the hypoxanthine-guanine phosphoribosyltransferase [HGPRT] assay) and micronuclei were observed in human lymphoblastoid cells cultured with 1,2-dichloroethane (Doherty et al., 1996; Crespi et al., 1985). Incubation with 1,2-dichloroethane resulted in increased micronuclei and DNA damage (by Comet assay) in human peripheral lymphocytes in the absence of exogenous metabolic activation (Tafazoli et al., 1998).

No other data on potential mechanisms were located. The observed genotoxic effects of 1,2-dichloroethane in hematopoietic cells and tissues *in vitro* and *in vivo* could plausibly be related to subsequent formation of tumors, although a direct connection between these events and 1,2-dichloroethane-induced circulatory system cancers has not been conclusively demonstrated.

Summary

1,2-Dichloroethane is likely to be carcinogenic to humans based on evidence of tumorigenicity in animal studies, including multiple tumor sites in male and/or female rats and/or mice by oral, inhalation, and/or dermal exposure. The occurrence of tumors in multiple tissues and treated groups is suggestive of a genotoxic mode of action, and most data relating to mode of action for 1,2-dichloroethane carcinogenicity are assays for genetic toxicity. Evidence from *in vivo* studies using multiple animal species and routes of exposure and *in vitro* studies using multiple test systems indicates that 1,2-dichloroethane and/or its metabolites can induce mutations, chromosomal aberrations, DNA damage, and DNA binding/adduct formation in certain test systems. The available data also show that biotransformation of 1,2-dichloroethane to reactive metabolites via a major CYP450-mediated oxidative pathway and a minor glutathione conjugation pathway contributes to the observed effects. *In vivo* and *in vitro* data showing genotoxicity and DNA binding/adduct formation in tissues where tumors associated with 1,2-dichloroethane exposure have been observed (mammary gland, lung, liver, and circulatory system) support that these effects could plausibly be related to formation of tumors in these tissues, although a direct connection between these events and 1,2-dichloroethane-induced carcinogenesis has not been conclusively demonstrated. Potential nongenotoxic modes of action were explored only in one study of rat mammary tissue, and no supporting results were obtained.

5 CANCER HAZARD IDENTIFICATION AND EVIDENCE INTEGRATION

Evidence in Humans

The 1,2-dichloroethane human epidemiology literature is similarly indeterminate as to whether 1,2-dichloroethane exposure causes cancer due to a lack of published studies. A few studies showed significant relationships between 1,2-dichloroethane and certain types of cancers, however these relationships existed in very specific subgroups and were not consistent across exposure groups, which limits our ability to draw conclusions from their results. For example, although Niehoff et al. (2019) found a slight increase in the risk for ER+ invasive breast cancer in the fourth quintile of exposure as compared with the first, this relationship was not significant in the fifth quintile of exposure as compared with the first. This study also did not find a significant relationship between 1,2-dichloroethane exposure and overall incidence of breast cancer, which was consistent with the only other study investigating this relationship (Garcia et al., 2015). Similarly, 1,2-dichloroethane exposure was associated with a borderline significant increase in pancreatic cancer, but only among Black females with low estimated exposure intensity (and not medium or high exposure intensity) (Kernan et al., 1999). Studies of brain cancer and kidney cancer showed no significant relationship with 1,2-dichloroethane exposure (Dosemeci et al., 1999; Austin and Schnatter, 1983).

Another study observed higher incidence of all-cause cancer than was expected in a cohort of workers when compared to the general population, but the statistical significance of this result was not reported, and the significance of all-cause cancer is not clear (BASF, 2005). This same study looked at many specific cancer SIRs as well, but none were statistically significantly elevated except for prostate cancer, which no other studies in the literature reported observing. Sobel et al. (1987) did not show a statistically significant relationship between 1,2-dichloroethane exposure and soft-tissue sarcoma, but also had very low statistical power with a sample size of seven 1,2-dichloroethane exposed participants. In general, more studies would be needed to draw conclusions about the weight of evidence for the relationship between 1,2-dichloroethane exposure and cancer from the epidemiologic literature, and none of the existing studies measured exposure in a way that could be used to estimate a quantitative dose-response relationship.

Evidence in Animals

Systematic review identified three high-quality 1,2-dichloroethane cancer studies available in animals. The NTP (1978) cancer study for 1,2-dichloroethane in Osborne-Mendel rats and B6C3F1 mice provides evidence of the carcinogenicity treated by oral gavage for 78 weeks. Male rats had significantly increased incidence of forestomach squamous-cell carcinomas and circulatory system hemangiosarcomas. Significant increases in mammary adenocarcinoma incidence in female rats and mice were observed. Alveolar/bronchiolar adenomas developed in mice of both sexes and females developed endometrial stromal polyps and sarcomas, while males developed hepatocellular carcinomas. However, the rat study for 1,2-dichloroethane was not utilized for cancer slope factor derivation due to the excessive animal deaths and pre-cancerous endometrial polyps in mice for 1,2-dichloroethane are not considered for cancer slope factor analysis. In addition, the high incidence of death in the rat study caused it to have an “uninformative” rating in systematic review, so cancer slope factors were not modeled from this data set.

In contrast, the oral cancer study in mice performed by NTP (1978) on 1,2-dichloroethane resulted in tumor types or pre-cancerous lesions (*i.e.*, hepatocellular carcinomas, endometrial polyps, hemangiosarcomas, and mammary gland tumors). The NTP (1978) oral study in 1,2-dichloroethane also

showed an excellent dose response for hepatocellular carcinomas (Figure 5-1). As a result, the cancer slope factor for 1,2-dichloroethane was selected from the NTP (1978) study in mice, which had a high systematic review rating (see Table 8-4). An oral cancer slope factor of 6.2×10^{-2} (mg/kg)/day was calculated and is in agreement with U.S. EPA (1987a) that also calculated a cancer slope factor on these data from hepatocellular carcinomas in male mice treated with for 1,2-dichloroethane.

A 26-week (3 times/week) 1,2-dichloroethane study in CB6F1-Tg rasH2@Jcl (rasH2) mice by Suguro et al. (2017) was considered for dermal exposure. In this study, mice dermally exposed to 126 mg (6300 mg/kg-bw/day based on the default body weight of 0.02 kg for a mouse) via shaved dorsal skin, resulted in bronchioloalveolar adenomas and adenocarcinomas in both male and female mice with bronchioloalveolar hyperplasia predominately in female mice. This study was not chosen for cancer dose-response assessment as only this dose was tested. In addition, this strain of mouse is also highly susceptible to cancer and due to severe clinical signs observed in the females, 5 of the 10 animals were euthanized prior to the scheduled study duration at 18 weeks. Thus, the cancer slope factor from NTP (1978) based on hepatocellular carcinomas was also utilized for dermal exposure.

Alkyl halides, such as 1,2-dichloroethane, are considered to be direct acting alkylating agents. Thus, it is considered to be hypothetical the relevance of metabolic saturation of liver metabolic capacity for the formation of oncogenic intermediates (OECD, 2002).

Additionally, the 1,2-dichloroethane inhalation cancer study by Nagano et al. (2006) produced similar tumors as observed in the 1,2-dichloroethane oral cancer study. The cancer data from Nagano et al. (2006) for 1,2-dichloroethane was utilized for the inhalation route. The highest estimated inhalation unit risk (IUR) is 7.1×10^{-6} (per $\mu g/m^3$) for combined mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas in female rats in the inhalation study.

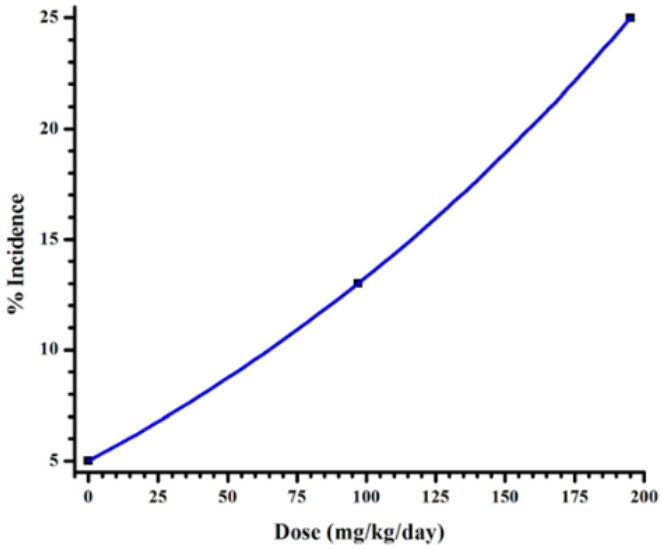

Figure 5-1. Hepatocellular Carcinomas Dose Response in Mice for 1,2-Dichloroethane (NTP (1978))

The OncoLogic™ model developed by the EPA evaluates the carcinogenic potential of chemicals following sets of knowledge rules based on studies of how chemicals cause cancer in animals and humans. 1,2-dichloroethane was categorized as a moderate concern for carcinogenicity based on its potential as a biological alkylating agent as vicinal alkyl halides such as 1,2-dichloroethane are

chemically reactive (Table 5-1). Table 5-2 outlines 1,2-dichloroethane associated precursor events to carcinogenicity.

Table 5-1. 1,2-Dichloroethane Oncologic Results

Parameter	1,2-Dichloroethane
Classification for carcinogenicity	Medium Concern
Chemistry	Vicinal alkyl dihalide
Chemical reactivity	Geminal alkyl dihalide < vicinal alkyl dihalide

Table 5-2. 1,2-Dichloroethane Precursor Events[a]

Parameter	1,2-Dichloroethane
Ames assay	+
DNA repair test rats	+
DNA repair test mice	+
Endometrial polyps	+
[a] Ames Assay positive with and without metabolic activation, Alkyl halides are directly reactive	

6 DOSE-RESPONSE ASSESSMENT

According to the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021), hazard endpoints that receive evidence integration judgments of *demonstrates* and *likely* are considered for dose-response analysis. Endpoints with *suggestive* evidence can be considered on a case-by-case basis. Studies that received high or medium overall quality determinations (or low-quality studies if no other data are available) with adequate quantitative information and sufficient sensitivity can be compared.

Because the health effect with the most robust and sensitive POD among these *suggestive* outcomes were derived from 1,2- dichloroethane, these data were used for risk characterization for each exposure scenario to be protective of other adverse effects as described in the sections below.

Data for the dose-response assessment were selected from oral and inhalation toxicity studies in animals specifically from 1,2-dichloroethane. Additionally, no usable PBPK models are available to extrapolate between animal and human doses or between routes of exposure using 1,2-dichloroethane-specific information. The PODs estimated based on effects in animals were converted to HEDs or cancer slope factors (CSFs) for the oral and dermal routes and HECs or Inhalation Unit Risks (IURs) for the inhalation route. For this conversion, EPA used guidance from U.S. EPA (2011a) to allometrically scale oral data between animals and humans. Although the guidance is specific for the oral route, EPA used the same HEDs and CSFs for the dermal route of exposure as the oral route because the extrapolation from oral to dermal routes is done using the human oral doses, which do not need to be scaled across species. EPA accounts for dermal absorption in the dermal exposure estimates, which can then be directly compared to the dermal HEDs.

For the inhalation route, EPA extrapolated the daily oral HEDs and CSFs to HECs and IURs using human body weight and breathing rate relevant to a continuous exposure of an individual at rest. For consistency, all HEDs and the CSF are expressed as daily doses and all HECs are based on daily, continuous concentrations (24 hours/day) using a breathing rate for individuals at rest. Adjustments to exposure durations, exposure frequencies, and breathing rates are made in the exposure estimates used to calculate risks for individual exposure scenarios.

6.1 Selection of Studies and Endpoints for Non-cancer Toxicity

The following subsections provide a description of the selection of critical non-cancer PODs for acute, short-term/subchronic and chronic exposures for 1,2-dichloroethane. The sections provide a summary of the evaluation of the possible PODs and the rationale for selection of the critical study (and POD) in a series of tables. The tables are intended to streamline the text of the forthcoming draft risk evaluation.

6.1.1 Uncertainty Factors Used for Non-cancer Endpoints

For the non-cancer health effects, EPA applied specific uncertainty factors (UF) to identify benchmark MOEs for acute, short term, and chronic exposure durations for each exposure route among studies that are used to estimate risks. U.S. EPA (1993) and U.S. EPA (2002) further discuss use of UFs in human health hazard dose-response assessment. A total uncertainty factor for each POD is calculated by multiplication of each of the five individual uncertainty factors. In general, the higher the total uncertainty factor applied to a POD to identify a benchmark MOE, the higher the uncertainty in the hazard value. The following five individual UFs are considered for each of the PODs identified for use in risk estimation. In the case of 1,1-dichloroethane, the database uncertainty factor was not used for any of the PODs.

1. **Interspecies Uncertainty Factor (UF_A) of 3**
   EPA uses data from oral toxicity studies in animals to derive relevant HEDs, and (U.S. EPA, 2011a) recommends allometric scaling (using the ¾ power of body weight) to account for interspecies toxicokinetics differences for oral data. When applying allometric scaling, EPA guidance recommends reducing the UFA from 10 to 3. The remaining uncertainty is associated with interspecies differences in toxicodynamics. EPA also uses a UF_A of 3 for the inhalation HEC that accounts for dosimetric adjustment and dermal HED values as these values are derived from the oral HED.

2. **Intraspecies Uncertainty Factor (UF_H) of 10**
   EPA uses a default UF_H of 10 to account for variation in sensitivity within human populations due to limited information regarding the degree to which human variability may impact the disposition of or response to, 1,2-dichloroethane.

3. **LOAEL-to-NOAEL Uncertainty Factor (UF_L) of 1 or 3**
   For the PODs chosen to calculate risks based on BMDL values, EPA used a UF_L of 1. EPA compared these values with other endpoints that were based on LOAELs, which used a UF_L of 3 to account for the uncertainty inherent in extrapolating from the LOAEL to the NOAEL.

4. **Subchronic-to-Chronic Duration Uncertainty Factor (UF_S) of 10**
   EPA uses a default of 10 to account for extrapolating from data obtained in a study with less-than-lifetime (subchronic) exposure to lifetime (chronic) exposure. A default value of 10 for this UF is applied to the NOAEL/LOAEL or BMDL/BMCL from the subchronic study on the assumption that effects from a given compound in a subchronic study occur at a 10-fold higher concentration than in a corresponding (but absent) chronic study

5. **Database Uncertainty Factor (UF_D) of 1**
   EPA considers the application of a database UF to account for the potential for deriving an under-protective POD due to an incomplete characterization of the chemical's toxicity. As the database for 1,2-dichlorethane possesses data that informs several toxicological endpoints, a UF_D of 1 was applied.

6.1.2 Non-cancer PODs for Acute Exposures

Oral

Table 6-1 shows the recommended acute oral study and POD for 1,2-dichloroethane followed by co-critical endpoints (PODs within the range of the recommended study) and other studies considered in support of the recommended POD.

When examining the 1,2-dichloroethane study database, a number of toxicological endpoints were identified. These studies were evaluated by systematic review and only four studies were considered for the acute, oral, non-cancer dose assessment (Table 6-10). In Cheever et al. (1990), the authors noted that a preliminary study on 4 month old Osborne-Mendel rats dosed with 150 mg/kg-bw by oral gavage of radiolabeled 1,2-dichloroethane identified that ^{14}C was almost completely eliminated within 24 hours after administration. Elimination of ^{14}C was found primarily in urine (49.7 to 51.5 percent) followed by expired air (35.5 to 39.6 percent), with only a small portion was detected as $^{14}CO_2$ in feces. This suggests that the kidneys are a potential target due to oral exposure to 1,2-dichloroethane.

In the Morel et al. (1999) acute, single exposure, oral gavage study in male Swiss OF1 mice treated with 0, 1,000, or 1,500 mg/kg-bw of 1,2-dichloroethane, a significant increase in damaged renal tubules (7.66

vs. 0.32 percent in controls) was seen only seen in the highest dose group with the lowest dose already above the limit dose. B6C3F1 mice in the Storer et al. (1984) study that were administered a single oral gavage dose at 0, 100, 200, 300, 400, 500, 600 mg/kg-bw resulted in absolute kidney weights increased at 300 mg/kg-bw doses and greater. Relative kidney weights in Storer et al. (1984) were also increased in the 300 mg/kg and higher dose groups along with serum BUN (serum BUN showed a trend increase but the 300 mg/kg/day dose was not statistically significant to control at N = 5; however, the BMD analysis using all data points together showed significance above 106 mg/kg/day). Thus, based on both histological and clinical chemistry parameters, the Storer et al. (1984) study based on mice kidney weight was identified as the recommended candidate for the acute oral POD. To calculate risks for the acute exposure duration in the risk evaluation, EPA used a daily HED of 19.9 mg/kg-bw (based on a $BMDL_{10}$ of 153 mg/kg-bw) from Storer et al. (1984) and based on a significant (13 percent) increase in relative kidney weight in male B6C3F1 mice administered a single dose of 1,2-dichloroethane at 100, 200, 300, or 400 mg/kg via oral gavage in corn oil. That study was given a high overall quality determination and a, uncertainty factor (UF) of 30 was used for the benchmark margin of exposure (MOE) during risk characterization (see Table 8-1).

Evaluation of the 1,2-dichloroethane studies also suggests the liver and respiratory system as targets of oral 1,2-dichloroethane exposure. In the Munson et al. (1982) study, an acute, single oral gavage to 1-2-dichloroethane in CD-1 mice identified a LD50 of 413 and 489 mg/kg for female and male mice, respectively. Upon necropsy of these animals, it was identified that the lungs and liver appeared to be the primary target organs.

In support of liver toxicity, in the study by Storer et al. (1984), B6C3F1 mice were administered a single dose of 1,2-dichloroethane at 100, 200, 300, or 400 mg/kg via oral gavage in corn oil and euthanized 4 hours later. It was identified that a statistically significant increase in DNA damage in hepatic nuclei was present in all dose groups, as characterized by single-strand breaks, when compared to controls. The study by Storer et al. (1984) also indicated increased IDH (also known as sorbitol dehydrogenase, SDH) and AAT (alanine aminotransferase) serum levels were also increased at the 200 mg/kg and higher doses in the B6C3F1 mice. In Cottalasso et al. (2002), a single gavage of 628 mg/kg of 1,2-dichloroethane in female Sprague-Dawley rats resulted in increased ALT, AST, and LDH compared to controls. Additionally, histological evaluation of the liver showed moderate steatosis. Increased malondialdehyde (MDA), a marker of lipid peroxidation, was also seen in the treated animals when compared to controls. Although clinical chemistry for liver enzyme-implicates liver injury due to 1,2-dichloroethane exposure, gross pathology changes (*e.g.,* in liver weight or quantified histological changes) were not identified.

With regard to the respiratory system, only the study by Salovsky et al. (2002), a single oral dose of 136 mg/kg-bw 1,2-dichloroethane in male Wistar rats resulted in increased total number of cells in the BALF of male Wister rats at 30 days after dosing. Histological changes were only presented qualitatively. Thus, this study was not identified as the POD due to limited quantitative data.

Inhalation

Table 6-2 shows the recommended acute inhalation study and POD for 1,2-dichloroethane followed by co-critical endpoints (*i.e.,* PODs within the range of the recommended study) and other studies considered in support of the recommended POD.

A route-to-route extrapolation from the acute Storer et al. (1984) 1,2-dichloroethane oral study was not conducted given the differences in absorption rates across routes, method of dosing effects on blood levels and hazards (*i.e.,* gavage bolus dose vs. slower inhalation dosing), the lack of a PBPK model, and the inherent uncertainties when performing oral-to-inhalation route extrapolations for a volatile solvent

(*i.e.*, most of the oral dose is eliminated in expired air). An 8-hour inhalation study in male and female rats exposed to 1,2-dichloroethane by Dow Chemical (2006b) was used identified. A $BMCL_{10}$ of 48.9 mg/m^3 and BMD of 81.4 mg/m^3 were identified based on degeneration with necrosis of the olfactory mucosa. The acute inhalation HEC for occupational and continuous exposure of 10.14 ppm (41.1 mg/m^3) and 2.42 ppm (9.78 mg/m^3), respectively, with a benchmark MOE of 30, was used for risk assessment of acute inhalation exposure (Table 8-1). The resulting RGDR value of 0.2 is the combined value for male (0.25) and female (0.16) F344 rats used to calculate HEC continuous (U.S. EPA, 2012a).

Dermal

No acute exposure studies on 1,2-dichloroethane via the dermal route were identified. Therefore, the acute oral HED of 19.9 mg/kg-bw/day was extrapolated for the dermal route, with a benchmark MOE of 30, and was used for risk assessment of acute dermal exposures (Table 8-1).

Table 6-1. Acute, Oral, Non-cancer POD-Endpoint Selection Table

Chemical/ Endpoint	POD (mg/kg/day)	Study Parameters	Comments
POD selected for risk evaluation of non-cancer for acute oral exposures			
1,2-Dichloroethane Kidney weight	BMDL = 153 BMD = 270 NOAEL = 200 mg/kg LOAEL = 300 mg/kg	Storer et al. (1984), Gavage, SR High B6C3F1 Mice – Male Single exposure (0, 200, 300, 400, 500, or 600 mg/kg)	Single exposure study with a POD dose virtually identical to the POD dose where resorptions were observed. This POD is protective for other endpoints such as narcosis, BUN, IDH, resorptions, etc. Death started at 400 mg/kg; LD_{50} (males) = 450 mg/kg).
Co-critical studies			
1,2-Dichloroethane, Blood urea nitrogen (BUN)	NOAEL = 200 LOAEL = 300	Storer et al. (1984), Gavage, SR High B6C3F1 Mice – Male Single exposure (0, 200, 300, 400, 500, or 600 mg/kg)	Adverse increase in BUN supporting kidney effects, not statistically significant due to low N=5.
1,2-Dichloroethane L-iditol dehydrogenase (IDH)	NOAEL = 200 LOAEL = 300	Storer et al. (1984), Gavage, SR High B6C3F1 Mice -Male Single exposure (0, 200, 300, 400, 500, or 600 mg/kg)	Nine-fold adverse increase in IDH marker of tissue damage (associated mostly with kidney and liver damage), not statistically significant due to low N=5.
Other studies/endpoints considered			
1,2-Dichloroethane Kidney histopathology	NOAEL = 1,000 LOAEL = 1,500	Morel et al. (1999), Gavage, SR High Swiss OF1 Mice – Male (0, 1,000, 1,500 mg/kg)	Significant increase in damaged renal tubules but lowest dose above the limit dose.
1,2-Dichloroethane Liver weight	LOAEL = 625	Moody et al. (1981), Gavage, SR Medium SD Rats – Male Single exposure (0, 625 mg/kg)	Increased liver weight. Dose is not a sensitive endpoint.
1,2-Dichloroethane Liver clinical chemistry	NOAEL = 134	Kitchin et al. (1993), Gavage, SR High SD Rats – Female Single exposure (0, 134 mg/kg)	No effects reported. Inadequate dosing (too low).
1,2-Dichloroethane Fetal resorptions	NOAEL = 160 LOAEL = 200 (Data not amenable for BMD modeling)	Payan et al. (1995), Gavage Pre-Natal Developmental, SR High SD Rats – Female Dosing GD 6–20 (0, 120, 160, 200, or 240 mg/kg)	The increases in non-implants and resorptions are difficult to interpret given the significant maternal toxicity at corresponding doses (30 and 49% at 200 and 240 mg/kg/day, respectively) consisting of decreases in maternal body weight gain, and the fact that there was no effect on the number of live fetuses per litter despite the changes in non-surviving implants/litter and resorption sites/litter. Therefore, cannot be used as POD.

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Chemical/ Endpoint	POD (mg/m^3)	Study Parameters	Comments
POD selected for non-cancer risk evaluation for acute inhalation exposures			
1,2-Dichloroethane Neurological	$BMDL_{10}$ = 48.9 mg/m^3 or 12.1 ppm NOAEL = 202 LOAEL = 405	Dow Chemical (2006b), SR High F344 Rats – Male 8 hours/day 1 days (0, 50, 100, 150, 200, 600, 2000 ppm; 0, 202, 405, 607, 809, 2,428, 8,095 mg/m^3)	Degeneration with necrosis of the olfactory neuroepithelial mucosa.
Co-critical endpoints			
1,2-Dichloroethane Reproductive toxicity/fetal development	Reproductive/ Developmental $BMDL_5$ = 25 pup BW decreased at 613 $BMDL_{10}$ = 50 mg/m^3 NOAEL = 305 LOAEL= 613	Rao et al. (1980), Vapor, SR Medium SD Rats – Both sexes Inhalation. Prior to mating, during gestation, and post-natally for two F1 generations (0, 25, 75, 150 ppm; 0, 102, 305 or 613 mg/m^3	Decreased body weight of selected F1B male weanlings at 150 ppm Study used for co-critical endpoints with $BMDL_{10}$ very close to that from the recommended endpoint. Considering NOAELs/LOAELs, using the recommended endpoint will be protective of the decreases in pup body weight. Also, portal of entry effects can be considered more sensitive than systemic effects.
Other studies/endpoints considered			
1,2-Dichloroethane Prenatal developmental	Reproductive/ Developmental Toxicity NOAEL = 1,200 Maternal Toxicity: NOAEL = 1,000 LOAEL = 1,200	Payan et al. (1995), Vapor, SR High SD Rats – Both sexes Inhalation exposure for 2 weeks. GD 6–20. 6 hours/day 7 days/week, at 0, 150, 200, 250, 300 ppm; 0, 610, 820, 1,000, 1,200 mg/m^3	Repro/Dev Toxicity: Pregnancy rate among females at 250 ppm was significantly lower ($p<0.05$). This was not observed at the highest concentration of 300 ppm. No other significant effects reported. Maternal Toxicity: 2/26 dams died at 300 ppm (highest dose). Maternal body weight gain at GD 6–21 was significantly decreased at 300 ppm. No mention of food consumption. NOAEL/LOAEL higher than recommended endpoint. Not amenable to BMD modeling.
1,2-Dichloroethane Prenatal developmental	Reproductive/ Developmental LOAEL = 405 Maternal Toxicity: NOAEL = 405 LOAEL = 1,214	Rao et al. (1980), Vapor, SR Medium SD Rats - Female Inhalation exposure for 10 days. GD 6–15. 7 hours/day 0, 100, 300 ppm (0, 405, 1,214 mg/m3)	Developmental Toxicity: A significant decrease in the incidence of bilobed thoracic centra was seen at 100 ppm however study essentially becomes a single dose study and not amenable to dose-response modeling due to the high maternal toxicity at 300 ppm (10/16 maternal rats died at 300 ppm). Therefore, this study is not acceptable for POD derivation.
1,2-Dichloroethane Liver	NOAEL = 2,527 LOAEL = 3,475	Brondeau et al. (1983), whole body inhalation chamber, SR Medium	Significant increases in serum GLDH and SDH levels were seen at ≥850 ppm (3,475 mg/m^3); serum ALT and AST were

Chemical/ Endpoint	POD (mg/m^3)	Study Parameters	Comments
		SD Rats – Male 0, 618, 850, 1056, 1304 ppm; 0, 2,527, 3,475, 4,318, 5,332 mg/m^3	significantly increased at 850 ppm (3,475 mg/m^3) but not at higher concentrations. Dose-response analysis inadequate. Histopathology and organ weight were not assessed.
1,2-Dichloroethane Liver, metabolic, kidney, neurological	Liver, Metabolic and Kidney (Organ Weight) Overall study NOAEL/LOAEL: Metabolic (Body Weight) NOAEL = 809 LOAEL = 2428	Dow Chemical (2006b), Vapor, SR High F344 Rats- Both sexes 4 or 8 hours: (0, 50, 100, 150, 200, 600, or 2,000 ppm; 202, 405, 607, 809, 2,428 or 8,095 mg/m^3)	Organ weight changes (liver, adrenal, kidney); histological changes (liver, kidney, olfactory mucosa); multiple FOB changes, bw changes were observed although most effects were inconsistent or transient but supportive of liver and kidney effects; the neurological effect (degeneration of the olfactory neuroepithelial mucosa) from this study was used as the recommended POD (see first entry above).
1,2-Dichloroethane Liver/kidney relative organ weights	Liver (relative organ weight): NOAEL = 5,111 LOAEL = 6,134 Kidney (relative organ weight): NOAEL: N/A LOAEL:4089	Francovitch et al. (1986), Vapor, SR Medium CD-1 Mice – Male 4 hours: (0, 1,000, 1,250, 1,500 ppm; 0, 4,089, 5,111 or 6,134 mg/m^3)	Organ weight changes and histology (liver and kidney); however, exposure group where these changes occurred, and negative control data were not reported. While study is supportive of liver and kidney effects, it is not suitable for dose-response analysis. Observed effects are occurring at higher concentrations than the recommended POD.
1,2-Dichloroethane Immunological/ streptococcal infection challenge	CD-1 (Female): NOAEL = 9.21 LOAEL = 21.6 SD Rats (Male): NOAEL: 801.2	Sherwood et al. (1987), Vapor, SR High CD-1 Mice - Female 3 hour single exposure; 0, 2.3, 5.4, 10.8 ppm; 0, 9.21, 21.6, 43.3 mg/m^3 SD Rats – Male 3 or 5 hour single exposure; 0, 10, 20, 50, 100, 200 ppm; 0, 40.1, 80.1, 200.3, 400.6 and 801.2 mg/m^3	Mice: Increased mortality from streptococcal challenge; decreased bactericidal activity; no effects in cell counts or phagocytic activity of alveolar macrophages; increased leucine aminopeptidase (LAP) activity. Rats: No effects observed
1,2-Dichloroethane Neurological	For 12 hours/day for 1 day: NOAEL = 2,500 LOAEL = 5,000 2, 4, or 6 hours/day for 1 day:	Qin-li et al. (2010), Vapor, SR Medium SD Rats: Both sexes 12 hours/day for 1 day: 0, 2,500, 5,000, 10,000 mg/m^3	12 hours/day for 1 day: No mortality observed; signs of abnormal behavior; effects on brain histology (edema corresponding with water content in the cortex, no details on severity or dose-response). 2, 4, or 6 hours/day for 1 day:

Chemical/ Endpoint	POD (mg/m^3)	Study Parameters	Comments
	LOAEL = 5,000	2, 4, or 6 hours/day for 1 day: 0 or 5000 mg/m^3	Effects on brain histology less severe than at 12 hours (edema corresponding with water content of cortex, perineural and perivascular spaces). These effects no suitable for dose-response analysis but are supportive of neurological effects seen in the recommended study and POD.
1,2-Dichloroethane Neurological	For 1.5 or 4 hours: NOAEL = 4,000	Zhou et al. (2016), Vapor, SR Medium SD Rats – Males 1.5 or 4 hours; 0, 4,000, or 12,000 mg/m^3	Effects on the brain lesions with edema, and a significant decrease in the number of fiber tracts were observed compared to control. Study not suitable for dose- response analysis. Study supports neurological effects seen in the recommended study and POD.
1,2-Dichloroethane Liver/kidney clinical chemistry	Liver Clinical Chemistry: NOAEL = 640 LOAEL = 2,020 Kidney weight/BUN: NOAEL = 640 LOAEL = 2,020 Mortality: NOAEL = 2,020 LOAEL = 4,339	Storer et al. (1984), Gas, SR High B6C3F1 Mice – Males 4 hours (0, 58, 499, 1072, and 1,946 ppm; 0, 640, 2,020, 4,339, and 7,876 mg/m3	Increased serum levels of IDH, ALT, and BUN; increased liver and kidney weights; evidence of DNA damage; and increased mortality (4/5 and 5/5 at ≥499 ppm) essentially reducing this study to a single dose study and unsuitable for dose-response analysis.

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6.1.3 Non-cancer PODs for Short-Term/Subchronic Exposures

Oral Short-Term/Subchronic

Table 6-3 shows the recommended short term/subchronic oral study and POD for 1,2-dichloroethane (followed by co-critical endpoints [PODs] within the range of the recommended study) and other studies considered in support of the recommended POD.

For 1,2- dichloroethane, a total of four animal toxicity studies were available and three had acceptable data quality for dose-response analysis and identification of the short-term/subchronic oral duration POD. There were no dermal data for the short-term/subchronic duration exposure.

Using the 1,2-dichloroethane database, the selected critical study was Munson et al. (1982). In this 14-day short-term study in CD1 mice of both sexes and dosed with 1,2-dichloroethane via oral gavage at doses of 0, 4.9, 49 mg/kg. Endpoints evaluated included body weight, hematology, gross necropsy, organ weights (liver, spleen, lungs, thymus, kidney, and brain), humoral immunity, and cell-mediated immunity. The treatment-related effect observed in this study was immunosuppression based on observed suppression of a cell-mediated immune response at doses 4.9 and 49 mg/kg/day. Co-critical endpoints identified in this same Munson et al. (1982) study included an observed 30 percent decrease in leukocytes at 49 mg/kg/day, and a dose-dependent trend of antibody forming cells/spleen towards immune suppression with 25 and 40 percent suppression at 4.9 and 49 mg/kg/day, respectively.

NTP (1991) provided additional support for immunotoxicity. It was a 13-week oral gavage study of F344/N rats dosed with 30, 60, 120, 240, or 480 mg/kg for males or 18, 37, 75, 150, or 300 for females of 1,2-dichloroethane that observed possible dose-related incidences of thymus necrosis. Female rat absolute thymus weight was decreased. The study quality was limited by lack of drinking water consumption reporting that would ensure consistent dosing of test animals throughout the study and by changes in thymus co-occurring with mortality. NTP (1991) also reported a statistically significant absolute and relative kidney weights at 60 and 120 mg/kg/day or 75 and 150 mg/kg/day in male or female rats, respectively. Increased absolute kidney weight was initially seen at 30 mg/kg in male mice.

EPA's independent convergence on Munson et al. (1982) for the non-cancer, oral, short-term POD selection is validated by the 2022 ATSDR Toxicological Profile for 1,2-Dichloroethane (ATSDR, 2022), which also identified immunosuppression as the most sensitive human health protective endpoint.

It is important to emphasize that immunotoxicity found in 1,2-dichloroethane databases is recognized as a cancer mechanism (Hanahan and Weinberg, 2011). Specifically, inflammatory cell recruitment that can actively promote tumor formation and was observed in Munson et al. (1982) through cell-mediated immune responses.

Several other studies were considered from across 1,2-dichloroethane databases, including changes in kidney organ weight from a drinking water study from 1,2-dichloroethane (NTP, 1991), as discussed; reproductive/developmental outcomes following exposure to 1,2-dichloroethane, including fetal resorptions and decreases in maternal body weight (Payan et al., 1995) and likely confounded results for fertility and implantation success for 1,2-dichloroethaneLane et al. (1982).

Inhalation

A 4-week, short-term study in male mice exposed to 1,2-dichloroethane by Zhang et al. (2017) with a $BMCL_5$ and BMC_5 of 6.6 ppm (26.7 mg/m^3) and 5.24 ppm (21.2 mg/m^3), was identified based on decreased sperm concentration. The short-term/subchronic inhalation HEC for occupational and

continuous exposure of 22 ppm (89 mg/m^3) and 5.2 ppm (21.2 mg/m^3), with a benchmark MOE of 100, was used to assess short-term/subchronic inhalation exposure (see Table 8-2).

Dermal

No short-term/subchronic exposure studies on 1,2-dichloroethane via the dermal route were located. Therefore, the short-term/subchronic oral HED for occupational and continuous exposures of 171 and 239 mg/kg-bw/day was extrapolated for the dermal route, with a benchmark MOE of 100, and was used to assess short-term dermal exposure (see Table 8-2).

Table 6-3. Short-Term/Subchronic, Oral, Non-cancer POD-Endpoint Selection Table

Chemical/Endpoint	POD (mg/kg/day)	Study Parameters	Comments
POD selected for non-cancer risk evaluation for short-term/subchronic oral exposures			
1,2-Dichloroethane Decreased cell based immune response	$LOAEL_{adj}$ = 4.9	Munson et al. (1982), Gavage, SR High CD1 Mice – Both sexes 14 days (0, 4.9, 49 mg/kg-day)	ATSDR (2022) Report for 1,2-dichloroethane confirms that immunosuppression is the most sensitive human health protective endpoint, Other similar chlorinated solvents demonstrate immunotoxicity.
Co-critical endpoints			
1,2-Dichloroethane Decreased leukocytes	$LOAEL_{adj}$ = 4.9	Munson et al. (1982), Gavage, SR High CD1 Mice – Both sexes 14 days (0, 4.9, 49 mg/kg-day)	Supports cell-based immunosuppression endpoint.
Other studies/endpoints considered			
1,2-Dichloroethane Immune (thymus)	NOAEL=240 mg/kg-day (males); 150 mg/kg-day (females) LOAEL= 480 mg/kg-day for thymus necrosis in males; 300 mg/kg-day for thymus necrosis in females	NTP (1991), Gavage, SR High F344 Rats – Both sexes 13 weeks (0, 30, 60, 120, 240, 480 mg/kg-day (males); 0, 18, 37, 75, 150, 300 mg/kg/day (females)	Qualitatively supports immunosuppression. However, thymus necrosis occurs at dosages where mortality was also occurring therefore cannot be used as a POD.
1,2-Dichloroethane Kidney weight	LOAEL = 30 (males) LOAEL = 75 (females)	NTP (1991), Gavage, SR High F344 Rats – Both sexes 13 weeks (0, 30, 60, 120, 240, 480 mg/kg-day (males); 0, 18, 37, 75, 150, 300 mg/kg/day (females)	Study was considered for POD selection but not selected as this is not the most sensitive endpoint compared to immunosuppression.
1,2-Dichloroethane, Fetal resorptions	NOAEL=160 LOAEL=200 (Data were not amenable for BMD modeling)	Payan et al. (1995), Gavage Pre-Natal Developmental, SR High SD Rats - Female Dosing GD6-20 (0, 120, 160, 200, or 240 mg/kg)	The increases in non-implants and resorptions are difficult to interpret given the significant maternal toxicity at corresponding doses (30 and 49% at 200 and 240 mg/kg/day, respectively) consisting of decreases in maternal bw gain, and the fact that there was no effect on the number of live fetuses per litter despite the changes in non-surviving implants/litter and resorption sites/litter. Therefore, cannot be used as POD.

Chemical/Endpoint	POD (mg/kg/day)	Study Parameters	Comments
1,2-Dichloroethane Decreases in maternal body weight gain	NOAEL=160 LOAEL=200 (BMD = 99.1; BMDL = 41.8)	Payan et al. (1995), Gavage Pre-Natal Developmental, SR High SD Rats - Female Dosing GD6-20 (0, 120, 160, 200, or 240 mg/kg)	A dose-related reduction in adjusted (for gravid uterine weight) maternal bodyweight gain during treatment occurred, with statistical significance achieved at the two highest doses (30 and 49% reduction compared with controls, $p < 0.05$). However, this POD is not as sensitive (LOAEL = 200; BMDL = 41.8) as the Immunotoxicity Endpoint ($LOAEL_{adj}$ = 4.9).
1,2-Dichloroethane Multigenerational/reproductive pup weight	LOAEL= 50	Lane et al. (1982), Drinking Water, SR High ICR Mice – Both Sexes Multigenerational (0, 5, 15 or 50 mg/kg-day)	Drinking water not measured to confirm actual dosage, therefore not reliable for a dose-response analysis. Also, not as sensitive (LOAEL = 50) as the Immunotoxicity Endpoint identified in the Munson et al. (1982), $LOAEL_{adj}$ = 4.9. Pup weight was biologically significantly (≥5%) decreased at ≥0.09 mg/ml (50mg/kg/day) in F1/B mice.
1,2-Dichloroethane Chronic 26-week dermal study Decreased body weight in females; increased distal tubular mild karyomegaly (both sexes); renal karyomegaly and tubular degeneration (females)	LOAEL= 6,300	Suguro et al. (2017), Dermal, SR High CB6F1- Tg rasH2@Jcl (rasH2) mice – Both sexes 3 days/week 26 weeks (0, 126 mg; 0, 6,300 mg/kg-day	Not considered acceptable for dose response assessment as the study used a single dose using transgenic mice.

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Table 6-4. Short-Term/Subchronic, Inhalation, Non-cancer POD-Endpoint Selection Table

Chemical Endpoint(s)	POD (mg/m^3)	Study Parameters	Comments
POD selected for non-cancer risk evaluation for short-term/subchronic inhalation exposures			
1,2-Dichloroethane Male reproductive	$BMDL_5$ = 21.2 mg/m3 NOAEL = 350 LOAEL = 700	Zhang et al. (2017), 4 week morphological analysis of sperm parameters, SR High Swiss Mice – Males 6 hours/day, 7 days/week, 4 weeks (0, 100, 350, 700 mg/m^3)	Decreases in sperm concentration.
Co-critical endpoints			
1,2-Dichloroethane Fetal development	Reproductive/ Developmental $BMDL_5$ = 25 Pup BW decreased at 613 $BMDL_{10}$ = 50 mg/m^3 NOAEL: 305 LOAEL: 613	Rao et al. (1980), Vapor, SR Medium SD Rats – Both sexes Inhalation. Prior to mating, during gestation, and post-natally for two F1 generations (0, 25, 75, 150 ppm; 0, 102, 305 or 613 mg/m^3	Decreased body weight of selected F1B male weanlings at 150 ppm. Study used for co-critical endpoints with $BMDL_5$ very close to that from the recommended endpoint. Considering NOAELs/LOAELs, using the recommended endpoint will be protective of the decreases in pup body weight. Also, portal of entry effects can be considered more sensitive than systemic effects.
Other studies/endpoints considered			
1,2-Dichloroethane Liver	LOAEL = 3,424	Brondeau et al. (1983), Vapor, SR Medium SD Rats – Males 6 hours/day for 2 or 4 days; 0 or 3424 mg/m^3	6 hours/day for 2 days: Significant increases in serum ALT, GLDH, and SDH levels ; liver histopathology and organ weight were not assessed. 6 hours/day for 4 days: Serum SDH levels were significantly increased. Liver histopathology and organ weight were not assessed.
1,2-Dichloroethane Liver	LOAEL = 619	Igwe et al. (1986c), Vapor, SR High SD Rats – Male 7 hours/day, 5 days/week, 4 weeks: 0, 153, 304, 455 ppm; 619, 1,230, and 1,842 mg/m^3	Increased relative liver weight and 5'-NT. Absolute liver weight was not reported. No changes in hepatic GST activity, hepatic DNA content, or serum enzymes ALT or SDH were observed at any concentration.
1,2-Dichloroethane Liver/reproductive/ metabolic/mortality	Immune: NOAEL = 1,842 Reproductive: NOAEL = 1,842	Igwe et al. (1986c), Vapor, SR High SD Rats – Male 7 hours/day, 5 days/week, 30 days: 0, 153, 304, 455 ppm; 619, 1,230, and 1,842 mg/m^3	Immune, Reproductive/Developmental: No effects on organ weight or histopathology. Liver: Increased relative liver weight, absolute liver weight was not reported.

Chemical Endpoint(s)	POD (mg/m^3)	Study Parameters	Comments
	Liver: LOAEL = 619 Mortality, Metabolic: NOAEL = 619 LOAEL = 1,230		Mortality: Occurred in 1/12 and 2/12 animals in 1,230 and 1,842 mg/m^3, respectively Metabolic: Decreased body weight. NOAEL/LOAEL higher than recommended endpoint. Not amenable to BMD modeling
1,2-Dichloroethane-Reproductive/ developmental/ maternal toxicity	Reproductive/ Developmental NOAEL = 1,200 Maternal Toxicity: NOAEL = 1,000 LOAEL = 1,200	Payan et al. (1995), Vapor, SR High SD Rats – Both Sexes Inhalation exposure for 2 weeks. GD 6–20. 6 hours/day 7 days/week, 0, 150, 200, 250, 300 ppm; 0, 610, 820, 1,000, 1,200 mg/m^3	Reproductive/Developmental Toxicity: Pregnancy rate among females at 250 ppm was significantly lower, but not at 300 ppm; no other significant effects reported. Maternal Toxicity: 2/26 dams died at 300 ppm (highest dose). Maternal body weight gain at GD 6–21 was significantly decreased at 300 ppm. No mention of food consumption. NOAEL/LOAEL higher than recommended endpoint. Not amenable to BMD modeling.
1,2-Dichloroethane Reproductive/ developmental; maternal toxicity	Reproductive/ Developmental LOAEL = 405 Maternal Toxicity: NOAEL = 405 LOAEL = 1,214	Rao et al. (1980), Vapor, SR Medium SD Rats – Female Inhalation exposure for 10 days. GD 6–-15. 7 hours/day. 0, 100, 300 ppm (0, 405, 1,214 mg/m^3)	Developmental Toxicity: A significant decrease in the incidence of bilobed thoracic centra was seen at 100 ppm however study essentially becomes a single dose study and not amenable to dose-response modeling due to the high maternal toxicity at 300 ppm (10/16 maternal rats died at 300 ppm). Therefore, this study is not acceptable for POD derivation.
1,2-Dichloroethane Immunological/ streptococcal infection challenge	CD-1 Mice: NOAEL = 9.21 SD Rats: NOAEL = 400.6	Sherwood et al. (1987), Vapor, SR High CD-1 Mice – Female 3 hours/day, 5 days/week, 5 days; 0, 2.3; 0, 9.21 mg/m^3 SD Rats – Male 5 hours/day, 5 days/week, 12 days; 0, 10, 20, 50, 100; 0, 40.1, 80.1, 200.3, 400.6 mg/m^3	CD-1 mice and SD rats showed no effects.
1,2-Dichloroethane Liver/metabolic	Liver: NOAEL = 350 Metabolic: NOAEL = 350 LOAEL = 700	Zeng et al. (2018), Aerosol, SR High Swiss Mice: Male 6 hours/day, 7 days/week, 28 days 0, 350, 700 mg/m^3	Liver: Increased absolute and relative liver weight, increased liver concentrations of glycogen, triglycerides, and free fatty acids at all concentrations; increased ALT (1.9-fold) at 700 mg/m^3; increased serum AST (1.3-fold to 1.7-fold) , triglycerides, and free fatty acids; decreased serum glucose at both exposure concentrations. Metabolic: Body weight was significantly reduced at 700 mg/m^3.

Chemical Endpoint(s)	POD (mg/m^3)	Study Parameters	Comments
1,2-Dichloroethane	Neurological, Reproductive, Immune/Hematological, Liver, Mortality, Metabolic, Kidney (Rat): Respiratory: NOAEL = 809 Liver, Metabolic and Kidney (Guinea Pig): NOAEL = 405	Spencer et al. (1951), Vapor, SR Medium Wistar Rats – Both sexes 7 hours/day 5 days/week 212 days*, (0, 100, 200, 400 ppm; 0, 405, 809, 1,619 mg/m3) *Although all exposure groups were intended for chronic duration exposures, animals at the high exposure level died within 14 days (females) and 56 days (males). Guinea Pigs – Both sexes 7 hours/day 5 days/week 248 days, (0, 100, 200, 400 ppm; 0, 405, 809, 1,619 mg/m^3)	Rats: High mortality at 400 ppm starting at 2 weeks; no other effects reported. Guinea Pigs: High mortality at 400 ppm starting at 2 weeks; reductions in body weight starting at 100 ppm; increases in liver weight; possible liver histopathology and changes in kidney weight, but incidence not reported.

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6.1.4 Non-cancer PODs for Chronic Exposures

Oral

Table 6-5 shows the recommended chronic oral study and POD for 1,2-dichloroethane followed by co-critical endpoints (PODs within the range of the recommended study) and other studies considered in support of the recommended POD.

No studies of chronic oral exposure in laboratory animals were considered suitable for POD determination (see Section F.3 for 1,2-dichloroethane). Therefore, the short-term/subchronic POD identified in Section 6.1.3 was also used for chronic exposure. The short-term/subchronic continuous HED was 0.636 mg/kg-bw/day and the worker HED was 0.890 mg/kg-bw/day (see Appendix F.2). The benchmark MOE for this POD is 1,000 based on 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, 3 for the use of a LOAEL to extrapolate a NOAEL (based on the dose-response), and 10 for extrapolating from a subchronic study duration to a chronic study duration for chronic exposures (see Table 8-3).

Inhalation

Table 6-6 shows the recommended chronic inhalation study and POD for 1,2-dichloroethane followed by co-critical endpoints (PODs within the range of the recommended study) and other studies considered in support of the recommended POD.

No chronic PODs were identified from studies for inhalation exposures to 1,2-dichloroethane. A 4-week short-term study in male mice exposed to 1,2-dichloroethane by Zhang et al. (2017) was used. A duration extrapolation from the 4-week short-term/subchronic to a chronic duration was conducted in order to account for uncertainty. A subchronic to chronic UF of 10 was thus applied for extrapolating from a subchronic to chronic study duration. A $BMCL_5$ and BMC_5 of 6.6 ppm (26.7 mg/m^3) and 5.24 ppm (21.2 mg/m^3), were identified based on decreased sperm concentration. The short-term/subchronic inhalation HEC for occupational and continuous exposure of 22 ppm (89 mg/m^3) and 5.2 ppm (21.2 mg/m^3), respectively, with a benchmark MOE of 300, was used for risk assessment of chronic inhalation exposure. Although an uncertainty regarding study duration may have been reduced by use of the chronic (Nagano et al., 2006) study that evaluated 1,2-dichloroethane, the study did not adequately evaluate non-cancer effects, preventing the determination of a non-cancer chronic POD.

Dermal

No chronic studies on 1,2-dichloroethane via the dermal route were located. Therefore, the chronic oral HED for occupational and continuous exposures of 0.89 and 0.636 mg/kg-bw/day, respectively, was extrapolated for the dermal route, with a benchmark MOE of 1,000, and was used for risk assessment of chronic dermal exposure (see Table 8-3).

1827 **Table 6-5. Chronic, Oral, Non-cancer POD-Endpoint Selection Table**

Chemical Endpoint(s)	POD (mg/kg/day)	Study Parameters	Comments
POD selected for non-cancer risk evaluation for chronic oral exposures			
1,2-Dichloroethane Decreased cell based immune response	$LOAEL_{adj}$ = 4.9	Munson et al. (1982), Gavage SR High CD1 Mice – Both sexes 14 days (0, 4.9, 49 mg/kg-day)	ATSDR (2022) Report for 1,2-dichloroethane confirms that immunosuppression is the most sensitive human health protective endpoint, Other similar chlorinated solvents demonstrate immunotoxicity.
Co-critical endpoints			
1,2-Dichloroethane Decreased leukocytes	$LOAEL_{adj}$ = 4.9	Munson et al. (1982), Gavage SR High CD1 Mice – Both sexes 14 days (0, 4.9, 49 mg/kg-day)	Supports cell-based immunosuppression endpoint
Other studies considered			
1,2-Dichloroethane Immune (thymus)	NOAEL = 240 mg/kg-day (males); 150 mg/kg-day (females) LOAEL = 480 mg/kg-day for thymus necrosis in males; 300 mg/kg-day for thymus necrosis in females	NTP (1991), Gavage, SR High (NTP 1991) F344 Rats – Both sexes 13 weeks (0, 30, 60, 120, 240, 480 mg/kg-day (males); 0, 18, 37, 75, 150, 300 mg/kg/day (females)	Qualitatively supports immunosuppression. However, thymus necrosis occurs at dosages where mortality was also occurring therefore cannot be used as a POD.
1,2-Dichloroethane Kidney weight	LOAEL = 30 (males) LOAEL = 75 (females)	NTP (1991), Gavage, SR High F344 Rats – Both sexes 13 weeks (0, 30, 60, 120, 240, 480 mg/kg-day (males); 0, 18, 37, 75, 150, 300 mg/kg/day (females)	Study was considered for POD selection but not selected as this is not the most sensitive endpoint compared to immunosuppression.
1,2-Dichloroethane Fetal resorptions	NOAEL = 160 LOAEL = 200 (Data were not amenable to modeling)	Payan et al. (1995), Gavage Prenatal Developmental, SR High SD Rats - Female Dosing GD6-20 (0, 120, 160, 200, or 240 mg/kg)	The increases in non-implants and resorptions are difficult to interpret given the significant maternal toxicity at corresponding doses (30 and 49% at 200 and 240 mg/kg/day, respectively) consisting of decreases in maternal bw gain, and the fact that there was no effect on the number of live fetuses per litter despite the changes in non-surviving implants/litter and resorption sites/litter. Therefore, cannot be used as POD.
1,2-Dichloroethane,	NOAEL = 160 LOAEL = 200	Payan et al. (1995), Gavage Prenatal Developmental, SR High	A dose-related reduction in adjusted (for gravid uterine weight) maternal bodyweight gain during treatment occurred,

Chemical Endpoint(s)	POD (mg/kg/day)	Study Parameters	Comments
Decreases in maternal body weight gain	(BMD = 99.1; BMDL = 41.8)	SD Rats - Female Dosing GD 6–20 (0, 120, 160, 200, or 240 mg/kg)	with statistical significance achieved at the two highest doses (30 and 49% reduction compared with controls, $p < 0.05$). However, this POD is not as sensitive (LOAEL = 200; BMDL = 41.8) as the Immunotoxicity Endpoint ($LOAEL_{adj}$ =4.9).
1,2-Dichloroethane Multigenerational/reproductive pup weight	LOAEL = 50	Lane et al. (1982), Drinking Water, SR High ICR Mice – Both Sexes Reproductive Toxicity (0, 5, 15 or 50 mg/kg-day)	Drinking water not measured to confirm actual dosage. Also, not as sensitive (LOAEL=50) as the Immunotoxicity Endpoint (LOAEL =4.9) Pup weight was biologically significantly (≥5%) decreased at ≥0.09 mg/ml (50mg/kg/day) in F1/B mice.
1,2-Dichloroethane 40-week chronic study Body weight/lymphoma	LOAEL = 150 (females)	Storer et al. (1995), Gavage, SR Medium ppG64 Mice – Both sexes 7 days/week for 40 weeks (0, 150, 300 mg/kg-day (female); 0, 100, 200 mg/kg/day (males)	Minimal endpoints evaluated, only non-cancer endpoints were body weight and lymphoma at 150. Doses adjusted due to substantial mortality females at 300 mg/kg/day. Clear dose-response could not be assessed.
1,2-Dichloroethane Chronic 26-week dermal study	LOAEL = 6300 Decreased body weight in females; increased distal tubular mild karyomegaly (both sexes); renal karyomegaly & tubular degeneration (females)	Suguro et al. (2017), Dermal, SR High CB6F1- Tg rasH2@Jcl (rasH2) mice – Both sexes 3 days/week 26 weeks (0, 126 mg; 0, 6300 mg/kg-day	Single dosage using transgenic mice.

Table 6-6. Chronic, Inhalation, Non-cancer POD-Endpoint Selection Table

Chemical-Endpoint	POD (mg/cm^3)	Study Parameters	Comments
POD selected for non-cancer risk evaluation for chronic inhalation exposures			
1,2-Dichloroethane Male reproductive	$BMDL_5$ = 21.2 mg/m^3 NOAEL: 350 LOAEL: 700	Zhang et al. (2017), 4 week morphological analysis of sperm parameters, SR High Swiss Mice – Male 6 hours/day 7 days/week 4 weeks (0, 100, 350, 700 mg/m^3)	Decreases in sperm concentration.
Co-critical endpoints			
1,2-Dichloroethane, Fetal development	Reproductive/ Developmental $BMDL_5$= 25 Pup BW decreased at 613 $BMDL_{10}$ = 50 mg/m^3 NOAEL: 305 LOAEL: 613	Rao et al. (1980), Vapor, SR Medium SD Rats – Both sexes Inhalation. Prior to mating, rats were exposed for 60 days (6 hours/day, 5 days/week). The rest of the time, exposed to 6 hours/day, 7 days/week, except from gestational day 21-post natal day 4 maternal exposure stopped to allow for delivery and rearing of the young). Two F1 generations were evaluated, 0,25,75,150 ppm; 0, 102, 305 or 613 mg/m^3	Decreased body weight of selected F1B male weanlings at 150 ppm. Study used for co-critical endpoints with $BMDL_{10}$ very close to that from the recommended endpoint. Considering NOAELs/LOAELs, using the recommended endpoint will be protective of the decreases in pup body weight. Also, portal of entry effects can be considered more sensitive than systemic effects.
Other studies considered			
1,2-Dichloroethane	Reproductive/ Developmental NOAEL: 1,200 Maternal Toxicity: NOAEL = 1000 LOAEL = 1,200	Payan et al. (1995), Vapor, SR High SD Rats – Both Sexes Inhalation exposure for 2 weeks. GD 6–20. 6 hours/day 7 days/week, 0, 150, 200, 250, 300 ppm; 0, 610, 820, 1,000, 1,200 mg/m^3	Repro/Dev Toxicity: Pregnancy rate among females at 250 ppm was significantly lower; not observed at the highest concentration of 300 ppm; no other significant effects reported. Maternal Toxicity: 2/26 dams died at 300 ppm (highest dose). Maternal body weight gain at GD 6–21 was significantly decreased at 300 ppm. No mention of food consumption. NOAEL/LOAEL higher than recommended endpoint. Not amenable to BMD modeling.
1,2-Dichloroethane	Reproductive/ Developmental LOAEL = 405 Maternal Toxicity: NOAEL = 405 LOAEL = 1214	Rao et al. (1980), Vapor, SR Medium SD Rats – Female Inhalation exposure for 10 days. GD 6–15. 7 hours/day.0, 100, 300 ppm (0, 405, 1,214 mg/m3)	Developmental Toxicity: A significant decrease in the incidence of bilobed thoracic centra was seen at 100 ppm however study essentially becomes a single dose study and not amenable to dose-response modeling due to the high maternal toxicity at 300 ppm (10/16 maternal rats died at 300 ppm). Therefore, this study is not acceptable for POD derivation.

Chemical-Endpoint	POD (mg/cm^3)	Study Parameters	Comments
1,2-Dichloroethane	Hematological: NOAEL = 202 LOAEL = 607 Liver: LOAEL = 20 Kidney: NOAEL = 202 LOAEL = 607	IRFMN (1978), Vapor, SR Medium SD Rats – Both sexes 7 hours/day, 5 days/week for 12 months: 0, 5, 10, 50, 150 ppm; 0, 20, 40, 202, 607 mg/m^3	Hemoglobin levels were significantly decreased in both sexes at 150 ppm; changes in hematocrit (increases rather than decreases) were of questionable biological significance and did not show a dose-response; decreases in cholesterol and calcium levels at ≥10 ppm; clinical chemistry signs of liver toxicity but did not show a dose-response, kidney BUN increases at 150 ppm; other kidney changes were male rat-specific and not relevant to humans.
1,2-Dichloroethane	Reproductive/Developmental, Mortality & Metabolic: NOAEL: 204 Liver: LOAEL: 204	Cheever et al. (1990), Vapor, SR High SD Rats – Both sexes 7 hours/day 5 days/week 104 weeks (0, 50 ppm; 0, 204 mg/m^3)	Gross testicular lesions were found in higher frequency in exposed males (24%) compared to control (10%) (data not shown and gross pathologic observations were not evaluated statistically); mortality similar in both treatment and control groups, survival rate in exposed rats (60 and 64%) was similar to control (58 and 54%) in males and females, respectively; absolute and relative liver weights were not different from controls.
1,2-Dichloroethane	Immunological/ Hematological, Liver, and Kidney: NOAEL = 809	IRFMN (1976), Vapor, SR Medium SD Rats – Both sexes 7 hours/day 5 days/week 24 weeks, (0, 5, 10, 50, 150, 250 ppm; 0, 20, 40, 202, 607, 1,012 mg/m3)* *Animals in the highest exposure group were exposed to 250 ppm for “a few weeks” and then the exposure concentration was reduced to 150 ppm due to acute toxicity. A reliable TWA concentration cannot be determined based on the information available in this report, IRFMN (1978) suggested that the change occurred after 12 weeks of exposure. If this is accurate, then the TWA exposure concentration for the high exposure group was 200 ppm.	All observed hematological, serum chemistry, and urinalysis changes observed either did not reach statistical significance, showed no clear relation to exposure concentration, and/or were not biologically significant.
1,2-Dichloroethane	Immunological/ Hematological, Liver, and Kidney: NOAEL = 607	IRFMN (1987), Vapor, SR Medium SD Rats – Both sexes	Significant decrease in segmented neutrophils in the high exposure group in males; no other hematological changes were observed; serum liver and kidney chemistry changes either did not reach statistical significance, showed no clear relation to

Chemical-Endpoint	POD (mg/cm^3)	Study Parameters	Comments
		7 hours/day 5 days/week 78 weeks, (0, 5, 10, 50, 150, 250 ppm; 0, 20, 40, 202, 607, 1012 mg/m^3)* *Animals in the highest exposure group were exposed to 250 ppm for "a few weeks" and then the exposure concentration was reduced to 150 ppm due to acute toxicity. A reliable TWA concentration cannot be determined based on the information available in this report, IRFMN (1978) suggested that the change occurred after 12 weeks of exposure. If this is accurate, then the TWA exposure concentration for the high exposure group was 200 ppm.	exposure, concentration, and/or were not biologically significant; no urinary changes were observed.
1,2-Dichloroethane	Mortality (Rats): NOAEL = 654 Mortality (Mice): NOAEL = 368	Nagano et al. (2006) F344 Rats – Both sexes 6 hours/day 5 days/week 104 weeks total, (0, 10, 40, 160 ppm; 0, 41, 164 or 654 mg/m3) Crj:BDF1 Mice – Both sexes 6 hours/day 5 days/week 104 weeks total, 0, 10, 30, 90 ppm; 0, 41, 123 or 368 mg/m^3)	Endpoints evaluated included mortality, clinical signs of toxicity, body weight, food consumption, hematology, blood biochemistry, urinalysis, organ weight, gross necropsy of organs and histopathology. No significant effects reported.
1,2-Dichloroethane	Immune/Hematological Nutritional/Metabolic, Liver, Mortality, and Kidney (Rats/Rabbits/Guinea Pigs/Cats): NOAEL = 405	Hofmann et al. (1971), Vapor, SR Medium SD Rats – Both sexes Bunte Rabbits – Both sexes Pirbright – White Guinea Pigs – Both sexes Cats – Both sexes 6 hours/day 5 days/week 17 weeks, (0, 100 ppm; 0, 405 mg/m^3)	The endpoints evaluated included mortality, body weights, hematological effects (blood counts, not further specified), liver effects (serum AST and ALT, liver weight, and liver histology), and renal effects (BUN and serum creatinine, urinary status – not further specified, kidney weight, and kidney histology); bromsulphthalein test in rabbits & cats does not indicate liver effects. Rats, cats, and guinea pigs: No significant effects reported. One of 4 rabbits showed increased BUN and kidney histology (not further specified); the observation of these effects in 1 rabbit was not considered adverse (or of questionable adversity).

Chemical-Endpoint	POD (mg/cm^3)	Study Parameters	Comments
1,2-Dichloroethane	Neurological, Liver, and Mortality (Rabbits): Not determined Hematological, Kidney, Liver, and Mortality (Monkeys): NOAEL = 405	Spencer et al. (1951), Vapor, SR Medium Rabbit – Both sexes 7 hours/day 5 days/week 248 days*, (0, 100, 400 ppm; 0, 405, 1,619 mg/m3) *The exact duration of exposure is unclear. At 400 ppm rabbits "tolerated" exposure for 232 days" and at 100 ppm, rabbits "tolerated" exposure for 248 days without signs of adverse effects; the time of termination is not specified. Monkeys – Males 7 hours/day 5 days/week 212 days*, (0, 100, 400 ppm; 0, 405, 1619 mg/m^3) *At 400 ppm both Monkeys were killed in a moribund state after 8 and 12 exposures, respectively. The duration noted above applies only to the 100 ppm group. Wistar Rats – Both sexes 7 hours/day 5 days/week 212 days*, (0, 100, 400 ppm; 0, 405, 1619 mg/m3) *Although all exposure groups were intended for chronic duration exposures, animals at the high exposure level died within 14 days (females) and 56 days (males). Guinea Pigs – Both sexes 7 hours/day 5 days/week 248 days, (0, 100, 200, 400 ppm; 0, 405, 809, 1,619 mg/m^3)	No significant effects reported in rabbits; histopathological changes reported in the liver and kidney in monkeys; mortality observed in rats and guinea pigs; uncertain signs of body weight changes, and possible signs of liver and kidney toxicity in guinea pigs but the data either did not show dose-response, or quantal data for these endpoints or incidence values and a statement whether any control animals exhibited these changes were not included.

6.2 Summary of Studies Not Considered/Considered Suitable for POD Determination of 1,2-Dichloroethane

According to U.S. EPA (2021) Draft Systematic Review Protocol, hazard endpoints that receive evidence integration judgments of *demonstrates* and *likely* would generally be considered for dose-response analysis. Endpoints with *suggestive* evidence can be considered on a case-by-case basis. Studies that received high or medium overall quality determinations (or low-quality studies if no other data are available) with adequate quantitative information and sufficient sensitivity can be compared. The only hazard outcome for which evidence *demonstrates* that 1,2-dichloroethane causes the effect was mortality. For neurological/behavioral effects, EPA's evidence integration judgment was *likely*. For nutritional/metabolic, renal/kidney, hepatic/liver, lung/respiratory, immune/hematological, and reproductive effects, EPA's evidence integration conclusion was that the evidence was *suggestive*. Finally, EPA concluded that the available evidence was *inadequate* to determine whether 1,2-dichloroethane induces developmental effects.

No human studies provided adequate information for POD determination. Animal studies of oral, inhalation, or dermal exposure that received *high* or *medium* quality determinations for one or more of these health outcomes were considered for dose-response information, with some exceptions. Studies that identified a NOAEL at the highest dose/concentration tested were not considered for dose-response assessment but were considered as part of evidence integration for the relevant health outcomes. In addition, acute lethality studies that did not include untreated or vehicle-treated controls, or other studies that did not present sufficient information to determine a NOAEL or LOAEL were not considered. Finally, only studies in intact, wild-type laboratory animal strains were considered for dose-response assessment. A small number of studies using partially-hepatectomized animals or transgenic models were excluded from consideration, as shown in the tables.

Table 6-7, Table 6-8 and Table 6-9 show the animal studies of oral, inhalation, and dermal exposure (respectively) that were excluded from consideration for dose-response assessment along with the reason for excluding each. Table 6-10 summarizes studies that were considered for dose-response assessment for 1,2-dichloroethane. Table 6-11, Table 6-12, Table 6-13, Table 6-14, and Table 6-15 summarize candidate PODs for acute, short-term/subchronic, or chronic durations via for oral or inhalation exposure.

Table 6-7. Oral Studies Not Considered Suitable for PODs for 1,2-Dichloroethane

Duration Category	Reference	HERO ID	Species	Specific Route	Rationale
Acute	Cottalasso et al. (1995)	200280	Rat	Gavage	Not suitable for POD due to dosing uncertainties
Acute	Dow Chemical (2006a)	625286	Rat	Gavage	Freestanding NOAEL[a]
Acute	Kettering Laboratory (1943)	4528351	Rabbit	Gavage	Uninformative
Acute	Kitchin et al. (1993)	6118	Rat	Gavage	Freestanding NOAEL[a]
Acute	Mellon Institute (1948)	5447301	Rat	Gavage	Uninformative
Acute	Mellon Institute (1948)	5447301	Mouse	Gavage	Uninformative
Acute	Mellon Institute (1948)	5447301	Rabbit	Gavage	Uninformative
Acute	Moody et al. (1981)	18954	Rat	Gavage	Not suitable for POD; evaluation limited to liver weight and data not shown
Acute	Munson et al. (1982)	62637	Mouse	Gavage	Low
Acute	Stauffer Chem Co (1973)	6569955	Rat	Gavage	Not suitable for POD; no control group
Acute	Milman et al. (1988)	200479	Rat	Gavage	Study of partially hepatectomized animals
Short-term	Dow Chemical (2006a)	625286	Rat	Gavage	Freestanding NOAEL[a]
Short-term	NTP (1978)	5441108	Mouse	Gavage	Freestanding NOAEL[a]
Subchronic	Milman et al. (1988)	200479	Rat	Gavage	Study of partially hepatectomized animals
Subchronic	Alumot et al. (1976)	194588	Rat	Diet	Freestanding NOAEL[a] (for 5-week female and 13-week male growth studies) not suitable for POD due to dosing uncertainties (for 5- to 7-week preliminary study)
Subchronic	NTP (1991)	1772371	Rat	Drinking water	Uninformative
Subchronic	NTP (1991)	1772371	Mouse	Drinking water	Uninformative
Subchronic	Munson et al. (1982)	62637	Mouse	Drinking water	Uninformative
Chronic	Alumot et al. (1976)	194588	Rat	Diet	Uninformative
Chronic	Klaunig et al. (1986)	200427	Mouse	Drinking water	Not suitable for POD due to reporting limitations
Chronic	Storer et al. (1995)	200612	Mouse	Gavage	Study of transgenic mice predisposed to cancer
Chronic	NTP (1978)	5441108	Mouse	Gavage	Not suitable for POD due to confounding by tumors
Chronic	NTP (1978)	5441108	Rat	Gavage	Uninformative
Reproduction/ Developmental	Lane et al. (1982)	62609	Mouse	Drinking water	Freestanding NOAEL[a]
Reproduction/ Developmental	WIL Research (2015)	7310776	Rat	Drinking water	Uninformative
Reproduction/ Developmental	Alumot et al. (1976)	194588	Rat	Diet	Uninformative

[a] No effects observed at highest dose tested for all apical health outcomes rated Low or higher.

1866 **Table 6-8. Inhalation Studies Not Considered Suitable for PODs for 1,2-Dichloroethane**

Duration Category	Reference	HERO ID	Species	Rationale
Acute	Brondeau et al. (1983)	200247	Rat	Not suitable for POD due to limited evaluations
Acute	Dow Chemical (2005)	10699112	Rat	Not suitable for POD determination; no control group
Acute	Dow Chemical (2017)	10699356	Rat	Not suitable for POD determination; no control group
Acute	Sherwood et al. (1987)	200590	Rat	Freestanding NOAEL[a]
Acute	Guo and Niu (2003)	200352	Rat	Uninformative
Acute	Jin et al. (2018a); Jin et al. (2018b)	5431556, 5557200	Mouse	Uninformative
Acute	Mellon Institute (1948)	5447301	Rat	Uninformative
Acute	Mellon Institute (1948)	5447301	Rabbit	Uninformative
Acute	Mellon Institute (1948)	5447301	Mouse	Uninformative
Acute	Spencer et al. (1951)	62617	Rat	Not suitable for POD determination; no control group
Acute	Zhang et al. (2011)	734177	Rat	Uninformative
Short-term	Brondeau et al. (1983)	200247	Rat	Not suitable for POD due to limited evaluations
Short-term	Dow Chemical (2014)	10609985	Rat	Freestanding NOAEL[a]
Short-term	Jin et al. (2018a); Jin et al. (2018b)	5431556, 5557200	Mouse	Uninformative
Short-term	Li et al. (2015)	4492694	Rat	Uninformative
Short-term	Pang et al. (2018)	4697150	Rat	Uninformative
Short-term	Sherwood et al. (1987)	200590	Rat	Freestanding NOAEL[a]
Short-term	Sherwood et al. (1987)	200590	Mouse	Freestanding NOAEL[a]
Short-term	Spencer et al. (1951)	62617	Rat	Uninformative
Short-term	Spencer et al. (1951)	62617	Guinea pig	Uninformative
Short-term	Sun et al. (2016c)	4451633	Mouse	Uninformative
Short-term	Wang et al. (2013)	1522109	Mouse	Uninformative
Short-term	Wang et al. (2014)	4453007	Mouse	Uninformative
Short-term	Zhang and Jin (2019)	5556105	Mouse	Uninformative
Subchronic	Hofmann et al. (1971)	1937626	Rat	Uninformative
Subchronic	Hofmann et al. (1971)	1937626	Guinea pig	Uninformative
Subchronic	Hofmann et al. (1971)	1937626	Cat	Not suitable for POD due to reporting limitations and small group size[b]
Subchronic	Hofmann et al. (1971)	1937626	Rabbit	Uninformative
Subchronic	Kettering Laboratory (1943)	4528351	Rabbit	Uninformative
Chronic	Cheever et al. (1990)	12097	Rat	Freestanding NOAEL[a]

Duration Category	Reference	HERO ID	Species	Rationale
Chronic	Hofmann et al. (1971)	1937626	Rat	Freestanding NOAEL[a] (17- and 26-week experiments)
Chronic	Hofmann et al. (1971)	1937626	Rabbit	Freestanding NOAEL[a] (17- and 26-week experiments)
Chronic	Hofmann et al. (1971)	1937626	Guinea pig	Freestanding NOAEL[a] (17- and 26-week experiments)
Chronic	Hofmann et al. (1971)	1937626	Cat	Freestanding NOAEL[a] (17-week experiment); Uninformative (26-week experiment)
Chronic	IRFMN (1976)	5447359	Rat	Freestanding NOAEL[a]
Chronic	IRFMN (1987)	94773	Rat	Freestanding NOAEL[a]
Chronic	IRFMN (1987)	94773	Mouse	Freestanding NOAEL[a]
Chronic	IRFMN (1987)	5447260	Rat	Freestanding NOAEL[a]
Chronic	Mellon Institute (1947)	1973131	Rat	Uninformative
Chronic	Mellon Institute (1947)	1973131	Dog	Not suitable for POD due to reporting limitations and small group size[b]
Chronic	Nagano et al. (2006)	200497	Rat	Freestanding NOAEL[a]
Chronic	Nagano et al. (2006)	200497	Mouse	Not suitable for POD due to confounding by tumors
Chronic	Spencer et al. (1951)	62617	Rat	Not suitable for POD due to variable exposure durations and reporting limitations
Chronic	Spencer et al. (1951)	62617	Guinea pig	Not suitable for POD due to variable exposure durations and reporting limitations
Chronic	Spencer et al. (1951)	62617	Rabbit	Not suitable for POD due to variable exposure durations, reporting limitations, and small group size[b]
Chronic	Spencer et al. (1951)	62617	Monkey	Not suitable for POD due to variable exposure durations, reporting limitations, and small group size[b]
Reproduction/ Developmental	Rao et al. (1980)	5453539	Rat	Freestanding NOAEL[a] (one-generation reproduction study)
Reproduction/ Developmental	Zhao et al. (1997)	77864	Rat	Uninformative
Reproduction/ Developmental	Zhao et al. (1989)	200708	Rat	Uninformative
Reproduction/ Developmental	Zhao et al. (1989)	200708	Mouse	Uninformative

[a] No effects observed at highest dose tested for all apical health outcomes rated Low or higher.
[b] Group size of 1–2 per exposure level.

Table 6-9. Dermal Studies Not Considered Suitable for PODs for 1,2-Dichloroethane

Duration Category	Reference	HERO ID	Species	Rationale
Acute	Kronevi et al. (1981)	58151	Guinea pig	Uninformative
Acute	Van Duuren et al. (1979)	94473	Mouse	Uninformative
Acute	Dow Chemical (1956)	725343	Rabbit	Low (no control; LD_{50} study)
Acute	Kettering Laboratory (1943)	4528351	Rabbit	Uninformative
Acute	Dow Chemical (1962)	5447286	Cattle	Low (no sex, strain or n/group reported)
Acute	Mellon Institute (1948)	5447301	Rabbit	Uninformative
Acute	Stauffer Chem Co (1973)	6569955	Rabbit	Negative for skin and eye irritation
Chronic	Van Duuren et al. (1979)	94473	Mouse	Uninformative
Chronic	Suguro et al. (2017)	4451542	Mouse	Study of transgenic mice predisposed to cancer

Table 6-10. Summary of Studies Considered for Non-cancer Dose-Response Assessment of 1,2-Dichloroethane

Reference	Duration Category (Duration)	Species, Strain, and Sex	Study Rating for Non-cancer Endpoints
Oral			
Storer et al. (1984)	Acute (once by gavage)	Mouse (B6C3F1, male)	High
Morel et al. (1999)	Acute (once by gavage)	Mouse (Swiss OF1, male)	High
Cottalasso et al. (2002)	Acute (once by gavage)	Rat (Sprague-Dawley, female)	Medium
Salovsky et al. (2002)	Acute (once by gavage)	Rat (Wistar, male)	Medium
Daniel et al. (1994)	Short-term (10 days by daily gavage)	Rat (Sprague-Dawley, males and female)	High
Munson et al. (1982)	Short-term (14 days by daily gavage)	Mouse (CD-1, male)	High
van Esch et al. (1977)	Short-term (2 weeks by gavage 5 days/week)	Rat (Wistar, male)	High
NTP (1978)	Short-term (6 weeks by gavage 5 days/week)	Rat (Osborne-Mendel, males and female)	Medium
Daniel et al. (1994)	Subchronic (90 days by daily gavage)	Rat (Sprague-Dawley, males and female)	High
van Esch et al. (1977)	Subchronic (90 days by gavage 5 days/week)	Rat (Wistar, males and female)	High
NTP (1991)	Subchronic (13 weeks by gavage, 5 days/week)	Rat (F344, males and female)	High
Payan et al. (1995)	Repro/Dev (15 days, GDs 6–20 by daily gavage)	Rat (Sprague-Dawley, female)	High
Inhalation			
Francovitch et al. (1986)	Acute (4 hours)	Mouse (CD, male)	Medium
Storer et al. (1984)	Acute (4 hours)	Mouse (B6C3F1, male)	High
Dow Chemical (2006b)	Acute (4 or 8 hours)	Rat (F344/ DUCRL, male and female)	High
Sherwood et al. (1987)	Acute (3 hours)	Mouse (CD-1, female)	High
Zhou et al. (2016)	Acute (1.5 or 4 hours)	Rat (Sprague-Dawley, male)	Medium

Reference	Duration Category (Duration)	Species, Strain, and Sex	Study Rating for Non-cancer Endpoints
Qin-li et al. (2010)	Acute (12 hours)	Rat (Sprague-Dawley, male and female)	Medium
Igwe et al. (1986b)	Short-term (30 days; 5 days/week; 7 hours/day)	Rat (Sprague-Dawley, male)	High
Zhang et al. (2017)	Short-term (1 or 4 weeks; 6 hours/day)	Mouse (Swiss, male)	High
Zeng et al. (2018)	Short-term (28 days; 6 hours/day)	Mouse (Swiss, male)	High
IRFMN (1978)	Chronic (12 months; 5 days/week; 7 hours/day)	Rat (Sprague-Dawley, male and female)	Medium
Rao et al. (1980)	Repro/Dev (10 days; 7 hours/day; GDs 6–15)	Rat (Sprague-Dawley, female)	Medium
Rao et al. (1980)	Repro/Dev (13 days; 7 hours/day; GDs 6–18)	Rabbit (New Zealand White, female)	Medium
Payan et al. (1995)	Repro/Dev (15 days; 6 hours/day; GDs 6–20)	Rat (Sprague-Dawley, female)	High
Dermal			
No data			

No dermal exposure studies of 1,2-dichloroethane were considered suitable for use in determining a POD. Table 6-11 through Table 6-15 summarize the NOAELs and LOAELs identified from the oral (acute and short-term/subchronic) and inhalation (acute, short-term/subchronic, and chronic) studies, respectively. Only the endpoint with the lowest LOAEL for a given study was included in the table (if the lowest LOAEL was for multiple endpoints, all were included in the table). Each NOAEL and LOAEL was converted to reflect continuous exposure ($NOAEL_{continuous}$ and $LOAEL_{continuous}$) using Equation_Apx A-3 and Equation_Apx A-4. After adjustment for continuous exposure, each oral NOAEL and LOAEL was converted to a HED using Equation_Apx A-5 and each inhalation NOAEL and LOAEL was converted to a HEC using Equation_Apx A-6 (for extrarespiratory effects) or Equation_Apx A-7 (for nasal effects).

Table 6-11. Summary of Candidate Acute, Non-cancer, Oral PODs for 1,2-Dichloroethane

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL (mg/kg-bw)	LOAEL (mg/kg-bw)	Basis for NOAEL/LOAEL	Candidate POD[b] (mg/kg-bw) (POD Type)	Reference	Study Rating for Target Organ/System
Renal/Kidney (*evidence suggests*)	Mouse (B6C3F1, 5 males/group)	Once (gavage)	NOAEL = 200 $NOAEL_{HED}$ = 26.0	LOAEL = 300 $LOAEL_{HED}$ = 39.0	Significantly increased relative kidney weight (13 percent higher than controls)	19.9 ($BMDL_{10HED}$ for kidney weight)	Storer et al. (1984)	High
	Mouse (Swiss OF1, 10 males/group)	Once (gavage)	NOAEL = 1,000 $NOAEL_{HED}$ = 130	LOAEL = 1,500 $LOAEL_{HED}$ = 195	Increased percentage of damaged proximal tubules	130 ($NOAEL_{HED}$)	Morel et al. (1999)	High
Hepatic/Liver (*evidence suggests*)	Rat (Sprague-Dawley; 10 females/group)	Once (gavage)	ND	LOAEL = 628 $LOAEL_{HED}$ = 151	Significantly increased ALT, AST, and LDH (45, 44, and 67% higher than controls, respectively) and liver steatosis	151 ($LOAEL_{HED}$)	Cottalasso et al. (2002)	Medium
Respiratory (*evidence suggests*)	Rat (Wistar, 4-6 males/group)	Once (gavage)	ND	LOAEL = 136 $LOAEL_{HED}$ = 32.6	Significantly increased total number of cells in BALF; inflammatory and noninflammatory histological changes in lung (data reported qualitatively)	32.6 ($LOAEL_{HED}$)	Salovsky et al. (2002)	Medium

Table 6-12. Summary of Candidate Short-Term/Intermediate, Non-cancer, Oral PODs for 1,2-Dichloroethane

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL (mg/kg-bw/day)	LOAEL (mg/kg-bw/day)	Basis for NOAEL/LOAEL	Candidate POD [b] (mg/kg-bw/day) (POD Type)	Reference	Study Rating for Target Organ/System
Mortality *(evidence demonstrates)*	Rat (SPF Wistar, 6 males/group)	2 weeks (gavage, 5 days/week)	NOAEL = 100 $NOAEL_{continuous}$ = 71.4 $NOAEL_{HED}$ = 7.1	LOAEL = 300 $LOAEL_{continuous}$ = 214 $LOAEL_{HED}$ = 51.4	Mortality in all animals (6/6 animals by day 5)	17.1 ($NOAEL_{HED}$)	van Esch et al. (1977)	High
Nutritional/ Metabolic *(evidence suggests)*	Rat (Sprague-Dawley; 25–26 females/group)	15 days GDs 6–20 (daily gavage)	$NOAEL_{continuous}$ = 158 $NOAEL_{HED}$ = 37.9	$LOAEL_{continuous}$ = 198 $LOAEL_{HED}$ = 47.5	Decreased absolute maternal body weight gain [c] on GDs 6–21 (reduced ≥30 percent relative to controls)	10.0 ($BMDL_{10HED}$ for maternal body weight)	Payan et al. (1995)	High
	Rat (Osborne-Mendel, 5/sex/group)	6 weeks (gavage, 5 days/week)	ND	LOAEL =40 $LOAEL_{continuous}$ = 29 $LOAEL_{HED}$ = 7.0	Decreased body weights (10 percent) in females	7.0 ($LOAEL_{HED}$)	NTP (1978)	Medium
Hepatic/Liver *(evidence suggests)*	Rat (Sprague-Dawley; 10/sex/group)	10 days (gavage, daily)	$NOAEL_{continuous}$ = 30 $NOAEL_{HED}$ = 7.2	$LOAEL_{continuous}$ = 100 $LOAEL_{HED}$ = 24	Significantly increased relative liver weights (14 percent relative to controls) and serum cholesterol levels (data not shown) in males	7.2 ($NOAEL_{HED}$)	Daniel et al. (1994)	High
	Rat (Sprague-Dawley; 10/sex/group)	90 days (gavage, daily)	$NOAEL_{continuous}$ = 37.5 $NOAEL_{HED}$ = 9.00	$LOAEL_{continuous}$ = 75 $LOAEL_{HED}$ = 18	Significantly increased relative liver weight (20 percent higher than controls) and serum ALP (data not shown) in males	9.00 ($NOAEL_{HED}$)	Daniel et al. (1994)	High
	Rat (SPF Wistar, 10/sex/group)	90 days (gavage, 5 days/week)	NOAEL = 30 $NOAEL_{continuous}$ = 21 $NOAEL_{HED}$ = 5.0	LOAEL = 90 $LOAEL_{continuous}$ = 64 $LOAEL_{HED}$ = 15	Significantly increased relative liver weight (13 percent higher than controls) in females	5.0 ($NOAEL_{HED}$)	van Esch et al. (1977)	Medium

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL (mg/kg-bw/day)	LOAEL (mg/kg-bw/day)	Basis for NOAEL/LOAEL	Candidate POD [b] (mg/kg-bw/day) (POD Type)	Reference	Study Rating for Target Organ/System
Renal/ Kidney *(evidence suggests)*	Rat (Sprague-Dawley; 10/sex/group)	90 days (gavage, daily)	$NOAEL_{continuous}$ = 37.5 $NOAEL_{HED}$ = 9.00	$LOAEL_{continuous}$ = 75 $LOAEL_{HED}$ = 18	Significantly increased relative kidney weights in males and females (18 and 15 percent higher than controls, respectively)	9.00 ($NOAEL_{HED}$)	Daniel et al. (1994)	High
	Rat (SPF Wistar, 10/sex/group)	90 days (gavage, 5 days/week)	NOAEL = 30 $NOAEL_{continuous}$ = 21 $NOAEL_{HED}$ = 5.0	LOAEL = 90 $LOAEL_{continuous}$ = 64 $LOAEL_{HED}$ = 15	Significantly increased relative kidney weight (17 and 16 percent higher than controls in males and females, respectively)	5.0 ($NOAEL_{HED}$)	van Esch et al. (1977)	Medium
	Rat (F344; 10/sex/group)	13 weeks (gavage, 5 days/week)	ND	LOAEL = 30 $LOAEL_{continuous}$ = 21 $LOAEL_{HED}$ = 5	Significantly increased absolute kidney weights in males (9 percent higher than controls)	3.4 ($BMDL_{10HED}$ for absolute kidney weight)	NTP (1991)	High
			NOAEL = 37 $NOAEL_{continuous}$ = 26 $NOAEL_{HED}$ = 6.2	LOAEL = 75 $LOAEL_{continuous}$ = 54 $LOAEL_{HED}$ = 13	Increased absolute and relative kidney weights in females (12 and 10 percent higher than controls, respectively)	6.2 ($NOAEL_{HED}$)		
Immune/ Hematological *(evidence suggests)*	Mouse (CD-1; 10-12 males/group)	14 days (daily gavage)	ND	$LOAEL_{continuous}$ = 4.89 $LOAEL_{HED}$ = 0.636	Suppression of humoral and cell-mediated immune responses	0.636 ($LOAEL_{HED}$)	Munson et al. (1982)	High

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Table 6-13. Summary of Candidate Acute, Non-cancer, Inhalation PODs for 1,2-Dichloroethane[a]

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL	LOAEL	Basis for NOAEL/LOAEL	Candidate POD[a] (POD Type)	Reference	Study Rating for Target Organ/System
Mortality *(evidence demonstrates)*	Mouse (CD-1, 10–15 males/group)	4 hours	ND	LOAEL = 4,050 mg/m^3 (1,000 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 675 mg/m^3 (167 ppm)	Dose-related increase in mortality compared with controls (quantitative data not reported)	675 mg/m^3 or 167 ppm ($LOAEL_{HEC}$)	Francovitch et al. (1986)	Medium
Renal/Kidney *(evidence suggests)*	Mouse (B6C3F1, 5 males/group)	4 hours	NOAEL = 639 mg/m^3 (158 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 107 mg/m^3 (26.3 ppm)	LOAEL = 2,020 mg/m^3 (499 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 337 mg/m^3 (83.2 ppm)	Significantly increased serum BUN and relative kidney weight (85 and 12 percent higher than controls, respectively)	207 mg/m^3 or 51.1 ppm ($BMCL_{10HEC}$ for relative kidney weight)	Storer et al. (1984)	High
Hepatic/Liver *(evidence suggests)*	Mouse (B6C3F1, 5 males/group)	4 hours	NOAEL = 639 mg/m^3 (158 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 107 mg/m^3 (26.3 ppm)	LOAEL = 2020 mg/m^3 (499 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 337 mg/m^3 (83.2 ppm)	Increased serum ALT (2-fold higher than controls [ns]) and SDH (11-fold higher than controls; $p \leq 0.05$)	107 mg/m^3 or 26.3 ppm ($NOAEL_{HEC}$)	Storer et al. (1984)	High
Lung/ Respiratory *(evidence suggests)*	Rat (F344/ DUCRL, 5/sex/group)	4 hours	NOAEL = 212 mg/m^3 (52.4 ppm) $NOAEL_{continuous}$ = 35.3 mg/m^3 (8.73 ppm) $NOAEL_{HEC}$ = 7.06 mg/m^3 (1.74 ppm)	LOAEL = 794.9 mg/m^3 (196.4 ppm) $LOAEL_{continuous}$ = 132.5 mg/m^3 (32.73 ppm) $LOAEL_{HEC}$ = 26.50 mg/m^3 (6.547 ppm)	Histological changes to the olfactory mucosa in males and females	1.75 mg/m^3 or 0.432 ppm ($BMCL_{10HEC}$ for degeneration with necrosis in males and females)	Dow Chemical (2006b)	High

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL	LOAEL	Basis for NOAEL/LOAEL	Candidate POD[a] (POD Type)	Reference	Study Rating for Target Organ/System
Lung/ Respiratory (evidence suggests)	Rat (F344/ DUCRL, 10/sex/group)	4 hours	ND	LOAEL = 794.9 mg/m^3 (196.4 ppm) $LOAEL_{continuous}$ = 132.5 mg/m^3 (32.73 ppm) $LOAEL_{HEC}$ = 26.50 mg/m^3 (6.547 ppm)	Histological changes to the olfactory mucosa in males and females	4.636 mg/m^3 or 1.145 ppm ($BMCL_{10HEC}$ for regeneration in males and females)	Dow Chemical (2006b)	High
	Rat (F344/ DUCRL, 5/sex/group)	8 hours	NOAEL 214 mg/m^3 (52.8 ppm) $NOAEL_{continuous}$ = 71.3 mg/m^3 (17.6 ppm) $NOAEL_{HEC}$ = 14.3 mg/m^3 (3.52 ppm)	LOAEL = 435.1 mg/m^3 (107.5 ppm) $LOAEL_{continuous}$ = 145.0 mg/m^3 (35.83 ppm) $LOAEL_{HEC}$ = 29.01 mg/m^3 (7.166 ppm)	Histological changes to the olfactory mucosa in males and females	9.78 mg/m^3 or 2.42 ppm ($BMCL_{10HEC}$ for degeneration with necrosis in males and females)	Dow Chemical (2006b)	High
Immune/ Hematological *(evidence suggests)*	Mouse (CD-1, 140 females/ group)	3 hours	NOAEL = 9.3 mg/m^3 (2.3 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 1.2 mg/m^3 (0.29 ppm)	LOAEL = 22 mg/m^3 (5.4 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 2.8 mg/m^3 (0.68 ppm)	Mortality following streptococcal challenge	1.2 mg/m^3 or 0.29 ppm ($NOAEL_{HEC}$)	Sherwood et al. (1987)	High (Note: Mice inhaled ~2E04 aerosolized streptococci 1 hour after exposure. This is unlikely to represent typical immunological challenges in humans).

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL	LOAEL	Basis for NOAEL/LOAEL	Candidate POD[a] (POD Type)	Reference	Study Rating for Target Organ/System
Neurological/ Behavioral *(evidence likely)*	Rat (Sprague-Dawley, 6 males/group)	1.5 hours	ND	LOAEL = 3,950 mg/m^3 (975.9 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 246.9 mg/m^3 (61.00 ppm)	Changes in brain histopathology	246.9 mg/m^3 or 61.00 ppm ($LOAEL_{HEC}$)	Zhou et al. (2016)	Medium
	Rat (Sprague-Dawley, 12/sex/group)	12 hours	NOAEL = 2,500 mg/m^3 (617.7 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 1,250 mg/m^3 (308.9 ppm)	LOAEL = 5,000 mg/m^3 (1,240 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 2,500 mg/m^3 (620 ppm)	Clinical signs of neurotoxicity and changes in brain histology	1250 mg/m^3 or 308.9 ppm ($NOAEL_{HEC}$)	Qin-li et al. (2010)	Medium

[a] BMCLs are presented as HECs for comparison with other candidate PODs. BMCL1SD = BMCL for benchmark response of 1 standard deviation change from control mean. $BMCL_{10}$ = BMCL for benchmark response of 10 percent relative deviation from control mean. $BMCL_{10}$ = BMCL for benchmark response of 10 percent extra risk.

Table 6-14. Summary of Candidate Short-Term/Intermediate, Non-cancer, Inhalation PODs for 1,2-Dichloroethane[a]

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL	LOAEL	Basis for NOAEL/LOAEL	Candidate POD[a] (POD Type)	Reference	Study Rating for Target Organ/System
Mortality *(evidence demonstrates)*	Rat (Sprague-Dawley, 12 males/group)	30 days 5 days/week 7 hours/day	NOAEL = 619 mg/m^3 (153 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 129 mg/m^3 (31.9 ppm)	LOAEL = 1,230 mg/m^3 (304 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 256 mg/m^3 (63.3 ppm)	Mortality (1/12 animals)	154 mg/m^3 or 38.0 ppm ($BMCL_{10HEC}$ for mortality)	Igwe et al. (1986b, 1986c)	High
	Rat (Sprague-Dawley, 16–30 females/group)	10 days 7 hours/day GD 6–15	NOAEL = 405 mg/m^3 (100 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 118 mg/m^3 (29.2 ppm)	LOAEL = 1,210 mg/m^3 (300 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 353 mg/m^3 (87.5 ppm)	Mortality (10/16 animals)	118 mg/m^3 or 29.2 ppm ($NOAEL_{HEC}$)	Rao et al. (1980)	Medium
	Rat (Sprague-Dawley, 26 females/ group)	15 days 6 hours/day GD 6–20	NOAEL = 1,030 mg/m^3 (254 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 258 mg/m^3 (63.5 ppm)	LOAEL = 1,330 mg/m^3 (329 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 333 mg/m^3 (82.3 ppm)	Mortality (2/26 dams)	258 mg/m^3 or 63.5 ppm ($NOAEL_{HEC}$)	Payan et al. (1995)	High
	Rabbit (New Zealand White, 19–21 females/ group)	13 days 7 hours/day GD 6–18	ND	LOAEL = 405 mg/m^3 (100 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 118 mg/m^3 (29.2 ppm)	Mortality (4/21 animals)	59.4 mg/m^3 or 14.7 ppm ($BMCL_{10HEC}$ for mortality)	Rao et al. (1980)	Medium

Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL	LOAEL	Basis for NOAEL/LOAEL	Candidate POD[a] (POD Type)	Reference	Study Rating for Target Organ/System
Hepatic/Liver *(evidence suggests)*	Mouse (Swiss, 10 males/ group)	28 days 6 hours/day	ND	LOAEL = 363.58 mg/m^3 (89.830 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 90.895 mg/m^3 (22.457 ppm)	Increased absolute and relative liver weights (≥10 percent higher than controls)	51.720 mg/m^3 or 12.778 ppm ($BMCL_{10HEC}$ for relative liver weight)	Zeng et al. (2018)	High
Reproductive/ Developmental *(evidence suggests)*	Mouse (Swiss, 5-15 males/ group)	4 weeks 6 hours/day	ND	LOAEL = 102.70 mg/m^3 (25.374 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 25.675 mg/m^3 (6.3435 ppm)	Changes in sperm parameters (increased total, sperm head, body, and tail abnormalities; decreased sperm concentration; decreased height of seminiferous tubules and height of germinal epithelium)	21.240 mg/m^3 or 5.2500 ppm ($BMCL_{5HEC}$ for sperm concentration) 18.815 mg/m^3 or 4.6486 ppm ($BMCL_{1SDHEC}$ for seminiferous tubule height) 8.6304 mg/m^3 or 2.1323 ppm ($BMCL_{1SDHEC}$ for germinal epithelium height)	Zhang et al. (2017)	High

[a] BMCLs are presented as HECs for comparison with other candidate PODs. $BMCL_{1SD}$ = BMCL for benchmark response of 1 standard deviation change from control mean. $BMCL_{10}$ = BMCL for benchmark response of 10 percent relative deviation from control mean. $BMCL_{10HEC}$ = BMCL for benchmark response of 5 percent relative deviation from control mean. $BMCL_{10}$ = BMCL for benchmark response of 10 percent extra risk.

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Target Organ/ System	Species (Strain, Sex, n/Group)	Exposure	NOAEL	LOAEL	Basis for NOAEL/LOAEL	Candidate POD[a] (POD Type)	Reference	Study Rating for Target Organ/System
Hepatic/Liver *(evidence suggests)*	Rat (Sprague-Dawley, 8-10/sex/group)	12 months 5 days/week 7 hours/day	NOAEL = 40 mg/m^3 (10 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 8.3 mg/m^3 (2.1 ppm)	LOAEL = 200 mg/m^3 (50 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 42 mg/m^3 (10 ppm)	Increased ALT (>2-fold higher than controls) and LDH (18 percent higher than controls) in males	8.3 mg/m^3 or 2.1 ppm ($NOAEL_{HEC}$)	IRFMN (1978)	Medium
			NOAEL = 40 mg/m^3 (10 ppm) $NOAEL_{continuous}$ = $NOAEL_{HEC}$ = 8.3 mg/m^3 (2.1 ppm)	LOAEL = 200 mg/m^3 (50 ppm) $LOAEL_{continuous}$ = $LOAEL_{HEC}$ = 42 mg/m^3 (10 ppm)	Increased ALT (>2-fold higher than controls) and LDH (25 percent higher than controls) in females	1.7 mg/m^3 or 0.42 ppm ($BMCL_{1SDHEC}$ for LDH in females)		

[a] BMCLs are presented as HECs for comparison with other candidate PODs. $BMCL_{1SD}$ = BMCL for benchmark response of 1 standard deviation change from control mean. $BMCL_{10}$ = BMCL for benchmark response of 10 percent relative deviation from control mean. $BMCL_{10}$ = BMCL for benchmark response of 10 percent extra risk.

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6.3 Endpoint Derivation for Carcinogenic Dose-Response Assessment

EPA used the oral cancer slope factors from 1,2-dichloroethane, based on hepatocellular carcinomas in male mice NTP (1978). The inhalation unit risk for 1,2-dichloroethane was based on read-cross from an inhalation study for 1,2-dichloroethane by Nagano et al. (2006). EPA conducted BMD modeling on these data as described below.

The BMD modeling of cancer incidence data was conducted with the EPA's BMD software (BMDS, version 3.3). Modeled concentrations were in units of ppm. For these data, the Multistage model was fit to the incidence data using a BMR of 10 percent ER. The Multistage cancer model was run for all polynomial degrees up to n–1 (where n is the number of dose groups including control). Adequacy of model fit was judged based on the chi-square goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest AIC was selected if the BMDLs were sufficiently close (< 3-fold); if the BMDLs were not sufficiently close (> 3-fold), model-dependence is indicated, and the model with the lowest reliable BMDL was selected.

Where applicable, the MS Combo model was used to evaluate the combined cancer risk of tumors observed in multiple tissues in a test group, assuming that the tumors in the different tissues occurred independently. MS Combo was run using the incidence data for the individual tumors and the polydegrees identified in the model runs for the individual tumors.

6.3.1 Cancer Dose-Response Assessment

IUR for Inhalation Exposures

In 1987, EPA's Integrated Risk Information System (IRIS) program derived an IUR of 2.6×10^{-5} (per $\mu g/m^3$) based on route-to-route extrapolation from the oral CSF derived at the same time. The inhalation cancer bioassay by Nagano et al. (2006) was not available at the time of the IRIS assessment.

IUR estimates based on the tumor data sets in Nagano et al. (2006) were calculated using the following equation (Equation 6-1):

Equation 6-1.

$$IUR = BMR/HEC$$

Where:

BMR = Benchmark response

HEC = Human equivalent concentration in $\mu g/m^3$

A BMR of 10 percent extra risk was selected for all data sets. HECs were calculating using the ratio of blood/gas partition coefficients, as shown in Gargas and Andersen (1989), estimated blood/air partition coefficients for 1,2-dichloroethane of 19.5 and 30.4 in humans and rats, respectively. Because the rat partition coefficient is greater than the human partition coefficient, the default ratio of 1 is used in the calculation in accordance with U.S. EPA (1994) guidance. A blood/air partition coefficient for mice was not available from the literature reviewed; thus, the default ratio of 1 was used to calculate HECs for data in mice.

Details of the BMD modeling are provided in *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling* (U.S. EPA, 2024a) and a summary of the BMCL, HEC, and IUR estimate for each data set are shown in Table 6-16.

Table 6-16. IUR Estimates for Tumor Data from Nagano et al. (2006) Study of 1,2-Dichloroethane Using Linear Low-Dose Extrapolation Approach

Species and Sex	Tumor Type	Selected Model	$BMCL_{10}$ (ppm)	$BMCL_{10}$ (µg/m^3)	HEC (µg/m^3)	IUR Estimate (µg/m^3)$^{-1}$
Male rats	Subcutaneous fibroma	Multistage 1-degree	7	28,332	28,332	3.5E−06
	Mammary gland fibroadenomas	Multistage 1-degree	17	68,807	68,807	1.5E−06
	Mammary gland fibroadenomas and adenomas combined	Multistage 3-degree	15	60,712	60,712	1.6E−06
	Peritoneal mesothelioma	Multistage 3-degree	19	76,901	76,901	1.3E−06
	Combined mammary gland, subcutaneous, and peritoneum tumors	MS Combo	5	20,237	20,237	4.9E−06
Female rats	Subcutaneous fibroma	Multistage 1-degree	17	68,807	68,807	1.5E−06
	Mammary gland adenomas	Multistage 1-degree	9	36,427	36,427	2.7E−06
	Mammary gland fibroadenomas	Multistage 1-degree	8	32,380	32,380	3.1E−06
	Mammary gland fibroadenomas and adenomas combined	Multistage 1-degree	5	20,237	20,237	4.9E−06
	Mammary gland adenocarcinoma	Multistage 3-degree	23	93,091	93,091	1.1E−06
	Mammary gland fibroadenomas adenomas, and adenocarcinomas combined	Multistage 1-degree	4	16,190	16,190	6.2E−06
	Combined mammary gland and subcutaneous tumors	MS Combo	4	16,190	16,190	6.2E−06
Female mice	Bronchiolo-alveolar adenomas	Multistage 3-degree	9	36,427	36,427	2.7E−06
	Bronchiolo-alveolar carcinomas	Multistage 2-degree	14	56,664	56,664	1.8E−06
	Bronchiolo-alveolar adenomas and carcinomas combined	Multistage 2-degree	7	28,332	28,332	3.5E−06
	Mammary gland adenocarcinomas	Multistage 3-degree	10	40,474	40,474	2.5E−06
	Hepatocellular adenomas	Multistage 3-degree	11	44,522	44,522	2.2E−06
	Hepatocellular adenomas and carcinomas combined	Multistage 2-degree	10	40,474	40,474	2.5E−06
	Combined lung, mammary gland, and liver tumors[a]	MS Combo	5	20,237	20,237	4.9E−06

[a] In addition to the tumor types shown in the table, EPA conducted BMD modeling on the combined incidence of lung, mammary gland, and liver tumors and endometrial stromal polyps to evaluate whether including the polyps would result in a lower $BMCL_{10}$. The $BMCL_{10}$ for combined tumors with polyps was 5 ppm (20 µg/m^3), unchanged from the $BMCL_{10}$ without the polyps.

The highest estimated IUR is 6.2×10^{-6} (per µg/m^3) for combined mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas in female rats in the inhalation study by Nagano et al. (2006).

CSF for Oral Exposures

The IRIS program derived an oral CSF of 9.1×10^{-2} (per mg/kg-bw/day) for 1,2-dichloroethane in 1987 based on the incidence of hemangiosarcomas in male rats in the chronic bioassay by NTP (1978), however, this study did not pass EPA systematic review. The IRIS CSF was derived using time-to-tumor modeling to account for intercurrent mortality of the rats in the NTP (1978) study. No updates to the time-to-tumor modeling approach have been made since the 1987 assessment. Hemangiosarcomas in male rats were determined to be the most sensitive species, strain, and site, however this study was deemed unacceptable by EPA systematic review. Although CSF does not account for other tumor types induced by 1,2-dichloroethane in the male rat, there is currently no time-to-tumor modeling approach available that accounts for multiple tumor types.

The IRIS program also derived an oral CSF for male mice based on hepatocarcinomas of 6.2×10^{-2} (per mg/kg-bw/day) also from the NTP (1978) study. No oral cancer bioassays of 1,2-dichloroethane have been published since the IRIS assessment. Therefore, the oral CSF for 1,2-dichloroethane from the NTP (1978) mouse study was selected for use in assessment of cancer risks associated with exposure to 1,2-dichloroethane. This mouse CSF was also used to calculate a drinking water unit risk of 1.8×10^{-6} per ug/L using a drinking water intake of 2 L/day and body weight of 70 kg.

CSF for Dermal Exposures

There are no reliable dermal cancer studies of 1,2-dichloroethane; thus, the CSF for 1,2-dichloroethane was obtained from route-to-route extrapolation using oral data. There are uncertainties associated with extrapolation from both oral and inhalation. Use of an oral POD for dermal extrapolation may not be preferred for chemicals known to undergo extensive liver metabolism because the "first-pass effect" that directs intestinally absorbed chemicals directly to the liver applies only to oral ingestion. In contrast, the accuracy of extrapolation of inhalation toxicity data for dermal PODs is dependent on assumptions about inhalation exposure factors such as breathing rate and any associated dosimetric adjustments. Whole-body inhalation studies may also already be incorporating some level of dermal absorption. Given these competing uncertainties, in the absence of data to support selection of either the oral CSF or inhalation IUR, the method resulting in the most protective dermal CSF was selected. The value of the oral CSF is 6.2×10^{-2} (per mg/kg-bw/day). For comparison, a CSF of 3.3×10^{-2} (per mg/kg-bw/day) was obtained using route-to-route extrapolation from the IUR of 6.0×10^{-6} per $\mu g/m^3$ (6.0×10^{-3} per mg/m^3) per Equation 6-2 as follows:

Equation 6-2.

$$\text{Dermal CSF (per mg/kg-bw/day)} = 6.0\times10^{-3}\ (\text{per mg/m}^3) \times (80\ \text{kg}/14.7\ \text{m}^3/\text{day})$$
$$= 3.3\times10^{-2}\ (\text{per mg/kg-bw/day})$$

The more protective value of 6.2×10^{-2} per mg/kg-bw/day based on the oral CSF was selected for the dermal CSF.

6.3.2 Summary of Continuous and Worker PODs

The continuous IUR was adjusted for occupational scenarios using equations provided in Equation_Apx A-13. Table 6-17 provides a summary of the cancer PODs for both continuous and occupational exposure scenarios.

Table 6-17. Summary of Cancer PODs for 1,2-Dichloroethane

Route	Continuous POD	Worker POD	Reference
Inhalation	6.0E−06 (per µg/m^3)	2.1E−06 (per µg/m^3)	Nagano et al. (2006)
Oral	6.2E−02 (per mg/kg-bw/day)	Same as continuous	NTP (1978)
Dermal	6.2E−02 (per mg/kg-bw/day)	Same as continuous	Route-to-route extrapolation from oral

6.4 Weight of Scientific Evidence Conclusions for Human Health Hazard

The weight of scientific evidence supporting the human health hazard assessment is based on the strengths, limitations, and uncertainties associated with the hazard studies identified. The weight of scientific evidence is summarized using confidence descriptors: robust, moderate, slight, or indeterminate. This approach is consistent with the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021). When weighing and integrating evidence to estimate the potential that 1,2-dichloroethane may cause a given non-cancer or cancer health hazard endpoint (*e.g.*, immune system, reproductive, and hepatocarcinomas), EPA uses several factors adapted from Sir Bradford Hill (Hill, 1965). These elements include consistency, dose-response relationship, strength of the association, temporal relationship, biological plausibility, and coherence among other considerations.

EPA considered evidence integration conclusions from Sections 3, 4, 5 and additional factors when choosing studies for dose-response modeling and for each exposure scenario (acute, short-term/subchronic, and chronic), as described in Section 6. Additional considerations pertinent to the overall hazard confidence levels include evidence integration conclusions, selection of the critical endpoint and study, relevance to the exposure scenario, dose-response considerations and PESS sensitivity.

Weight of Scientific Evidence Conclusions

For complete details on weight of scientific evidence conclusions within evidence streams, see the evidence profile tables for each organ domain in Appendix B. For a more detailed description of the hazard database and weight of scientific evidence evaluation see *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021) for details on the process of evidence evaluation and integration.

PESS

Relevant data on lifestages and target organs were evaluated to identify potentially susceptible subpopulations exposed to 1,2-dichloroethane. An evaluation of 1,2-dichloroethane in animals identified non-cancer effects such as (1) increased kidney weight (reported by Storer et al. (1984)); (2) degeneration with necrosis of the olfactory mucosa (reported by Dow Chemical (2006b)); (3) suppression of immune response (reported by Munson et al. (1982)); and (4) decreases in sperm concentrations (reported by Zhang et al. (2017)); and cancer effects such as (5) liver cancer (based on hepatocarcinomas in male mice (NTP, 1978); and (4) combined mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas Nagano et al. (2006). These effects were considered as representative of the potential for greater biological susceptibility across subpopulations. In addition, significant decreases in maternal body weight gain were observed in a prenatal developmental toxicity study by Payan et al. (1995), which could support the pregnant female as having greater biological susceptibility.

Although information on other considerations potentially impacting greater biological susceptibility (such as pre-existing disease, lifestyle activities, sociodemographic factors, nutritional status, genetic predispositions, or other chemical co-exposures and non-chemical stressors), was sparse, there is some information on 1,2-dichloroethane as impacting greater biological susceptibility. For example, individuals with impaired renal function based on evidence that 1,2-dichloroethane is nephrotoxic in animals, people with compromised immune systems may be particularly susceptible to exposure to 1,2-dichlorethane based on evidence that 1,2-dichloroethane is immunotoxic, individuals with chronic respiratory disease because of the effects on the olfactory mucosa induced by 1,2-dichloroethane, and finally, impacts on male reproduction based on evidence that 1,2-dichloroethane causes decreases in sperm concentration in animals.

For PESS, specifically susceptibility, across the database for 1,2-dichloroethane, uncertainty exists based on limited number of studies, and the differences in results and comprehensiveness of endpoints assessed towards specific health outcomes across studies.

6.4.1 Overall Confidence – Strengths, Limitations, Assumptions, and Key Sources of Uncertainty in the Human Health Hazard Assessment

1,2-dichloroethane lacked adequate data by the dermal route for any exposure duration. Therefore, EPA used a route-to-route extrapolation approach from the available 1,2-dichloroethane oral data to fill in the dermal data gap. EPA also has high confidence in this approach. Since both oral and dermal routes are similar metabolically and by-pass first pass metabolism through the liver, and since oral ADME studies showed that most of the 1,2-dichloroethane oral dose was eliminated unchanged in expired air, oral PODs were used for extrapolation via the dermal route.

EPA has high confidence in the human health hazard database for 1,2-dichloroethane and in the selection of the critical PODs. This is based on several reasons. First, all studies used to assess the hazards for 1,2-dichloroethane were rated high to medium in SR. Second, critical non-cancer effects that were ultimately selected as PODs for quantitative risk estimates (kidney toxicity, neurotoxicity, immunotoxicity, and reproductive toxicity), were considered the most sensitive and biologically relevant effects, supported by multiple lines of evidence that spanned across species, routes, and durations of exposure (see Section 6.1 and endpoint selection tables: Table 6-1, Table 6-2, Table 6-3, Table 6-4, Table 6-5, and Table 6-6).

While EPA has high confidence in the hazard identification of PODs used for quantitative risk estimates, there are some uncertainties in the 1,2-dichloroethane database. For example, while there were several studies via the chronic exposure duration for both oral and inhalation exposures, none of those studies were selected for the chronic POD for a variety of reasons including the identified NOAELs/LOAELs were higher than the recommended endpoint, or there were limited endpoints evaluated, or other methodological issues (see endpoint selection tables: Table 6-5 and Table 6-6). As a result, subchronic data was used for the chronic POD and an uncertainty factor (UF_s) of 10 was applied to account for the use of a short-term study for long-term (chronic) assessment.

Table 6-18 presents a summary of confidence for each hazard endpoint and relevant exposure duration based on critical human health hazards considered for the acute, short-term/intermediate, chronic, and lifetime exposure scenarios used to calculate risks.

EPA considered evidence integration conclusions from Sections 3, 4, 5 and additional factors listed below when choosing studies for dose-response modeling and for each relevant exposure scenario (acute, short-term/intermediate, and chronic), as described in Section 6.4.

2085 **Table 6-18. Confidence Summary for Human Health Hazard Assessment**

Hazard Domain	Evidence Integration Conclusion	Selection of Most Critical Endpoint and Study	Relevance to Exposure Scenario	Dose-Response Considerations	PESS Sensitivity	Overall Hazard Confidence
Acute non-cancer						
Oral						
Kidney	+++	+++	+++	++	++	Robust
Inhalation						
Neurotoxicity[a]	+++	+++	+++	++	+++	Robust
Short-term/intermediate non-cancer						
Oral						
Immunotoxicity	+++	+++	+++	++	+++	Robust
Inhalation						
Reproductive	+++	+++	+++	++	+++	Robust
Chronic non-cancer						
Oral						
Immunotoxicity	+++	+++	++	++	+++	Robust
Inhalation						
Reproductive	+++	+++	++	++	+++	Robust
Cancer						
Cancer[b c]	+++	+++	+++	+++	+++	Robust

+ + + Robust confidence suggests thorough understanding of the scientific evidence and uncertainties. The supporting weight of the scientific evidence outweighs the uncertainties to the point where it is unlikely that the uncertainties could have a significant effect on the hazard estimate.
+ + Moderate confidence suggests some understanding of the scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize hazard estimates.
+ Slight confidence is assigned when the weight of the scientific evidence may not be adequate to characterize the scenario, and when the assessor is making the best scientific assessment possible in the absence of complete information. There are additional uncertainties that may need to be considered.
[a] Degeneration with necrosis of olfactory mucosa
[b] Oral based on hepatocellular carcinomas
[c] Inhalation based on combined tumors (mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas)

2086
2087

7 POTENTIALLY EXPOSED OR SUSCEPTIBLE SUBPOPULATIONS

EPA considered PESS throughout the exposure assessment and throughout the hazard identification and dose-response analysis. EPA has identified several factors that may contribute to a group having increased exposure or biological susceptibility. Examples of these factors include lifestage, preexisting disease, occupational and certain consumer exposures, nutrition, and lifestyle activities.

For the 1,2-dichloroethane draft risk evaluation, EPA accounted for the following PESS groups: infants exposed to drinking water during formula bottle feeding, subsistence and Tribal fishers, pregnant women and people of reproductive age, individuals with compromised immune systems or neurological disorders, workers, people with the aldehyde dehydrogenase-2 mutation which is more likely in people of Asian descent, lifestyle factors such as smoking cigarettes or secondhand smoke, and communities who live near facilities that emit 1,2-dichloroethane.

Table 7-1 summarizes how PESS were incorporated into the risk evaluation and the remaining sources of uncertainty related to consideration of PESS.

Additional information on other factors that could possibly impact greater biological susceptibility following exposure to 1,2-dichloroethane—such as more comprehensive information on pre-existing diseases in humans, lifestyle activities, nutritional status, or other chemical co-exposures and non-chemical stressors—was limited.

2109 **Table 7-1. Summary of PESS Categories in the Draft Risk Evaluation and Remaining Sources of Uncertainty**

PESS Categories	Potential Sources of Biological Susceptibility Incorporated into Hazard Assessment
Lifestage	Direct evidence of a reproductive/developmental effect was the basis for the chronic inhalation POD used for risk estimation. Other reproductive/developmental data was difficult to interpret across the chemical databases, including fetal resorptions. 1,2-dichloroethane partitions in the milk of women exposed dermally (ATSDR, 2022; Urusova, 1953) Children in households that smoke cigarettes, receiving secondhand smoke, may be exposed to higher levels of 1,2-dichloroethane (ATSDR, 2022); (Wang 2012). The increase in susceptibility due to secondhand smoke is not known and is a source of uncertainty in part reliant on proximity to the smoker, space ventilation, and frequency of smoking/number of cigarettes smoked. Evidence in mice revealed a statistically significant increase in benign uterine endometrial stromal polyps in high-dose analog 1,2-dichloroethane females which may have implications for women of childbearing age, or fertility challenges. Evidence also from mice showed changes in sperm parameters in decreases in sperm count following short-term exposures to the analog 1,2-dichloroethane. Potential susceptibility of older adults due to toxicokinetic differences was addressed through a UF of 10 for human variability.
Pre-existing Disease	Indirect evidence suggesting chronic liver disease may delay detoxification was addressed qualitatively and through the UF of 10 for human variability. (ATSDR, 2022) indicates concern for individuals with compromised immune systems exposed to 1,2-dichloroethane. Observed impaired motor activity and CNS depression, from evidence in rats following 1,2-dichloroethane exposure, have potential implications for greater susceptibility in people with Parkinson's Disease, other neurological disorders. The increase in susceptibility due to pre-existing disease is not known and is a source of uncertainty.
Lifestyle Activities	People that smoke cigarettes may be exposed to higher levels of 1,2-dichloroethane. Mean concentration of 0.32 µg/m3 (0.079 ppb) in homes of smokers vs. the home of nonsmokers of 0.03 µg/m3 (0.007 ppb) (ATSDR, 2022).
Occupational Exposures	EPA did not identify occupational exposures that influence susceptibility.
Sociodemographic	EPA did not identify sociodemographic factors that influence susceptibility.
Geography and site-specific	EPA did not specifically identify geography and/or site-specific factors that influence susceptibility.
Nutrition	EPA did not identify nutritional factors that influence susceptibility.
Genetics/ Epigenetics	Indirect evidence that genetic variants may increase susceptibility of the target organ was addressed through a UF of 10 for human variability. However, a known metabolite of 1,2-dichloroethane is the reactive 2-chloroacetaldehyde supporting that a PESS group are people with the aldehyde dehydrogenase-2 mutation which is more likely in people of Asian descent which have increased rates of cancer due to decreased reactive aldehyde clearance, which is not addressed by the UFH (~28–54 percent incidence in Asians, ~7 million in the United States). Cancer studies in animals with the aldehyde dehydrogenase-2 clearance enzyme mutation are not available to quantitatively assess this PESS group.
Other Unique Activities	EPA did not identify unique activities that influence susceptibility.
Aggregate Exposures	Not relevant to susceptibility.
Other Chemical and Nonchemical Stressors	EPA did not identify other chemical and nonchemical stressors that influence susceptibility.

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8 PODS FOR NON-CANCER AND CANCER HUMAN HEALTH HAZARD ENDPOINTS

Table 8-1, Table 8-2, and Table 8-3 list the non-cancer PODs and corresponding HECs, HEDs, and UFs that EPA used in the draft 1,2-dichloroethane risk evaluation to estimate risks following acute, short-term/subchronic, and chronic exposure, respectively. Table 8-4 provides the cancer PODs for evaluating lifetime exposure.

2117 **Table 8-1. PODs and Toxicity Values Used to Estimate Non-cancer Risks for Acute Exposure Scenarios[a]**

Target Organ/ System [a]	Species/ Gender	Duration/ Route	Study POD/Type	Effect	Worker HEC [b] (mg/m^3) [ppm]	Continuous HEC [b] (mg/m^3) [ppm]	Worker HED [c] (mg/kg-bw/day)	Continuous HED [c] (mg/kg-bw/day)	Uncertainty Factors [g]	Total Uncertainty Factors	Reference	Data Quality
Renal	Mice (male)	**Oral** 1-day oral gavage	$BMDL_{10}$ = 153 mg/kg BMD = 270 mg/kg	Increased kidney weight	N/A	N/A	19.9	19.9	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1	30 [d]	Storer et al. (1984)	High
Neurological	Rats (males and females combined)	**Inhalation** 8-hour inhalation	BMC_{10} = 48.9 mg/m^3 or 12.1 ppm	Degeneration with necrosis of the olfactory mucosa	(41.1 mg/m^3) [10.14 ppm]	(9.78 mg/m^3) [2.42 ppm]	N/A	N/A	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1	30 [e]	Dow Chemical (2006b)	High
Renal	Mice (male)	**Dermal (extrapolated from oral)** 1-day oral gavage	$BMDL_{10}$ = 153 mg/kg BMD=270 mg/kg	Increased kidney weight	N/A	N/A	19.9	19.9	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1	30 [f]	Storer et al. (1984)	High

Target Organ/ System [a]	Species/ Gender	Duration/ Route	Study POD/Type	Effect	Worker HEC [b] (mg/m^3) [ppm]	Continuous HEC [b] (mg/m^3) [ppm]	Worker HED [c] (mg/kg-bw/day)	Continuous HED [c] (mg/kg-bw/day)	Uncertainty Factors [g]	Total Uncertainty Factors	Reference	Data Quality

[a] See Section 3 for details.
[b] $BMCL_{10}$ of 48.9 mg/m^3 continuous adjusted × RGDR value (0.2) = 9.78 mg/m^3 for the HEC for continuous (adjusted for 24 hours). The HEC for the worker is the HEC_{cont} × 4.2 (hours in a week divided by the # of working hours in a week; 168/40) = 60.1 mg/m^3. Both HEC worker and continuous were converted to ppm by dividing by a factor of 4.05 (based 24.45/MW).
[c] $BMDL_{10}$ of 153 × DAF (0.13 $BW^{3/4}$ for mice) = 20.3 mg/kg. All oral PODs were first adjusted to 7 days/week and inhalation PODs adjusted to 24 hours/day, 7 days/week (continuous exposure). All continuous oral PODs were then converted to HEDs using DAFs. Dermal PODs were set equal to the oral HED. It is often necessary to convert between ppm and mg/m^3 due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all inhalation PODs in equivalents of both units to avoid confusion and errors. PODs converted for use in worker exposure scenarios were adjusted to 8 hours/day, 5 days/week and converted to HECs.
[d] POD identified from acute exposure by the **oral route** to 1,2-dichloroethane. An acute-duration oral HED for both worker and continuous exposure of 5.56 mg/kg-bw/day was used for risk assessment of acute oral exposure, with a total uncertainty factor of 30, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability.
[e] POD identified from acute exposure by the **inhalation route** to 1,2-dichloroethane. An acute-duration inhalation HEC of 10.14 ppm for worker and 2.42 ppm for continuous exposures was used for risk assessment of acute inhalation exposure, with a total uncertainty factor of 30, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability.
[f] No PODs were identified from acute exposure by the **dermal route** to 1,2-dichloroethane; therefore, route-to-route extrapolation from the oral route was used to identify a POD. An acute-duration dermal HED for both worker and continuous exposure of 5.56 mg/kg-bw/day was used for risk assessment of acute dermal exposure, with a total uncertainty factor of 30, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability.
[g] UF = uncertainty factor; UF_A = extrapolation from animal to human (interspecies); UF_H = potential variation in sensitivity among members of the human population (intraspecies); UF_L = use of a LOAEL to extrapolate a NOAEL; UF_S = use of a short-term study for long-term risk assessment; UF_D = to account for the absence of key data (*i.e.*, lack of a critical study).

Table 8-2. PODs and Toxicity Values Used to Estimate Non-cancer Risks for Short-Term Exposure Scenarios[a]

Target Organ System	Species	Duration/ Route	Study POD/ Type	Effect	Worker HEC [b] (ppm) [mg/m^3]	Continuous HEC [b] (ppm) [mg/m^3]	Worker HED [c] (mg/kg-bw/day)	Continuous HED [c] (mg/kg-bw/day)	Uncertainty Factors [g]	Total Uncertainty Factors	Reference	Data Quality
Immune System	Mice (male)	**Oral 1,2-dichloroethane data** 14-days oral gavage	$LOAEL_{adj}$ = 4.89 mg/kg	Suppression of immune response (AFCs/spleen)	N/A	N/A	0.890	0.636	UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 1 UF_D = 1	100[d]	Munson et al. (1982)	High
Reproductive	Mice (male)	**Inhalation 1,2-dichloroethane data** 4-week morphological analysis of sperm parameters/ inhalation	$BMCL_5$ = 21.2 mg/m^3	Decreases in sperm concentration	(89.0 mg/m^3) [22.0 ppm]	(21.2 mg/m^3) [5.2 ppm]	N/A	N/A	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1	30[e]	Zhang et al. (2017)	High
Immune System	Mice (male)	**Dermal (extrapolated from oral) 1,2-dichloroethane data** 14-days oral gavage	$LOAEL_{adj}$ = 4.89 mg/kg	Suppression of immune response (AFCs/spleen)	N/A	N/A	0.890	0.636	UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 1 UF_D = 1	100[f]	Munson et al. (1982)	High

Target Organ System	Species	Duration/ Route	Study POD/ Type	Effect	Worker HEC [b] (ppm) [mg/m^3]	Continuous HEC [b] (ppm) [mg/m^3]	Worker HED [c] (mg/kg-bw/day)	Continuous HED [c] (mg/kg-bw/day)	Uncertainty Factors [g]	Total Uncertainty Factors	Reference	Data Quality

[a] See Section 3 for details.
[b] $BMCL_5$ = 21.2 mg/m^3 was adjusted to continuous adjusted (with no respiratory effects, there is no RGD; the blood:air ratio = 1, based on Equation_Apx A-7; therefore, the HEC_{cont} is the same as the adjusted POD of 21.2 mg/m^3. The HEC worker is the HEC_{cont} × 4.2 (hours in a week divided by the # of working hours in a week; 168/40) = 89.0 mg/m^3. Both HEC worker and continuous converted to ppm divided by a factor of 4.05 (based 24.45/MW).
[c] All oral PODs were first adjusted to 7 days/week. All continuous oral PODs were then converted to HEDs using DAFs. Dermal PODs were set equal to the oral HED. It is often necessary to convert between ppm and mg/m^3 due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all PODs in equivalents of both units to avoid confusion and errors. PODs converted for use in worker exposure scenarios were adjusted to 8 hours/day, 5 days/week and converted to HECs.
[d] POD identified from short-term/subchronic exposure by the **oral route** to 1,2-dichloroethane. A short-term/subchronic-duration oral HED for worker of 0.890 mg/kg-bw/day and a HED for continuous exposure of 0.636 mg/kg-bw/day was used for risk assessment of short-term/subchronic oral exposure, with a total uncertainty factor of 100, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, and 3 for use of a LOAEL to extrapolate a NOAEL (based on the dose-response).
[e] POD identified from short-term/subchronic exposure by the **inhalation route** to 1,2-dichloroethane. A short-term/subchronic-duration inhalation HEC for worker exposure of 89.0 mg/m^3, and a HEC for continuous exposure of 21.2 mg/m^3, was used for risk assessment of short-term/subchronic inhalation exposure, with a total uncertainty factor of 30, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability.
[f] No PODs were identified from short-term/subchronic exposure by the **dermal route** to 1,2-dichloroethane; therefore, route-to-route extrapolation from the oral route was used to identify a POD. A short-term/subchronic-duration dermal HED for worker of 0.890 mg/kg-bw/day and a HED for continuous exposure of 0.636 mg/kg-bw/day was used for risk assessment of short-term/subchronic dermal exposure, with a total uncertainty factor of 100, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, and 3 for use of a LOAEL to extrapolate a NOAEL (based on the dose-response).
[g] UF = uncertainty factor; UF_A = extrapolation from animal to human (interspecies); UF_H = potential variation in sensitivity among members of the human population (intraspecies); UF_L = use of a LOAEL to extrapolate a NOAEL; UF_S = use of a short-term study for long-term risk assessment; UF_D = to account for the absence of key data (*i.e.*, lack of a critical study).

2123 **Table 8-3. PODs and Toxicity Values Used to Estimate Non-cancer Risks for Chronic Exposure Scenarios[a]**

Target Organ System	Species	Duration/ Route	Study POD/ Type	Effect	Worker HEC [b] (ppm) [mg/m^3]	Continuous HEC [b] (ppm) [mg/m^3]	Worker HED [c] (mg/kg-bw/day)	Continuous HED [c] (mg/kg-bw/day)	Uncertainty Factors [g]	Total Uncertainty Factors	Reference	Data Quality
Immune System	Mice (male)	**Oral 1,2-dichloroethane data** 14-days oral gavage	$LOAEL_{adj}$ = 4.89 mg/kg	Suppression of immune response (AFCs/spleen)	N/A	N/A	0.890	0.636	UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 10 UF_D = 1	1,000[d]	Munson et al. (1982)	High
Reproductive	Mice (male)	**Inhalation 1,2-dichloroethane data** 4-week morphological analysis of sperm parameters/ inhalation	$BMCL_5$ = 21.2 mg/m^3	Decreases in sperm concentration	(89.0 mg/m^3) [22.0 ppm]	(21.2 mg/m^3) [5.2 ppm]	N/A	N/A	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 10 UF_D = 1	300[e]	Zhang et al. (2017)	High
Immune System	Mice (male)	**Dermal (extrapolated from oral) 1,2-dichloroethane data** 14-days oral gavage	$LOAEL_{adj}$ = 4.89 mg/kg	Suppression of immune response (AFCs/spleen)	N/A	N/A	0.890	0.636	UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 10 UF_D = 1	1,000[f]	Munson et al. (1982)	High

Target Organ System	Species	Duration/ Route	Study POD/ Type	Effect	Worker HEC [b] (ppm) [mg/m^3]	Continuous HEC [b] (ppm) [mg/m^3]	Worker HED [c] (mg/kg-bw/day)	Continuous HED [c] (mg/kg-bw/day)	Uncertainty Factors [g]	Total Uncertainty Factors	Reference	Data Quality

[a] See Section 3 for details.
[b] $BMCL_5$ = 21.2 mg/m^3 was adjusted to continuous adjusted (with no respiratory effects, there is no RGD; the blood/air ratio = 1, based on Equation_Apx A-7; therefore, the HEC_{cont} is the same as the adjusted POD of 21.2 mg/m^3. The HEC worker is the HEC_{cont} × 4.2 (hours in a week divided by the # of working hours in a week; 168/40) = 89.0 mg/m^3. Both HEC worker and continuous converted to ppm divided by a factor of 4.05 (based 24.45/MW).
[c] All oral PODs were first adjusted to 7 days/week. All continuous oral PODs were then converted to HEDs using DAFs. Dermal PODs were set equal to the oral HED. It is often necessary to convert between ppm and mg/m^3 due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all PODs in equivalents of both units to avoid confusion and errors. PODs converted for use in worker exposure scenarios were adjusted to 8 hours/day, 5 days/week and converted to HECs.
[d] POD identified from chronic exposure by the **oral route** to 1,2-dichloroethane. A chronic-duration oral HED for worker of 0.890 mg/kg-bw/day and a HED for continuous exposure of 0.636 mg/kg-bw/day was used for risk assessment of chronic oral exposure, with a total uncertainty factor of 1000, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, 3 for the use of a LOAEL to extrapolate a NOAEL (based on the dose-response), and 10 for extrapolating from a subchronic study duration to a chronic study duration.
[e] POD identified from chronic exposure by the **inhalation route** to 1,2-dichloroethane. The chronic-duration inhalation HEC for worker exposure of 89.0 mg/m^3, and a HEC for continuous exposure of 21.2 mg/m^3, was used for risk assessment of chronic inhalation exposure, with a total uncertainty factor of 300, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, and 10 for extrapolating from a subchronic study duration to a chronic study duration.
[f] No PODs were identified from chronic exposure by the **dermal route** to 1,2-dichloroethane; therefore, route-to-route extrapolation from the oral route was used to identify a POD. A chronic-duration dermal HED for worker of 0.890 mg/kg-bw/day and a HED for continuous exposure of 0.636 mg/kg-bw/day was used for risk assessment of chronic dermal exposure, with a total uncertainty factor of 1000, based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, 3 for the use of a LOAEL to extrapolate a NOAEL (based on the dose-response), and 10 for extrapolating from a subchronic study duration to a chronic study duration.
[g] UF = uncertainty factor; UF_A = extrapolation from animal to human (interspecies); UF_H = potential variation in sensitivity among members of the human population (intraspecies); UF_L = use of a LOAEL to extrapolate a NOAEL; UF_S = use of a short-term study for long-term risk assessment; UF_{DB} = to account for the absence of key data (*i.e.*, lack of a critical study).

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Table 8-4. Cancer PODs for 1,2-Dichloroethane Lifetime Exposure Scenarios

Exposure Assumption[a]	Oral Slope Factor[b]	Dermal Slope Factor[b]	Inhalation Unit Risk[c]	Drinking Water Unit Risk[d]	Extra Cancer Risk Benchmark
Continuous Exposure	0.062 per mg/kg/day	0.062 per mg/kg/day	7.1E−06 (per µg/m^3) 2.9E−02 (per ppm)	1.8E–06 per ug/L	1E−06 (general population)
Worker	0.062 per mg/kg/day	0.062 per mg/kg/day	2.4E−06 (per µg/m^3) 9.5E−03 (per ppm)	1.8E–06 per ug/L	1E−04 (occupational)

[a] Cancer slope factor and unit risk will be derived based on continuous exposure scenarios. Due to the exposure averaging time adjustments incorporated into lifetime exposure estimates, separate cancer hazard values for occupational scenarios are not required.
[b] The oral CSF for male mice based on hepatocarcinomas was 6.2×10−3 (per mg/kg-bw/day) in a reliable study NTP (1978). Cancer PODs from 1,2-dichloroethane based on hepatocellular carcinomas in male mice NTP (1978). Due to scarcity of data, route-to-route extrapolation from the oral slope factor is used for the dermal route.
[c] Cancer inhalation PODs from 1,2-dichloroethane based on based on combined mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas in female rats Nagano et al. (2006).
[d] Therefore, the oral CSF for 1,2-dichloroethane from the reliable NTP mouse cancer study NTP (1978) was selected for use in assessment of cancer risks associated with exposure to 1,2-dichloroethane. This mouse CSF was used to calculate a drinking water unit risk of 1.8 E–06 per ug/L using a drinking water intake of 2 L/day and body weight of 70 kg.

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Appendix A CALCULATING DAILY ORAL HUMAN EQUIVALENT DOSES AND HUMAN EQUIVALENT CONCENTRATIONS

For 1,2-dichloroethane, all data considered for PODs are obtained from oral animal toxicity studies in rats and mice. Because toxicity values for 1,2-dichloroethane are from oral and inhalation animal studies, EPA must use an extrapolation method to estimate human equivalent doses (HEDs) and human equivalent concentrations (HECs). The preferred method would be to use chemical-specific information for such an extrapolation. However, there are no 1,2-dichloroethane-specific PBPK models, and EPA did not locate other 1,2-dichloroethane information to conduct a chemical-specific quantitative extrapolation. In the absence of such data, EPA relied on the guidance from U.S. EPA (2011b), which recommends scaling allometrically across species using the three-quarter power of body weight ($BW^{3/4}$) for oral data. Allometric scaling accounts for differences in physiological and biochemical processes, mostly related to kinetics.

A.1 Equations

This section provides equations used in calculating non-cancer PODs, including air concentration conversions (ppm to mg/m^3 and the converse), adjustments for continuous exposure, calculation of human equivalent concentrations (HECs) and human equivalent doses (HEDs), and route-to-route extrapolation calculations. All PODs were initially derived for continuous exposure scenarios (7 days/week, and 24 hours/day for inhalation). See Appendix A.1.5 for the calculated continuous exposure PODs as well as PODs converted for use in occupational exposure scenarios (8 hours/day, 5 days/week).

A.1.1 Air Concentration Unit Conversion

It is often necessary to convert between ppm and mg/m^3 due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all PODs in equivalents of both units to avoid confusion and errors. Equation_Apx A-1 presents the conversion of the HEC from ppm to mg/m^3 and Equation_Apx A-2 shows the reverse conversion.

Equation_Apx A-1. Converting ppm to mg/m^3

$$HEC_{continuous}\ (mg/m^3) = HEC_{continuous}\ (ppm) * (molecular\ weight/24.45)$$

Equation_Apx A-2. Converting mg/m^3 to ppm

$$HEC_{continuous}\ (ppm) = HEC_{continuous}\ (mg/m^3) * (24.45/molecular\ weight)$$

For 1,2-dichloroethane, the molecular weight used in the equations is 98.96 mg/mmol.

A.1.2 Adjustment for Continuous Exposure

Non-cancer PODs for oral studies are adjusted from the exposure scenario of the original study to continuous exposure following Equation_Apx A-3.

Equation_Apx A-3. Adjusting Non-cancer Oral POD for Continuous Exposure

$$POD_{continuous} = POD_{study} \times (days - week_{study}/days - week_{continous})$$

Where:

$days - week_{continuous}$ = 7 days

Non-cancer PODs for inhalation studies are adjusted from the exposure scenario of the original study to continuous exposure following Equation_Apx A-4.

Equation_Apx A-4. Adjusting Non-cancer Inhalation POD for Continuous Exposure

$$POD_{continuous} = POD_{study} \times (hours - day_{study}/hours - day_{continous}) \times (days - week_{study}/days - week_{continous})$$

Where:

$hours - day_{continous}$ = 24 hours

$days - week_{continous}$ = 7 days

A.1.3 Calculation of HEDs and HECs from Animal PODs

Consistent with U.S. EPA (2011b) guidance, oral PODs from animal studies are scaled to HEDs using Equation_Apx A-5.

Equation_Apx A-5. Calculation of Continuous HED from Continuous Animal Oral POD

$$HED_{\text{continous}} = POD_{\text{continous}} \times DAF$$

Where:

$HED_{continous}$ = human equivalent dose for continuous exposure (mg/kg-day)

$POD_{continous}$ = oral POD assuming daily doses (mg/kg-day)

DAF = dosimetric adjustment factor (unitless)

DAFs for scaling oral animal PODs to HEDs are calculated using Equation_Apx A-6.

Equation_Apx A-6. Calculating DAF for Oral HED Calculation

$$DAF = \left(\frac{BW_A}{BW_H}\right)^{\frac{1}{4}}$$

Where:

DAF = dosimetric adjustment factor (unitless)

BW_A = body weight of species used in toxicity study (kg)

BW_H = body weight of adult human (kg)

U.S. EPA (2011b) presents DAFs for extrapolation to humans from several species. However, because those DAFs used a human body weight of 70 kg, EPA has updated the DAFs using a human body weight of 80 kg from the EPA *Exposure Factors Handbook* (U.S. EPA, 2011a). EPA used the body weights of 0.025 and 0.25 kg for mice and rats, respectively, as presented in U.S. EPA (2011b). The resulting DAFs for mice and rats are 0.13 and 0.24, respectively. For guinea pigs, EPA used a body weight of 0.43 kg, resulting in a DAF of 0.27.

U.S. EPA (1994) guidance was used to convert animal inhalation PODs to HECs. Effects in animals exposed to 1,2-dichloroethane by inhalation consisted of systemic (extrarespiratory) effects. Therefore, consistent with U.S. EPA (1994) guidance, the HEC for extrarespiratory effects is calculated by multiplying the animal POD by the ratio of the blood/gas partition coefficients in animals and humans. Equation_Apx A-7 shows the HEC calculation for extrarespiratory effects.

Equation_Apx A-7. Calculation of HEC from Animal Inhalation POD

$$HEC = POD_{continuous} \times \frac{\left(\frac{HB}{g}\right)_A}{\left(\frac{HB}{g}\right)_H}$$

Where:

$\frac{\left(\frac{HB}{g}\right)_A}{\left(\frac{HB}{g}\right)_H}$ = blood/air partition coefficient for animals (A) to humans (H)

Blood/air coefficients for 1,2-dichloroethane were 19.5 in humans and 30 in rats (Gargas et al., 1989). Blood/air partition coefficients for other species were not located. When the animal blood/air partition coefficient is greater than the human blood/air partition coefficient, the default ratio of 1 is used in the calculation in accordance with U.S. EPA (1994) guidance.

Nasal effects were observed in one study of F344 rats exposed by inhalation to 1,2-dichloroethane (Dow Chemical, 2006b). For nasal effects, in accordance with U.S. EPA (1994) guidance, the HEC was calculated using the regional gas dose ratio for extrathoracic effects ($RGDR_{ET}$) using Equation_Apx A-8.

Equation_Apx A-8. Calculating HEC Using Animal Inhalation POD and $RGDR_{ET}$

$$HEC_{\text{continuous}} = POD_{\text{continuous}} \times RGDR_{ET}$$

Where:

$HEC_{continuous}$ = human equivalent concentration for continuous exposure (mg/m^3)
$POD_{continuous}$ = animal POD for continuous exposure (mg/m^3)
$RGDR_{ET}$ = regional gas dose ratio for extrathoracic effects (unitless)

The $RGDR_{ET}$ for nasal effects in F344 rats was calculated as shown in Equation_Apx A-9.

Equation_Apx A-9. Calculating $RGDR_{ET}$ in Rats

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \Big/ \frac{V_{E_h}}{SA_h}$$

Where:

$RGDR_{ET}$ = regional gas dose ratio for extrathoracic effects (unitless)
V_{E_a} = ventilation rate for male and female F344 rats = 0.211 L/minute (U.S. EPA, 1994)
SA_a = surface area of the extrathoracic region in rats = 15 cm^2 (U.S. EPA, 1994)
V_{E_h} = ventilation rate for humans = 13.8 L/minute (U.S. EPA, 1994)
SA_h = surface area of the extrathoracic region in humans = 200 cm^2 (U.S. EPA, 1994)

The $RGDR_{ET}$ for nasal effects in F344 rats calculated using the equation above is 0.2.

A.1.4 Cancer Inhalation Unit Risk

For cancer risk assessment, an Inhalation Unit Risk (IUR) can be converted to a Cancer Slope Factor (CSF) using the exposure parameters described above for non-cancer conversions, as in Equation_Apx A-10.

Equation_Apx A-10. Calculating CSF from IUR

$$CSF = IUR \times \frac{BW_H}{IR_R}$$

Where:

CSF = oral cancer slope factor based on daily exposure (per mg/kg-day)
IUR = inhalation unit risk based on continuous daily exposure (per mg/m^3)
BW_H = body weight of adult humans (kg) = 80
IR_R = inhalation rate for an individual at rest (m^3/day) = 14.7

A.1.5 Conversion of Continuous PODs to Occupational PODs

All PODs were initially derived for continuous exposure, and then converted to an equivalent POD for occupational exposure for convenience in risk calculations. Equation_Apx A-11 and Equation_Apx A-12 were used to convert from continuous to occupational exposure scenarios for oral and inhalation non-cancer PODs, respectively.

Equation_Apx A-11. Adjusting Non-cancer Oral POD from Continuous to Occupational Exposure

$$POD_{occupational} = POD_{continuous} \times (7/5\ days/week)$$

Equation_Apx A-12. Adjusting Non-cancer Inhalation POD from Continuous to Occupational Exposure

$$POD_{occupational} = POD_{continuous} \times (24/8\ hours/day) \times (7/5\ days/week)$$

To adjust a continuous IUR for occupational scenarios, Equation_Apx A-13 was used (days per week adjustment is not required because it is already accounted for in the Lifetime Average Daily Concentration).

Equation_Apx A-13. Adjusting Continuous IUR For Occupational Scenarios

$$IUR_{occupational} = IUR_{continuous} \times (hours - day_{occupational}/hours - day_{continuous})$$

A.1.6 Summary of Continuous and Worker Non-cancer PODs

Each of the continuous non-cancer PODs described in the preceding sections was converted to an equivalent POD for occupational exposure for convenience in risk calculations. Equations used to convert from continuous to occupational exposure scenarios for oral and inhalation exposure, respectively are provided in A.1.5. Table_Apx A-1 provides a summary of the non-cancer PODs for both continuous and occupational exposure scenarios for 1,2-dichloroethane.

Table_Apx A-1. Summary of Non-cancer PODs for 1,2-Dichloroethane

Route	Duration	Continuous POD	Worker POD	Benchmark MOE	Reference
Oral	Acute	19.9 mg/kg-bw/day	19.9 mg/kg-bw/day	30	Storer et al. (1984)
	Short/Intermediate-term	0.636 mg/kg-bw/day	0.890 mg/kg-bw/day	100	Munson et al. (1982)
	Chronic	0.636 mg/kg-bw/day	0.890 mg/kg-bw/day	1,000	Munson et al. (1982)
Inhalation	Acute	9.78 mg/m^3	41 mg/m^3	30	Dow Chemical (2006b)
	Short/Intermediate-term	21.2 mg/m^3	89 mg/m^3	30	Zhang et al. (2017)
	Chronic	21.2 mg/m^3	89 mg/m^3	300	Zhang et al. (2017)
Dermal (Route-to-Route Extrapolation from Oral)	Acute	19.9 mg/kg-bw/day	19.9 mg/kg-bw/day	30	Storer et al. (1984)
	Short/Intermediate-term	0.636 mg/kg-bw/day	0.890 mg/kg-bw/day	100	Munson et al. (1982)
	Chronic	0.636 mg/kg-bw/day	0.890 mg/kg-bw/day	1,000	Munson et al. (1982)

Appendix B EVIDENCE INTEGRATION TABLES FOR NON-CANCER FOR 1,2-DICHLOROETHANE

Table_Apx B-1. 1,2-Dichloroethane Evidence Integration Table for Reproductive/Developmental Effects

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on reproductive/developmental effects				
Evidence from human studies				*Overall WOSE judgement for reproductive/developmental effects based on integration of information across evidence streams:* Evidence indicates that 1,2-dichloroethane likely causes effects on male reproductive structure and/or function under relevant exposure conditions. Evidence is inadequate to determine whether 1,2-dichloroethane may cause effects on the developing organism. There is no evidence that 1,2-dichloroethane causes effects on female reproductive structure and/or function.
• A case-control study examined the association between proximity to point sources of chlorinated solvents and birth defects. Exposure was assessed based on metrics that combined residential distances to industrial sources and annual amounts of chemicals released (using EPA's Toxic Release Inventory), and birth defects were assessed using Texas birth registries. The geocoded address of mothers on day of delivery and the amount of solvent was used in the Emission Weighted Probability model to assign each mother an exposure risk value (Brender et al., 2014). Study quality: High • A retrospective cohort study examined the association between chlorinated solvents in drinking water and birth outcomes in 75 New Jersey towns. Exposure was based on measurements of chlorinated solvents in public water supplies in the maternal town of residence at the time of birth. Birth outcomes and some covariate data were obtained from birth certificates, fetal death certificates, and the NJ Birth Defects Registry (Bove, 1996; Bove et al., 1995). Study quality: Medium	Biological gradient/dose-response: • In women of all ages, any exposure to 1,2-dichloroethane (based on residential proximity to air emissions) was positively associated with neural tube defects OR=1.28 (CI 1.01, 1.62) and in particular spina bifida OR=1.64 (CI 1.24, 2.16). In analyses by intensity of exposure, significant trends were observed for spina bifida and also for septal heart defects. • Exposure to 1,2-dichloroethane in drinking water (detected vs. not detected) was positively associated with major cardiac defects (OR= 2.81, 95 percent CI 1.11, 6.65). This category of heart defects did not include septal defects, which were evaluated separately. Quality of the database:	Magnitude and precision: • Effect sizes were small and associations weak for all 1,2-dichloroethane outcomes in both studies (ORs ≤ 2.81, lower 95% CI ≤ 1.24). The association between 1,2-dichloroethane in drinking water and major cardiac defects was based on a very small number of cases (6 with detectable 1,2-dichloroethane). • In the Texas study, elective terminations lacked a vital record, so 31% of mothers with neural tube defects were not geocoded. • In both studies, there was the potential for exposure misclassification for mothers that changed residences between the first trimester (period relevant to morphogenesis of birth defects) and delivery, because exposure was based on residence at delivery. Consistency:	*Key findings*: In high and medium quality studies, associations were observed between 1,2-dichloroethane exposure and various birth defects (neural tube defects including spina bifida and heart defects of different types). However, the effect sizes were small, the associations were weak and in some cases based on very low group sizes, results of the studies were not consistent (neural tube defects/spina bifida in one study but not the other; different types of cardiac defects in the two studies), and both studies were limited in various ways (*e.g.*, incomplete data on neural tube defects, potential exposure misclassification, questionable temporality, co-exposures to other chemicals that were also associated with the same defects). *Overall WOSE judgement for reproductive/developmental*	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
	• Positive associations were found in high and medium quality studies.	• No significant associations were observed between 1,2-dichloroethane exposure in public water supplies and neural tube defects, septal heart defects, or total cardiac defects. Biological plausibility and human relevance: • There was limited evidence of temporality (exposure prior to outcome) in either study. In both studies, subjects had multiple overlapping exposures, and positive associations with spina bifida or neural tube defects, heart defects, and other defects were found for many of the other chemicals considered in the analyses.	*effects based on human evidence:* • Indeterminate	
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Effects on male reproductive organs				
• An inhalation study in rats evaluated testis weight and gross and microscopic pathology of the testes after 30 days exposure (Igwe et al., 1986b) Study quality: High • An inhalation study in a single dog evaluated testis histopathology after 6 months exposure (Mellon Institute, 1947) Study quality: Medium • An inhalation study in mice evaluated testis and epididymis weight, sperm parameters and morphology, histology of the testis, seminiferous tubules, and	Biological gradient/dose-response: • In mice exposed by inhalation for one week, decreased sperm concentration and motility, increased sperm abnormalities, and occasional testicular and epididymal histopathology changes) were seen at 700 mg/m^3. After 4 weeks, effects seen at ≥ 350 mg/m^3 included more pronounced sperm changes,	Quality of the database: • No studies of sperm parameters in any species other than mice were available. Consistency: • No testicular histopathology changes were observed in mice exposed by drinking water for subchronic duration. • No testicular histopathology changes	*Key findings*: In high-quality studies, mice exposed to 1,2-dichloroethane by inhalation or intraperitoneal injection, but not by drinking water, exhibited effects on testicular pathology and sperm parameters. Most of the data in rats indicated no effect on the testes (or other reproductive organs); however, sperm parameters were not evaluated in rats.	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
caput epididymis, and plasma and testis hormone levels after 1- or 4-week exposure (Zhang et al., 2017) Study quality: High • An inhalation study in rats and guinea pigs evaluated weight and gross and microscopic pathology of the testes after up to 212 and 246 days of exposure, respectively (Spencer et al., 1951) Study quality: Medium • A one-generation reproduction study in rats exposed by inhalation evaluated histopathology of F0 testes after 176 days of exposure (Rao et al., 1980) Study quality: Medium • An inhalation cancer bioassay in rats evaluated gross pathology of the accessory sex organs, testes, and seminal vesicles and histopathology of the prostate and testes after 2 years exposure (Cheever et al., 1990) Study quality: High • Gavage studies in rats evaluated testes weights, gross pathology of the testes, and histopathology (testes, seminal vesicles, prostate, and preputial gland) after 10- or 90-day exposures (Daniel et al., 1994) Study quality: High • A gavage study in rats evaluated testes weights and histopathology of the testes, epididymis, seminal vesicles, and prostate after 13 weeks exposure (NTP, 1991) Study quality: High • A gavage cancer bioassay in mice evaluated comprehensive histopathology after 78 weeks	more extensive/severe histological effects, and increases in plasma and testicular testosterone and LH and testicular GnRH. Consistency: • Mice exposed to ≥5 mg/kg/day by daily intraperitoneal injection for 5 days exhibited reduced spermatogenesis, loss of spermatogonia, histopathology changes in the testes, and sterility.	were observed in rats, guinea pigs, or a single dog exposed by inhalation for durations between 30 and 246 days. • No testicular histopathology changes were observed in rats exposed by intraperitoneal injection for 30 days or by gavage for subchronic durations.	*Overall WOSE judgement for male reproductive tract effects based on animal evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
exposure (NTP, 1978) Study quality: High • A drinking water study in mice evaluated testes weights and histopathology of the testes, epididymis, seminal vesicles, and prostate after 13 weeks exposure (NTP, 1991) Study quality: High • A dermal cancer bioassay in transgenic mice susceptible to cancer evaluated testes weights and histopathology of the prostate, seminal vesicle, and epididymis after 26 weeks exposure (Suguro et al., 2017) Study quality: High • An intraperitoneal injection study in mice evaluated histopathology of the testes 8 to 46 days after a 5-day exposure and histopathology and fertility for up to 9 months after a 5-day exposure plus 45 days recovery for spermatogenesis turnover (Daigle et al., 2009) Study quality: High • An intraperitoneal injection study in rats evaluated testis weight and gross and microscopic pathology of the testes after 30 days exposure (Igwe et al., 1986b) Study quality: Medium				
Effects on female reproductive organs				
• An inhalation study in female rats evaluated serum prolactin levels and morphometry and histopathology of mammary tissue after at least 28 days exposure (Dow Chemical, 2014) Study quality: High • A one-generation reproduction study in female rats exposed by inhalation evaluated histopathology of F0		Consistency: • Several high- and medium-quality studies of rats and mice exposed by inhalation, gavage, drinking water, and/or dermal contact reported no treatment-related changes in	*Key findings*: Inhalation studies in rats, oral studies in rats and mice, and a dermal study in mice observed no effects of 1,2-dichloroethane on female reproductive organ weights or histopathology.	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
ovaries and uterus after 176 days of exposure (Rao et al., 1980) Study quality: Medium • An inhalation cancer bioassay in female rats evaluated gross and microscopic pathology of the mammary tissue, ovaries, and uterus after 2 years exposure (Cheever et al., 1990) Study quality: High • Gavage studies in rats evaluated ovary weights, gross pathology of the ovaries, and histopathology (ovaries, uterus, clitoral gland, and mammary gland) after 10- or 90-day exposures (Daniel et al., 1994) Study quality: High • A gavage cancer bioassay in mice evaluated comprehensive histopathology after 78 weeks exposure (NTP, 1978) Study quality: High • A drinking water study in mice and a gavage study in rats evaluated histopathology of the uterus, mammary gland, clitoral gland, and ovaries after 13 weeks exposure (NTP, 1991) Study quality: High • A dermal cancer bioassay in transgenic mice susceptible to cancer evaluated ovary weights and histopathology of the uterus, mammary gland, and vagina after 26 weeks exposure (Suguro et al., 2017) Study quality: High		reproductive organ weights or histopathology.	*Overall WOSE judgement for female reproductive tract effects based on animal evidence:* • Moderate evidence of no effect.	
Effects on reproduction or offspring				
• An inhalation study in male and female rats evaluated numbers of live and dead pups; and pup weight, sex,	Biological gradient/dose-response:	Magnitude and precision: • The apparent body weight decrease in selected male	*Key findings*: In a high-quality study, sterility was observed in male	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
gross pathology, liver and kidney weights, and liver and kidney histopathology after one generation exposure (Rao et al., 1980) Study quality: Medium • Inhalation studies in female rats and rabbits evaluated numbers of corpora lutea; numbers of live, dead, and resorbed fetuses; fetal weight, length, and sex; external and skeletal alterations; and cleft palate after gestational exposure (Rao et al., 1980) Study quality: Medium • Inhalation and gavage studies in female rats evaluated pregnancy outcomes and fetal external, skeletal, and visceral examinations after gestational exposure (Payan et al., 1995) Study quality: High • A drinking water study in male and female mice evaluated fertility and gestation indices, numbers of implantations and resorptions, viability and lactation indices, litter size, pup weight, and teratology after multigenerational exposure (Lane et al., 1982) Study quality: High • An intraperitoneal injection study in male mice evaluated male fertility for up to 9 months after a 5-day exposure plus 45 days recovery for spermatogenesis turnover (Daigle et al., 2009) Study quality: High	• An apparent decrease in necropsy body weight was observed at the high concentration of 150 ppm in a small subset of male F1B weanling rats exposed by inhalation in a one-generation study. • Male mice exposed by daily intraperitoneal injection at ≥ 10 mg/kg-d for 5 days exhibited permanent sterility (defined as sterility for 6 months or longer).	F1B weanlings at 150 ppm was based on only 5 male weanlings per group, was not statistically significantly different from controls, was not seen in female weanlings, and is not supported by the study authors' analysis of the full data set, which showed no effect on neonatal body weight or growth of pups to weaning in either F1A or F1B litters.	mice exposed by intraperitoneal injection. Evidence for effects on weanling pup body weight after inhalation exposure is weak and inconsistent. *Overall WOSE judgement for developmental effects based on animal evidence:* • Slight	
Evidence in mechanistic studies				
• An *in vivo* inhalation study in male rats evaluated elemental content in the testes after 30 days exposure (Que et al., 1988).	Biological gradient/dose-response: • Inhalation exposure to 1,2-dichloroethane did not alter	Biological plausibility and human relevance:	*Key findings*: Evidence for inhibition of CREM/ CREB signaling and apoptosis in testes of male	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• An *in vivo* inhalation study in male mice evaluated mRNA expression in the testis and genetic damage in spermatozoa after 1- or 4-week exposure (Zhang et al., 2017) • An *in vivo* study in mice exposed by intratesticular injection evaluated testicular DNA synthesis (Borzelleca and Carchman, 1982).	zinc concentration in the testes. Statistically significant changes in other element concentrations included decreased Al, Hg, and S and increased Ca and P at the highest tested concentration (1840 mg/m^3 or 455 ppm) • Expression consistent with inhibition of CREM/ CREB signaling and the induction of apoptosis was observed in the testis of mice. • Intratesticular injection of 1,2-dichloroethane resulted in a 53% decrease in testicular DNA synthesis in mice at the highest dose tested (250 mg/kg) but not at doses ≤100 mg/kg.	• The biological relevance of the altered element content in the testes is uncertain. • The human relevance of intratesticular injection exposure is uncertain.	mice exposed to 1,2-dichloroethane *in vivo* support observed effects on testes pathology, sperm morphology, and fertility in this species. *Overall WOSE judgement for reproductive/developmental effects based on mechanistic evidence:* • Moderate	

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2936 **Table_Apx B-2. 1,2-Dichloroethane Evidence Integration Table for Renal Effects**

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence Integration Summary Judgement on Renal Effects				
Evidence from human studies			Indeterminate	*Overall WOSE judgement for renal effects based on integration of information across evidence streams:* Evidence indicates that 1,2-dichloroethane likely causes renal effects under relevant exposure circumstances.
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Studies evaluating histopathology in conjunction with other renal endpoints: • Acute inhalation studies in male and female rats and male mice evaluated kidney histopathology and weight after a single 4-hour exposure (Dow Chemical, 2006b); Study quality: High. (Francovitch et al., 1986); Study quality: Medium. • A short-term inhalation study in male rats evaluated kidney histopathology and weight and after 30 days of exposure (Igwe et al., 1986b); Study quality: High. • A chronic inhalation study in F0 male and female rats evaluated kidney histopathology and weight after exposure in a reproduction study from pre-breeding through the generation of 2 litters (Rao et al., 1980). Study quality: Medium. • Chronic inhalation studies in male and female rats evaluated kidney histopathology, kidney weight, and/or clinical chemistry after 212 days or 17-weeks of exposure (Spencer et al., 1951), (Hofmann et al., 1971); Study quality: Medium. • Chronic inhalation studies in a single dog, guinea pigs, and rabbits evaluated kidney histopathology, kidney weight, and/or clinical chemistry after 6 months, 212 days, or 17 weeks of exposure (Mellon Institute, 1947), (Spencer et al., 1951), (Hofmann et al., 1971); Study quality: Medium. • Short-term and subchronic gavage studies in male and female rats evaluated kidney and	Biological gradient/dose-response: • In acute inhalation studies: ○ Rats exhibited significantly increased incidences of basophilia of the renal tubular epithelium (males) or degeneration/ necrosis (females) in addition to significantly increased absolute and relative kidney weights (≥10%, both sexes) at 8212 mg/m^3 (2029 ppm). ○ Male mice exhibited significantly increased kidney weights (>10%) and BUN (86%) at ≥2,020 mg/m^3 (≥499 ppm). ○ In a chronic inhalation study in rats, a statistically significant increase in BUN (~50%) was reported at 607 mg/m^3 (150 ppm). ○ In acute gavage studies, male mice exhibited significant increases in relative kidney weight (>10%) at ≥300 mg/kg and significantly increased percentage of damaged renal proximal tubules at 1,500 mg/kg.	Biological gradient/dose response: • High-quality short-term and chronic inhalation studies found no treatment-related effects on kidney weight or histopathology in rats exposed up to 647 mg/m^3 (159.7 ppm) or mice exposed up to 368 mg/m^3 (89.8 ppm) • High-quality short-term gavage studies found no treatment-related effects on kidney histopathology, kidney weight, or BUN in rats (both sexes) exposed up to 300 mg/kg-day or on kidney weight or gross pathology in mice (both sexes) exposed up to 49 mg/kg-day. • High-quality subchronic gavage studies in male and female rats found no treatment-related histopathology changes at doses up to 150 mg/kg-day. • A high-quality chronic gavage cancer bioassay in mice found no treatment-related effects on kidney histopathology at doses up to 299 mg/kg-day.	*Key findings*: Several high- and medium-quality studies found associations between 1,2-dichloroethane exposure and increased kidney weights, BUN, and/or renal tubular histopathology in rats (both sexes) and mice following inhalation, oral, dermal, and intraperitoneal injection exposures. *Overall WOSE judgement for renal effects based on animal evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
bladder histopathology, kidney weight, and/or clinical chemistry, and/or urinary chemistry after 10 or 13 weeks of exposure (Daniel et al., 1994), (NTP, 1991); Study quality: High. • A subchronic drinking water study in male and female mice evaluated kidney histopathology, weight of kidney and urinary bladder, and BUN after 13 weeks of exposure (NTP, 1991); Study quality: High. • A dermal cancer bioassay in male and female transgenic mice susceptible to cancer evaluated kidney histopathology and weight after 26 weeks exposure (Suguro et al., 2017); Study quality: High. • A short-term intraperitoneal injection study in male rats evaluated kidney histopathology, kidney weight, and/or clinical chemistry after 30 days of exposure (Igwe et al., 1986b); Study quality: Medium. Studies evaluating histopathology only: • An acute inhalation study in rats, mice, rabbits, and guinea pigs evaluated microscopic kidney pathology after 1.5- to 7-hour exposures (Heppel et al., 1945); Study quality: Medium. • Subchronic and chronic inhalation studies in rats, rabbits, guinea pigs, and dogs evaluated kidney histopathology after 13 to 35 weeks of exposure (Heppel et al., 1946); Study quality: Low or Medium. • Inhalation cancer bioassays in male and female rats and mice evaluated histopathology of the kidney and urinary bladder after 2 years exposure (Cheever et al., 1990), (Nagano et al., 2006); Study quality: High.	○ In subchronic gavage studies, rats exhibited significantly increased kidney weights (>10%, both sexes) at ≥30 mg/kg-day and increased BUN (20%, males) at 120 mg/kg-day. ○ In a subchronic drinking water study, mice exhibited significantly increased incidences of tubular regeneration (males) at ≥781 mg/kg-day and significantly increased kidney weights (>10%, both sexes) at 244–448 mg/kg-day. ○ In an acute intraperitoneal injection study in male mice, a statistically significant increase in relative kidney weight was observed at ≥400 mg/kg reaching >10% at 500 mg/kg. Consistency: • Renal histopathology changes were also reported in studies that were limited by lack of reporting on control findings. These included: ○ Degeneration of renal tubular epithelium in rats and rabbits after acute inhalation exposure. ○ Increased severity of renal tubular damage in mice			

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• An acute gavage study in male mice evaluated kidney immunohistochemistry after a single exposure (Morel et al., 1999). Study quality: High. • A gavage cancer bioassay in male and female mice evaluated kidney histopathology after 78 weeks of exposure (NTP, 1978); Study quality: High. Studies evaluating kidney weight, gross pathology, and/or clinical chemistry: • An acute inhalation study in mice evaluated kidney weight and BUN levels after a 4-hour exposure (Storer et al., 1984); Study quality: High. • Chronic inhalation studies in male and female rats evaluated serum chemistry and urinalysis parameters after 6, 12, or 18 months of exposure (IRFMN, 1987, 1978, 1976); Study quality: Medium. • An acute gavage study in male mice evaluated kidney weight and BUN after a single exposure (Storer et al., 1984); Study quality: High. • A short-term gavage study in male and female mice evaluated kidney weight and gross pathology after 14 days exposure (Munson et al., 1982); Study quality: High. • Acute intraperitoneal injection studies in male rats and mice evaluated kidney weight and serum chemistry parameters after a single exposure (Livesey, 1982), (Storer and Conolly, 1985), (Storer et al., 1984); Study quality: High; (Storer and Conolly, 1983); Study quality: Medium. • A short-term intraperitoneal injection study in male mice evaluated kidney gross	after acute inhalation exposure. ○ Moderate fatty degeneration of the kidney in guinea pigs after chronic inhalation exposure. ○ Mild karyomegaly of distal tubules and tubular degeneration in transgenic mice after chronic dermal exposure. Biological plausibility and human relevance: • Metabolism of 1,2-dichloroethane via glutathione-S-transferase is believed to yield a reactive episulfonium ion which can form the potent nephrotoxic conjugate S-(2-chloroethyl)-DL-cysteine.			

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
pathology after 5 days of exposure (NTP, 1978); Study quality: High.				
Evidence in mechanistic studies (none)			• Indeterminate	

Table_Apx B-3. 1,2-Dichloroethane Evidence Integration Table for Hepatic Effects

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on hepatic effects				
Evidence from human studies				*Overall WOSE judgement for hepatic effects based on integration of information across evidence streams:* Evidence suggests, but is not sufficient to conclude, that 1,2-dichloroethane may cause hepatic effects under relevant exposure conditions.
• A cohort study of 251 male workers from 4 vinyl chloride monomer (VCM) manufacturing plants evaluated associations between exposure to airborne 1,2-dichloroethane (in conjunction with low exposure to VCM) and serum AST, ALT, and GGT. Personal and area air sampling were used to determine VCM and 1,2-dichloroethane exposures and group participants by job category into low 1,2-dichloroethane (job medians of 0.26-0.44 ppm) or moderate 1,2-dichloroethane (job medians of 0.77-1.31 ppm) plus low VCM (job medians of 0.18-0.39 ppm). (Cheng et al., 1999). Study quality: Medium	Biological gradient/dose-response: • Increased odds of abnormal serum AST (>37 IU/L) and ALT (>41 IU/L) were observed when comparing the moderate-1,2-dichloroethane/low-VCM group with the low-1,2-dichloroethane/low-VCM group (OR = 2.2, 95% CI = 1.0–5.4 for abnormal AST; OR = 2.1, 95% CI = 1.1–4.2 for abnormal ALT).	Magnitude/precision: • Exposure concentrations in the low- and moderate-1,2-dichloroethane groups were overlapping. Biological plausibility/human relevance: • All subjects were also exposed to vinyl chloride monomer, a known liver toxicant.	*Key findings*: In a medium-quality study, increased odds of abnormal serum liver enzyme levels were observed among workers with higher exposure to 1,2-dichloroethane, in a cohort with co-exposure to vinyl chloride. *Overall WOSE judgement for hepatic effects based on human evidence:* Indeterminate	
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Studies evaluating histopathology in conjunction with other liver endpoint(s): • Acute inhalation studies in male and female rats and male mice evaluated	Biological gradient/dose-response: • In an acute inhalation study, rats exhibited minimal histological changes in the liver at 8212.3 mg/m^3	Consistency: • In a high-quality short-term inhalation study in rats, no treatment-related effects on liver weight, serum chemistry	*Key findings*: Several high- and medium-quality studies in rats and mice found associations between 1,2-dichloroethane	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
liver weight and histopathology after single 4- and/or 8- hour exposures (Dow Chemical, 2006b); Study quality: High. (Francovitch et al., 1986); Study quality: Medium • A short-term inhalation study in male rats evaluated serum chemistry (ALP, SDH, and 5'NT), liver weight, and histopathology after 30 days exposure (Igwe et al., 1986b, c) Study quality: High • Subchronic and chronic inhalation studies in male and female rats, rabbits, cats, and guinea pigs evaluated serum chemistry (ALT and AST), bromsulphthalein retention, liver weight and/or histopathology after up to 17 weeks exposure (Hofmann et al., 1971) Study quality: Medium. • Chronic inhalation studies in male and female rats and guinea pigs, male monkeys, and a single dog evaluated hepatic lipids/cholesterol, liver function, liver weight, and/or histopathology after 170-248 days exposure (Spencer et al., 1951) Study quality: Medium. (Mellon Institute, 1947) Study quality: Medium. • Chronic inhalation cancer bioassays in male and female rats and mice evaluated liver weight and histopathology after 2 years exposure (Nagano et al., 2006; Cheever et al., 1990) Study quality: High. • A one-generation inhalation reproduction study in rats evaluated parental liver weight and	(2029.0 ppm). Liver weight changes were small (<10%) and inconsistent. • In an acute inhalation study, male mice exhibited a significant increase in relative liver weight (>10%) at 6071 mg/m^3 (1500 ppm). Histological observations in the liver included hepatocyte swelling, swollen nuclei, fat accumulation, and occasional small areas of necrosis (incidence and severity were not reported) • In a chronic inhalation cancer bioassay, male (but not female) rats exhibited increased absolute (but not relative) liver weight (>10%) at 204 mg/m^3 (50 ppm) • In a short-term gavage study, male (but not female) rats had significantly increased relative liver weight (>10%) and serum cholesterol at 100 mg/kg-day in the absence of histopathology changes. • In subchronic gavage studies, male and female rats exhibited significantly increased relative liver weights (>10%) at ≥75 mg/kg-day in the absence of biologically significant serum chemistry changes or treatment-related histopathology changes. • In a subchronic drinking water study, male and female mice exhibited significantly increased (>10%) absolute and relative liver weights at ≥ 2,478 mg/kg-day in the absence of treatment-related histopathology changes. Consistency:	or histopathology were observed in rats at concentrations up to 1840 mg/m^3 (455 ppm). • In high-quality chronic inhalation cancer bioassays in rats and mice, no significant effects on liver weight or histology were observed at concentrations up to 646.4 mg/m^3 (159.7 ppm and 363 mg/m3 (89.8 ppm), respectively.	exposure and increased liver weights, serum enzymes, and/or histopathology changes following inhalation, oral, and intraperitoneal injection exposures. *Overall WOSE judgement for hepatic effects based on animal evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
histopathology after up to 176 days exposure (Rao et al., 1980) Study quality: Medium. • An acute gavage study in female rats evaluated serum chemistry (ALT, AST, and LDH) and histopathology after a single dose (Cottalasso et al., 2002) Study quality: Medium. • Short-term and subchronic gavage studies in male and female rats evaluated serum chemistry, liver weight, and liver histopathology after 10-day and 13-week exposures (Daniel et al., 1994; NTP, 1991); Study quality: High. • A subchronic drinking water study in male and female mice evaluated liver weight and histopathology after 13 weeks exposure (NTP, 1991) Study quality: High. • A chronic dermal cancer bioassay in male and female transgenic mice evaluated liver weights and histopathology after 26 weeks exposure (Suguro et al., 2017) Study quality: High. Studies evaluating liver histopathology only: • Acute inhalation studies in rats, mice, rabbits, and guinea pigs evaluated gross and microscopic liver pathology after 1.5- to 7-hour exposures (Heppel et al., 1945). Study quality: Medium • Subchronic- and chronic inhalation studies in male and/or female rats, rabbits, guinea pigs, dogs, and cats evaluated liver histopathology after 5	• Hepatic histopathology changes and liver weight increases were also reported in low- and medium-quality studies that were limited by lack of quantitative data reporting and variable exposure regimens. The lesions included: ○ Congestion, fatty degeneration, and/or necrosis in rats, mice, rabbits, and guinea pigs after acute to short-term inhalation exposures that were sometimes lethal. ○ Cloudy swelling, fatty degeneration, necrosis, and/or occasional fat vacuoles in rats and guinea pigs after subchronic to chronic inhalation exposure. ○ Moderate steatosis in rats without biologically significant changes in AST or ALT after a single gavage dose. • In studies that did not evaluate histopathology, findings included: ○ Biologically and/or statistically significant increases in serum SDH and ALT in mice exposed for 4 hours by inhalation. ○ Increased serum ALT, SDH and/or glutamate dehydrogenase in rats after single or repeated inhalation exposures. ○ Increased liver weight in mice exposed by inhalation for 28 days. ○ Increased ALT and AST in rats after single gavage dose. ○ Increased relative liver weight and biologically significant increases in serum SDH and ALT in mice			

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
to 35 weeks of exposure (Heppel et al., 1946); Study quality: Medium or Low. • A chronic gavage cancer bioassay in male and female mice evaluated liver histopathology after 78 weeks of exposure (NTP, 1978) Study quality: High. Studies evaluating only liver weight, gross pathology and/or clinical chemistry: • An acute inhalation study in male mice evaluated liver weight and serum chemistry (Storer et al., 1984) Study quality: High. • Acute- and short-term inhalation studies in male rats evaluated serum chemistry (Brondeau et al., 1983) Study quality: Medium. • A short-term inhalation study in male mice evaluated liver weight and serum chemistry (Zeng et al., 2018) Study quality: High. • Chronic inhalation studies in male and female rats evaluated serum chemistry (IRFMN, 1987, 1978, 1976) Study quality: Medium. • Acute gavage studies in male and female rats evaluated serum chemistry and/or liver weight (Kitchin et al., 1993); Study quality: High. (Cottalasso et al., 1995) Study quality: Medium. • An acute gavage study in male mice evaluated liver weight and serum chemistry (Storer et al., 1984) Study quality: High.	after a single gavage or intraperitoneal dose.			

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• A short-term gavage study in male and female mice evaluated liver weight and gross pathology (Munson et al., 1982) Study quality: High. • A subchronic dietary study in rats evaluated serum chemistry (Alumot et al., 1976). Study quality: Medium • Acute, short-term, and subchronic intraperitoneal injection studies in male rats and male mice evaluated liver weight, serum chemistry, and/or gross pathology (Storer and Conolly, 1985; Storer et al., 1984; Livesey, 1982); Study quality: High. (Daigle et al., 2009; Igwe et al., 1986b; Storer and Conolly, 1983) Study quality: Medium.				
Evidence in mechanistic studies				

• An *in vivo* inhalation study in male rats evaluated elemental content in the liver after 30 days exposure (Que et al., 1988).
• An *in vivo* inhalation study in male mice evaluated hepatic micro-RNA (miR) expression and gluconeogenesis (Zeng et al., 2018).
• *In vivo* genotoxicity tests were conducted in the liver of male mice after single inhalation, oral, and intraperitoneal exposures (Storer et al., 1984).
  ○ An *in vivo* intraperitoneal injection study in male mice evaluated hepatic enzyme induction (Paolini et al., 1994).
  ○ A series of studies *in vivo* in rats and *in vitro* in rat hepatocytes evaluated effects on
	Biological gradient/dose-response:
	• 1,2-Dichloroethane induced DNA damage after oral and intraperitoneal (but not inhalation) exposure.
	• 1,2-Dichloroethane induced a dose-related increase in PROD activity (a probe for CYP450 2B1) in mice.
	Oxidative stress:
	• Incubation of rat liver slices with 1,2-dichloroethane (up to 10 mM for up to 30 minutes) resulted in dose-and time-dependent increases in MDA production.
	• Levels of GSH were significantly decreased in rat hepatocytes cultured with 4.4 to 6.5 mM 1,2-dichloroethane for up to 1 hour.
	• Free radicals were detected in rat hepatocytes cultured with 1,2-
		Biological gradient/dose-response:
		• Rat hepatocytes exposed to 1,2-dichloroethane for 1 hour at 1.2 mM did not show significantly decreased GSH.
		Consistency:
		• Rat hepatocytes cultured with 10 mM 1,2-dichloroethane for 2 hours did not show evidence of lipid peroxidation (*i.e.*, increased PCOOH or PEOOH levels).
			Key findings:
			Available data on liver toxicity mechanisms are limited and nonspecific. Hepatic enzyme induction was demonstrated in mice exposed by intraperitoneal injection. Limited *in vitro* data indicate that 1,2-dichloroethane may increase oxidative stress or impair glucose and/or lipid metabolism in mice and in rat hepatocytes and liver slices.
			Overall WOSE judgement for hepatic effects based on mechanistic evidence:
			• Indeterminate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
glycolipoprotein metabolism (Cottalasso et al., 2002; Cottalasso et al., 1995; Cottalasso et al., 1994). ○ *In vitro* studies in rat hepatocytes or rat liver slices evaluated oxidative stress parameters (Cottalasso et al., 1994; Suzuki et al., 1994; Jean and Reed, 1992; Thomas et al., 1989; Tomasi et al., 1984). ○ An *in vitro* study in rat hepatocytes incubated with the cysteine S conjugate of 1,2-dichloroethane, S-(2-chloroethyl)-DL-cysteine (CEC), evaluated cytotoxicity related to oxidative stress (Webb et al., 1987).	dichloroethane under anaerobic (but not aerobic) conditions. • The cysteine S conjugate of 1,2-dichloroethane was cytotoxic and depleted GSH in hepatocytes; co-treatment with antioxidants and GSH precursors mitigated these effects. *Effects on gluconeogenesis and glycolipoprotein metabolism:* • Inhalation exposure increased miR-451a expression and decreased glycerol gluconeogenesis in the liver of exposed mice. • Rats treated with 1,2-dichloroethane via gavage showed impairment of glycoprotein biosynthesis. • 1,2-dichloroethane treatment increased retention and decreased secretion of glycolipoproteins in rat hepatocytes.			

[a] Based on a density for 1,2-dichloroethane of 1.25 g/cm^3.
5'-NT = 5'-nucleotidase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; F = female; GGT = gamma-glutamyl transferase; GLDH = glutamate dehydrogenase; GSH = glutathione; LDH = lactate dehydrogenase; M = male; MDA = malondialdehyde; ODC = orinithine decarboxylase activity; PCOOH = phosphatidylcholine hydroperoxide; PEOOH = phosphatidylethanolamine hydroperoxide; PROD = pentoxyresorufin dealkylation; SDH = sorbitol dehydrogenase.

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Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on immune/hematological effects				
Evidence from human studies (none)			Indeterminate	*Overall WOSE judgement for immune/hematological effects based on integration of information across evidence streams:* Evidence indicates that 1,2-dichloroethane likely causes immune system suppression under relevant exposure conditions.
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Studies of immune function: • An inhalation study evaluated mortality from *Streptococcus zooepidemicus* aerosol challenge in female mice and lymphocyte stimulation, alveolar macrophage inhibition, and pulmonary bactericidal activity against *Klebsiella pneumoniae* in female mice and male rats after exposure once or for 5 (mice) or 12 (rats) days (Sherwood et al., 1987) Study quality: High • An oral gavage study in male mice evaluated hematology (including coagulation), humoral immunity (spleen cell antibody response), cell-mediated immunity (delayed hypersensitivity response), spleen and thymus weight, and gross necropsy after 14 days (Munson et al., 1982) Study quality: High Studies of hematology, organ weights, and histopathology: • Inhalation studies in rats, mice, rabbits, and guinea pigs (sex not specified) evaluated gross pathology and histopathology of the spleen after acute exposures (Heppel et al., 1945). Study quality: Medium • An inhalation study in male rats evaluated spleen weight, gross pathology, and histopathology after 30 days exposure (Igwe et al., 1986b) Study quality: High • Inhalation studies in rats, rabbits, guinea pigs, monkeys, cats and a single dog evaluated hematology (and/or clotting parameters or IgM) and/or spleen histopathology after 5 to 35 weeks of exposure (Heppel et al., 1946)	Biological gradient/dose-response: • Female mice exposed by inhalation for 3 hours exhibited a concentration-related increase in mortality due to *S. zooepidemicus* infection at concentrations ≥22 mg/m^3 (5.4 ppm). Mortality incidences were 1.5 and 2.1-fold higher than controls at 22 and 43.7 mg/m^3, respectively. Female mice also exhibited a small decrease in bactericidal activity against *K. pneumoniae* at 43.7 mg/m^3 (10.8 ppm). • In a gavage study, decreased humoral and cell-mediated immune responses were observed in male mice after 14 days exposure to ≥4.89 mg/kg-day; decreased leukocyte counts were observed at 48.9 mg/kg-day. • In a gavage study in rats, small decreases in erythrocyte count, hemoglobin, and hematocrit were observed in both sexes along with increased platelets (both sexes) and	Consistency: • Male rats exhibited no effects in the *K. pneumoniae* challenge assays after exposures up to 810 mg/m^3 for 5 hours or up to 405 mg/m^3 for 12 days. • In a study rated uninformative due to decreased drinking water intake at the high dose of 189 mg/kg-day, no effect on humoral or cell-mediated immune responses or leukocyte counts were observed in mice exposed to doses of 3, 24, or 189 mg/kg-day via drinking water for 90 days. • No treatment-related changes in hematology were observed in a gavage study of male rats exposed to doses up to 120 mg/kg-day for 13 weeks, or in studies of several species exposed by inhalation for durations from 5 weeks to 2 years. • Multiple studies of several species exposed by inhalation or oral administration for acute, subchronic, or chronic durations showed no effects	*Key findings*: In high-quality inhalation and gavage studies of immune function in mice, an association between 1,2-dichloroethane exposure and immunosuppression was observed; a more limited inhalation study in rats and a longer-term drinking water study in mice rated Uninformative did not show any effects. Evidence from other studies showed only small effects on hematology and no effects on relevant organ weights or histopathology. *Overall WOSE judgement for immune/hematological effects based on animal evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
(Mellon Institute, 1947) (Spencer et al., 1951) (IRFMN, 1987, 1978, 1976) (Hofmann et al., 1971) Study quality: Low to Medium • Inhalation cancer bioassays in male and female rats and mice evaluated hematology and/or comprehensive histopathology after 2 years exposure (Cheever et al., 1990) (Nagano et al., 2006) Study quality: High • A drinking water study in male and female mice evaluated comprehensive histopathology after 13 weeks exposure (NTP, 1991) Study quality: High • Gavage studies in male and female rats evaluated hematology, spleen and/or thymus weights, and comprehensive histopathology after 10- and/or 90-day exposures (Daniel et al., 1994) (NTP, 1991) Study quality: High • A gavage cancer bioassay in male and female mice evaluated comprehensive histopathology after 78 weeks exposure (NTP, 1978) Study quality: High • A gavage cancer bioassay in male and female transgenic mice susceptible to cancer evaluated hematology and histopathology of the thymus, spleen, lymph nodes, and bone marrow after 40 weeks exposure (Storer et al., 1995) Study quality: Medium • A dermal cancer bioassay in male and female transgenic mice susceptible to cancer evaluated thymus and spleen weights and histopathology of the lymph nodes, thymus, and bone marrow after 26 weeks exposure (Suguro et al., 2017) Study quality: High Studies Rated Uninformative: • An oral study in male mice evaluated hematology, humoral immunity (spleen cell antibody response), cell-mediated immunity (delayed hypersensitivity response), spleen	leukocytes (females only) after 90 days at 150 mg/kg-day. • In a subchronic gavage study, increased incidences of thymus necrosis were observed in male and female rats that died prematurely (≥240 mg/kg-day in males and at 300 mg/kg-day in females).	on relevant organ weights or histopathology. Biological plausibility and human relevance: • In the mouse inhalation study, mice were exposed for 30 minutes to aerosols of streptococcal bacteria (~2×10^4 inhaled viable streptococci). The relevance of this immune challenge to typical human bacterial exposures is uncertain.		

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
cell response to mitogens, function of the reticuloendothelial system, spleen and thymus weight, and gross necropsy after 90 days drinking water exposure. (Munson et al., 1982)				
Evidence in mechanistic studies				
• An *in vitro* study investigated phagocytic activity of mouse peritoneal macrophages incubated with 1,2-dichloroethane (Utsumi et al., 1992). • Cell-free and *in vitro* studies investigated 1,2-dichloroethane effects on erythrocyte glutathione-S-transferase (GST) (Ansari et al., 1987) • An inhalation study in rats evaluated elemental content in the spleen after 30 days exposure to 1,2-dichloroethane (Que et al., 1988).	Biological gradient/dose-response: • 1,2-Dichloroethane induced dose-related reductions in erythrocyte GST activity in both the cell-free experiment and in human erythrocytes *in vitro*. • 1,2-Dichloroethane reduced macrophage phagocytic activity to 76% of control levels at a concentration of 200 mM.		*Key findings*: Limited *in vitro* data showed reductions in macrophage phagocytic activity and erythrocyte GST activity after exposure to 1,2-Dichloroethane. *Overall WOSE judgement for immune/hematological effects based on mechanistic evidence:* • Indeterminate	

Table_Apx B-5. 1,2-Dichloroethane Evidence Integration Table for Neurological/Behavioral Effects

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on neurological/behavioral effects				
Evidence from human studies				*Overall WOSE judgement for neurological/behavioral effects based on integration of information across evidence streams:*
• Case reports of human exposure to 1,2-dichloroethane by inhalation or ingestion indicated clinical signs of neurotoxicity (dizziness, tremors, paralysis, coma) as well as histopathology changes in the brain at autopsy (ATSDR 2022). • Workers exposed to 1,2-dichloroethane for extended periods have developed cerebral			*Key findings*: Case reports document clinical signs of neurotoxicity and brain histopathology changes in humans exposed to 1,2-dichloroethane by inhalation or ingestion.	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
edema and toxic encephalopathy (ATSDR 2022).			*Overall WOSE judgement for neurological/behavioral effects based on human evidence:* • Slight	Evidence indicates that 1,2-dichloroethane likely causes neurological/ behavioral effects under relevant exposure circumstances.
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Studies evaluating neurobehavioral endpoints: • An inhalation study in male and female rats evaluated clinical signs, functional observational battery (FOB), grip performance, landing foot splay, rectal temperature, motor activity, brain weight, and gross and microscopic pathology of nervous system tissues after 4 hours exposure (Hotchkiss et al., 2010; Dow Chemical, 2006b) Study quality: High • A range-finding inhalation study in male and female rats evaluated detailed clinical observations (cage-side, hand-held, and open-field; recorded systematically) and gross pathology (tissues not specified) after 4 hours exposure (Dow Chemical, 2005) Study quality: High • An intraperitoneal injection study in male mice evaluated righting reflex, bridge test, and operant tests after single exposure (Umezu and Shibata, 2014) Study quality: High Studies evaluating neuropathology: • An inhalation study in male rats evaluated clinical signs and brain MRI and histopathology after 1.5- or 4-hour exposures (Zhou et al., 2016) Study quality: Medium • An inhalation study in male and female rats evaluated clinical signs, histology	Biological gradient/dose-response: • In rats exposed by inhalation once for four hours, neurobehavioral changes including incoordination, palpebral closure, decreased sensory responses, and decreased motor activity were seen at ≥ 7,706 mg/m^3 (1904 ppm) one hour after exposure but not at subsequent times up to 15 days later. • In rats exposed by inhalation for ≥ 1.5 hours to ≥ 4000 mg/m^3 brain edema was seen, and microstructural alterations were detected by diffusion MRI 3 days after exposure. • In rats exposed by inhalation to ≥ 5,000 mg/m^3, increased water content in the cortex was observed after ≥2-hour exposure and edema and histopathological changes in the brain were observed by light and transmission electron microscopy at the end of ≥ 6-hour exposure. • In animals of several species exposed by inhalation for up to 12 hours, clinical signs including hyperactivity, weakness, sedation,	Consistency: • No treatment-related brain weight or histopathology changes were seen in nervous system tissues 15 days after single 4-hr exposure up to 8,212.3 mg/m^3 (2,029.0 ppm). • No histopathology changes were observed in the brain, sciatic nerve, or spinal cord of rats exposed by inhalation for 204 mg/m^3 (50.4 ppm) for 2 years in a cancer bioassay. • No clinical signs of toxicity or histopathology changes in the brain or sciatic nerve were observed in rats exposed by gavage to up to 300 mg/kg-d for 10 days or 150 mg/kg-d for 90 days. • No histopathology changes were observed in the brain, sciatic nerve, or spinal cord of mice exposed via drinking water for 13 weeks, by gavage for 78 weeks in a cancer bioassay, or in transgenic mice exposed by	*Key findings*: Several high- and medium-quality studies using rats exposed to 1,2-dichloroethane by inhalation or gavage or mice exposed by intraperitoneal injection showed the occurrence of neurobehavioral changes, clinical signs of neurotoxicity, and/or changes in brain histopathology. *Overall WOSE judgement for neurological/behavioral effects based on animal evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
and electron microscopy, and water content of the brain after 2-, 4-, 6-, or 12-hour exposures (Qin-li et al., 2010) Study quality: Medium • An inhalation cancer bioassay in male and female rats evaluated brain, sciatic nerve, and spinal cord gross and/or microscopic pathology after 2 years exposure (Cheever et al., 1990) Study quality: High • A gavage study in male and female rats evaluated clinical signs, brain weight, and gross and/or microscopic pathology of the brain and sciatic nerve after 10- or 90-day exposure (Daniel et al., 1994) Study quality: High • A gavage study in male and female rats evaluated clinical signs, brain weight, and histopathology of the brain, sciatic nerve, and spinal cord after 13 weeks exposure (NTP, 1991) Study quality: High • A drinking water study in male and female mice evaluated clinical signs, brain weight, and histopathology of the brain, sciatic nerve, and spinal cord after 13 weeks exposure (NTP, 1991) Study quality: High • A gavage cancer bioassay in male and female mice evaluated clinical signs and histopathology of the brain/meninges after 78 weeks exposure (NTP, 1978) Study quality: Medium • A dermal cancer bioassay in male and female transgenic mice evaluated clinical signs, brain weights, and brain, spinal cord, and sciatic nerve histopathology	dysphoria, and/or trembling were reported. • In rats exposed by gavage for 13 weeks, clinical signs of neurotoxicity (including tremors and abnormal posture) and necrosis in the cerebellum were observed at ≥240 mg/kg-day. Consistency: • Mice exposed by intraperitoneal injection showed a dose-related decrease in response rate in lever-pressing operant behavior test at ≥ 62.5 mg/kg but no effects on other tests.	dermal application for 40 weeks in a cancer bioassay. • Exposure to 1,2-dichloroethane did not alter brain weights of rats exposed by gavage for up to 90 days or in mice exposed by gavage for 14 days or drinking water for 90 days.		

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
after 26 weeks exposure (Suguro et al., 2017) Study quality: High Studies evaluating clinical signs, brain weight, and/or gross pathology: • Inhalation studies in rats, mice, rabbits, and guinea pigs evaluated clinical signs of neurotoxicity after 1.5- to 7-hour exposures (Heppel et al., 1945) Study quality: Medium • An inhalation study in male and female rats and guinea pigs and male monkeys evaluated clinical signs and/or brain histology after up to 35 weeks exposure (Spencer et al., 1951) Study quality: High • A gavage study in male rats evaluated clinical signs and gross pathology after a single exposure (Stauffer Chem Co, 1973) Study quality: Medium • A gavage study in male and female mice evaluated brain weight and gross pathology after 14-day exposure (Munson et al., 1982) Study quality: High • An intraperitoneal (intraperitoneal) injection study of fertility in male mice evaluated gross pathology of the brain after 5-day exposure (Daigle et al., 2009) Study quality: Medium				
Evidence in mechanistic studies				
• *In vivo* inhalation studies in mice aimed at identifying mechanisms of brain edema induced by 1,2-dichloroethane evaluated aquaporin and matrix metalloproteinases protein expression or ATP generation and tight junction protein expression after 1-, 2-, or 3-day exposure (Wang et al., 2018a; Wang et al., 2014).	Biological gradient/dose-response: • Exposure to 1,2-dichloroethane upregulated the mRNA and/or protein expression of aquaporin and a matrix metalloproteinase (MMP9). • Exposure to 1,2-dichloroethane resulted in decreased expression of		*Key findings*: 1,2-dichloroethane may downregulate tight junction proteins and energy production and upregulate aquaporin and a matrix metalloproteinase in the brains of exposed	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• An *in vivo* oral study in rats evaluated neurotransmitter levels in the brain after a single exposure (Kanada et al., 1994). • *In vitro* studies in rat astrocytes exposed to 2-chloroethanol (metabolite of 1,2-dichloroethane) evaluated the roles of mitochondrial function, glutamate metabolism, matrix metalloproteinases, and MAPK cell signaling in cerebral edema induced by 1,2-dichloroethane (Wang et al., 2018b; Wang et al., 2017; Sun et al., 2016a; Sun et al., 2016b).	tight junction proteins (occludin and ZO-1) and mRNA, increased free calcium, decreased ATP content, and decreased ATPase activity in the brains of mice. Consistency: • Exposure to 2-chloroethanol *in vitro* resulted in decreased ATPase activity, mitochondrial function (membrane potential), and glutamate metabolism (expression of enzymes involved in glutamate metabolism) in rat astrocytes. Exposure also upregulated matrix metalloproteinases (MMP2 and MMP9) via increased p38 MAPK signaling. Pretreatment with the antioxidant N-acetyl-l-cysteine mitigated effects on p38 and MMP levels, suggesting a role for oxidative stress.		mice. *Overall WOSE judgement for neurological/behavioral effects based on mechanistic evidence:* • Slight	

2948 **Table_Apx B-6. 1,2-Dichloroethane Evidence Integration Table for Respiratory Tract Effects**

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on respiratory tract effects				
Evidence from human studies (none)			• Indeterminate	*Overall WOSE judgement for respiratory tract effects based on integration of information across evidence streams:* Evidence suggests, but is not sufficient to conclude, that 1,2-dichloroethane may cause nasal effects under relevant exposure conditions.
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Studies examining upper and lower respiratory tract: • An acute inhalation study in male and female rats evaluated BAL, lung weight, and histopathology of the respiratory tract including nasal cavity 24 hours after 4- or 8-hour exposures (Hotchkiss et al., 2010; Dow Chemical, 2006b). Study quality: High • An inhalation cancer bioassay in male and female rats evaluated histopathology of the respiratory tract including nasal cavity after 104 weeks of exposure (Cheever et al., 1990). Study quality: High • Two gavage studies in rats evaluated lung weight and histopathology of the lungs and nasal cavity and turbinates after 10 and 90 days of exposure (Daniel et al., 1994). Study quality: High • A gavage study in male and female rats evaluated histopathology of the respiratory tract including nasal cavity and turbinates, after 13 weeks of exposure (NTP, 1991). Study quality: High • A drinking water study in male and female mice evaluated histopathology of the respiratory tract including nasal cavity and turbinates, after 13 weeks of exposure (NTP, 1991). Study quality: High • A dermal cancer bioassay in male and female transgenic mice susceptible to cancer evaluated lung weight and histopathology of the nasal cavity, trachea, and lungs after 26	Biological gradient/dose-response: • In a high-quality study, dose-related increased incidences and/or severity of degeneration/ necrosis of the nasal olfactory mucosa occurred in male and female rats after inhalation exposures ≥795 mg/m^3 (≥196.4 ppm) for 4 hours or ≥ 435 mg/m^3 (≥107.5 ppm) for 8 hours. Regeneration of the olfactory epithelium was seen in groups sacrificed 15 days after a 4-hour exposure to 795 mg/m^3 (196.4 ppm). • Lung effects including a transient decrease in ALP in BALF and histopathology changes (edema, vacuolar changes, desquamation, atelectasis, macrophage proliferation, and inflammation) were reported in rats after a single gavage dose of 136 mg/kg.	Biological gradient/dose-response: • No treatment-related nasal lesions were observed in cancer bioassays of rats exposed by inhalation up to 654 mg/m^3 (160 ppm) for 2 years. • High-quality studies in rats did not show effects of 1,2-dichloroethane on the lung after gavage exposure up to 150 mg/kg/day for 90 days. Magnitude and precision: • Group sizes were small (5/sex) in the acute inhalation study that observed nasal lesions. Consistency: • High- and medium-quality studies in rats did not show effects of 1,2-dichloroethane on the lung after chronic inhalation exposure up to 810 mg/m3 (200 ppm) for 212 days or up to 654 mg/m^3 (160 ppm) for 2 years. • High-quality studies in mice did not show effects of 1,2-dichloroethane on the lungs after 14 days of gavage exposure up to 49 mg/kg/day or 13 weeks of drinking water	*Key findings*: In a high-quality study, an association between 1,2-dichloroethane inhalation exposure and nasal lesions was observed in rats exposed to concentrations ≥ 435 mg/m^3 (≥107.5 ppm). Although one medium-quality study reported lung lesions in rats after a single gavage dose, high- and medium-quality studies of longer duration and higher doses, as well as a high-quality study of acute inhalation exposure, did not show effects of 1,2-dichloroethane on lower respiratory tract tissues of rats. *Overall WOSE judgement for respiratory effects based on animal evidence:* • Slight to moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
weeks of exposure (Suguro et al., 2017). Study quality: High Studies examining only lower respiratory tract: • An inhalation cancer bioassay in male and female rats and mice evaluated lung weight and histopathology after 104 weeks of exposure (Nagano et al., 2006). Study quality: High • An inhalation study in male and female rats and guinea pigs evaluated lung weight and histopathology after ~170 - 246 days (Spencer et al., 1951). Study quality: Medium • A gavage study in male rats evaluated BALF, lung weight, and lung histopathology 1 to 30 days after a single dose (Salovsky et al., 2002). Study quality: Medium • A gavage study in mice evaluated lung weight and gross pathology after 14 days of exposure (Munson et al., 1982). Study quality: High • A gavage study in male and female mice evaluated the lungs, bronchi, and trachea for histopathology after 78 weeks of exposure (NTP, 1978). Study quality: High • An intraperitoneal injection study in male rats evaluated lung weight and histopathology (Igwe et al., 1986b). Study quality: Medium • An intratracheal injection lethality study in rats (sex NS) evaluated gross pathology of the lungs at death or 3 days after a single dose (Dow Chemical, 1989). Study quality: Medium		exposure up to 4926 mg/kg/day. • A medium-quality study in guinea pigs did not show effects of 1,2-dichloroethane on the lungs after exposure up to 1620 mg/m^3 (400 ppm) for 246 days. • BAL parameters, lung weight, and lung histopathology were not affected in rats exposed by inhalation up to 8212.26 mg/m^3 (2029.0 ppm) for 4 hours. Quality of the database: • Lung histopathology data in the acute gavage study that reported lung effects were presented qualitatively. Biological plausibility and human relevance: • Lung tumors are associated with chronic inhalation or gavage exposure in mice and with subchronic dermal exposure in susceptible transgenic mice. Increases in lung weight and preneoplastic lesions, such as hyperplasia, in some of these studies are related to tumor development and not indicative of a separate nonneoplastic effect on the lung.		
Evidence in mechanistic studies (none)			• Indeterminate	

2951 **Table_Apx B-7. 1,2-Dichloroethane Evidence Integration Table for Nutritional/Metabolic Effects**

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on nutritional/metabolic effects				
Evidence from human studies (none)			• Indeterminate	*Overall WOSE judgement for nutritional/ metabolic effects based on integration of information across evidence streams:* Evidence suggests that 1,2-dichloroethane may cause nutritional/ metabolic effects under relevant exposure conditions.
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Body weight was evaluated in the following studies: • Acute inhalation studies in male and female rats (Dow Chemical, 2006b); Study quality: High. • Short-term inhalation studies in male mice (Zeng et al., 2018; Zhang et al., 2017); Study quality: High. • A short-term inhalation study in female rats (Dow Chemical, 2014); Study quality: High. • Short-term, subchronic, and chronic inhalation studies in male and/or female rats, mice, rabbits, dogs, guinea pigs, monkeys, and cats (Spencer et al., 1951; Heppel et al., 1946); Study quality: Medium or Low. • A one-generation inhalation reproduction study in rats (Rao et al., 1980); Study quality: Medium. • Chronic inhalation cancer bioassays in male and female rats (Nagano et al., 2006; Cheever et al., 1990); Study quality: High. • An acute oral gavage study in male rats (Moody et al., 1981); Study quality: Medium. • A gavage study in female rats exposed during gestation (Payan et al., 1995); Study quality: High.	Biological gradient/dose-response: Treatment-related adverse[a] effects on body weight occurred in high or medium quality studies of (species, route, exposure level and duration): • Mouse inhalation: ○ ≥707 mg/m^3 (175 ppm), males, 4 weeks • Guinea pig inhalation: ○ 405 mg/m^3 (100 ppm) in females and 809 mg/m^3 (200 ppm) in males, up to 246 d • Rat gavage: ○ ≥40 mg/kg-day, females, 6 weeks ○ 150 mg/kg-day, males, 13 weeks ○ 198 mg/kg-day, maternal weight gain, GD 6–20 • Mouse drinking water: ○ 4,207 mg/kg-day in males and ≥647 mg/kg-day in females, 13 weeks Consistency: • Decreased body weight was observed in male transgenic mice exposed to 200 mg/kg-day by gavage for 40 weeks.	Biological gradient/dose-response: No treatment-related adverse effects on body weight occurred in high or medium quality studies of (species, route, exposure level, and duration): • Rat inhalation: ○ ≤8,212 mg/m^3 (2029 ppm), males and females, 4 hours ○ 832 mg/m^3 (205 ppm), females, 4 weeks ○ ≤809 mg/m^3 (200 ppm), males and females, up to 212 d ○ ≤648 mg/m^3 (160 ppm), males and females, 2 years • Monkey inhalation: ○ 405 mg/m^3 (100 ppm), males, up to 212 days • Rat gavage: ○ 625 mg/kg-day, males, single dose ○ ≤300 mg/kg-day, males, and females, 10 d ○ ≤100 mg/kg-day, males, 2 weeks ○ ≤90 mg/kg-day, males, and females, 13 weeks ○ ≤120 mg/kg-day in males and ≤150 mg/kg-day in females, 13 weeks Consistency: • Body weight was not affected in low quality inhalation studies of female dogs exposed to 1,540 mg/m^3 (380.5	*Key findings*: Decreased body weight was reported in mice and guinea pigs exposed by inhalation and rats and mice exposed orally to 1,2-dichloroethane in high- and medium-quality studies. Several high- and medium-quality studies in a few species via various routes of exposure reported no effect on body weight, sometimes at lower exposure levels and/or shorter exposure durations. *Overall WOSE judgement for nutritional/metabolic effects based on animal evidence:* • Slight	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• A short-term gavage study in male and female mice (Munson et al., 1982); Study quality: High. • Short-term and subchronic gavage studies in male and female rats (Daniel et al., 1994; NTP, 1991; van Esch et al., 1977); Study quality: High. (NTP, 1978); Study quality Medium. • A subchronic drinking water study in male and female mice (NTP, 1991); Study quality: High. • A subchronic dietary study in rats (Alumot et al., 1976); Study quality: Medium. • A multigenerational drinking water study in mice (Lane et al., 1982); Study quality: High. • Chronic gavage and dermal studies in transgenic mice susceptible to cancer (Suguro et al., 2017; Storer et al., 1995); Study quality: High. • Short-term intraperitoneal injection studies in male rats and male mice (Daigle et al., 2009); Study quality: High; (Igwe et al., 1986b); Study quality: Medium.		ppm) for 34–35 weeks or male rabbits exposed to 730 mg/m^3 (180 ppm) for 13–25 weeks. • Body weight was not affected in rats given feed fumigated with 1,2-dichloroethane in a 13-week study with dose uncertainties. • Body weight was not affected in male transgenic mice exposed to dermal doses up to 6,300 mg/kg-day for 26 weeks. • Body weight was not affected after intraperitoneal administration in male rats given 150 mg/kg-day for 30 days or in male mice given 40 mg/kg-day for 5 days.		
Evidence in mechanistic studies (none)			• Indeterminate	

[a] In adult animals, decreases in body weight of at least 10% change from control are considered adverse unless the changes are attributable to food or drinking water intake decreases due to palatability. Statistically significant decreases (relative to controls) in maternal body weight gain during gestation are considered adverse. Effects on body weight of offspring at ages up to sexual maturity are considered developmental effects.

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2953 **Table_Apx B-8. 1,2-Dichloroethane Evidence Integration Table for Mortality**

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on mortality				
Evidence from human studies				*Overall WOSE judgement for mortality effects based on integration of information across evidence streams:* Evidence indicates that 1,2-dichloroethane may cause death under relevant exposure circumstances and lethal levels have been identified in animal studies.
• A retrospective cohort mortality study evaluated all-cause mortality in 7849 white male petrochemical plant workers followed from 1950 to 1983. SMRs were calculated using age-, race-, and calendar year-specific mortality rates of males in the United States (Teta et al., 1991). Study quality: Medium • A retrospective cohort mortality study evaluated all-cause mortality in 251 employees of an herbicide manufacturing facility between 1979 and 1987, followed until 2003. SMRs were calculated using age- and gender-specific mortality rates in the United States. (BASF, 2005). Study quality: Medium		Biological plausibility and human relevance: • Two limited retrospective cohort studies found no increase in mortality of workers with presumed exposure to 1,2-dichloroethane (and other chemicals) relative to the general U.S. population.	*Key findings*: Limited epidemiological data show no increase in mortality among workers with presumed exposure to 1,2-dichloroethane but are insufficient to draw any broader conclusions. *Overall WOSE judgement for mortality effects based on human evidence:* • Indeterminate	
Evidence from apical endpoints in *in vivo* mammalian animal studies				
• Acute-duration inhalation studies evaluated mortality in rats, mice, and guinea pigs (Dow Chemical, 2017, 2006b; Storer et al., 1984; Spencer et al., 1951), Study quality: High.(Qin-li et al., 2010; Francovitch et al., 1986; Heppel et al., 1945), Study quality: Medium • Short-term- and subchronic-duration inhalation studies evaluated mortality in rats, guinea pigs, mice, rabbits, dogs, and cats (Dow Chemical, 2014; Payan et al., 1995; Igwe et al., 1986b), Study quality: High. (Rao et al., 1980; Heppel et al., 1946), Study quality: Medium • Chronic-duration inhalation studies evaluated mortality in rats, mice, rabbits,	Biological gradient/dose-response: Treatment-related deaths[a] or effects on survival occurred in studies of (species, route, exposure, and intended duration): • Rat inhalation: ○ 10,200 mg/m^3 (2,520 ppm), 4 hours ○ 4,050 mg/m^3 (1,000 ppm), 7 hours ○ 1,230 mg/m^3 (455 ppm), 30 d ○ ≥730 mg/m^3 (0.73 mg/L), 6 weeks	Biological gradient/dose-response: No treatment-related[1] deaths/effects on survival were seen in studies of (species, route, exposure, duration): • Rat inhalation: ○ ≤8,212 mg/m^3 (2,029 ppm), 4 hours ○ 5,000 mg/m^3, 2–6 hours ○ 630.6 mg/m^3 (155.8 ppm), 8 hours ○ 10,000 mg/m^3, 12 hours ○ 404 mg/m^3, 17 weeks ○ ≤646.4 mg/m^3 (158 ppm), 2 years	*Key findings*: Treatment-related increases in the incidence of mortality were observed in several animal species exposed to 1,2-dichloroethane via inhalation, oral, or dermal exposure for acute, short-term/intermediate, or chronic durations in multiple studies. *Overall WOSE judgement for mortality effects based on animal evidence:* • Robust	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
guinea pigs, dogs, monkeys, and cats (Nagano et al., 2006; Cheever et al., 1990), Study quality: High. (Hofmann et al., 1971; Spencer et al., 1951), Study quality: Medium; (Heppel et al., 1946), Study quality: Low or Medium; (Mellon Institute, 1947), Study quality: Low • Acute-duration gavage studies evaluated mortality in rats and mice (Kitchin et al., 1993; Storer et al., 1984; Moody et al., 1981). Study quality: High; (Stauffer Chem Co, 1973). Study quality: Medium • Short-term- and subchronic-duration gavage studies evaluated mortality in rats (Daniel et al., 1994; NTP, 1991). Study quality: High • Chronic-duration gavage studies evaluated mortality in wild type and transgenic mice (Storer et al., 1995; NTP, 1978). Study quality: High • A subchronic drinking water study evaluated mortality in mice (NTP, 1991). Study quality: High • Chronic-duration drinking water studies evaluated mortality in mice (Klaunig et al., 1986; Lane et al., 1982). Study quality: High • An acute-duration dermal exposure study evaluated mortality in rabbits (Dow Chemical, 1956), Study quality: Medium • A chronic-duration dermal exposure study evaluated mortality in transgenic mice (Suguro et al., 2017), Study quality: High • A single dose intratracheal exposure study evaluated mortality in rats (Dow Chemical, 1989), Study quality: Medium	○ 1,214 mg/m^3 (300 ppm), gestational exposure • Mouse inhalation: ○ ≥4,339 mg/m^3 (1,072 ppm), 4 hours ○ 6,071 mg/m^3 (1,500 ppm), 7 hours • Rabbit inhalation: ○ 12,100 mg/m^3 (3,000 ppm), 7 hours ○ 6,071 mg/m^3 (1,500 ppm), 5 d ○ 1,980 mg/m^3 (490 ppm), 6 weeks ○ 1,540 mg/m^3 (1.54 mg/L), 20 weeks ○ ≥405 mg/m^3 (100 ppm), gestational exposure • Guinea pig inhalation: ○ 6,071 mg/m^3 (1,500 ppm), 7 hours ○ 3,900 mg/m^3 (3.9 mg/L), 4 d ○ 730 mg/m^3 (0.73 mg/L), 25 weeks • Dog inhalation: ○ 3,900 mg/m^3 (3.9 mg/L), 5 weeks • Cat inhalation: ○ 3,900 mg/m^3 (3.9 mg/L), 11 weeks • Rat gavage: ○ ≥1,000 mg/kg, once ○ ≥240 mg/kg-day, 90 days • Mouse gavage: ○ ≥400 mg/kg, once ○ 150 mg/kg-day, 40 weeks (female transgenic) • Mouse drinking water:	• Mouse inhalation: ○ ≤700 mg/m^3, 1 week ○ 420 mg/m^3, 4 weeks ○ ≤363 mg/m^3 (89.8 ppm), 2 years • Rabbit, guinea pig, and cat inhalation: ○ 404 mg/m^3, 17 weeks • Rat gavage: ○ 625 mg/kg, once ○ 150 mg/kg-day, 90 days ○ 240 mg/kg-day, gestational exposure • Mouse drinking water: ○ 2,710 mg/kg-day, 90 days (male) • Mouse intraperitoneal: ○ 600 mg/kg, once		

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• Single dose intraperitoneal injection studies evaluated mortality mice (Umezu and Shibata, 2014; Storer et al., 1984), Study quality: High; (Storer and Conolly, 1983), Study quality: Medium; (Crebelli et al., 1999), Study quality: Low	○ 4,926 mg/kg-day, 90 days (female) • Rabbit dermal: ○ 2,800 mg/kg (LD50), 24 hours • Rat intratracheal: ○ 120 mg/kg, once • Mouse intraperitoneal: ○ 486 mg/kg (LD50), once			
Evidence in mechanistic studies (none)			• Indeterminate	

[a] Apart from chronic bioassays, most studies did not report statistical significance of mortality incidences. For the purpose of hazard identification, deaths were considered to be related to treatment if they occurred at a higher incidence than in controls, occurred at the highest dose tested or with a relationship to dose, and were not attributed to factors unrelated to treatment (accident or disease). For chronic-duration studies, only statistically significant, treatment-related effects on survival were included.

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Appendix C EVIDENCE INTEGRATION TABLES FOR CANCER FOR 1,2-DICHLOROETHANE

Table_Apx C-1. 1,2-Dichloroethane Cancer Evidence Integration Table

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Evidence integration summary judgement on cancer effects				
Evidence from human studies				*Overall WOSE judgement for cancer effects based on integration of information across evidence streams:* Evidence indicates that 1,2-dichloroethane likely causes cancer under relevant exposure circumstances.
Breast cancer				
• A prospective study of women from the California Teacher Study Cohort, for which the U.S. EPA's National-Scale Air Toxics Assessment (NATA) was used to estimate exposure, evaluated the association between 1,2-dichloroethane exposure and the incidence of invasive breast cancer (Garcia et al., 2015). Study quality: High • A prospective study of women from the Sister Study Cohort, for which the U.S. EPA's NATA was used to estimate exposure, evaluated the association between 1,2-dichloroethane and the incidence of invasive breast cancer and/or ductal carcinoma *in situ* (Niehoff et al., 2019). Study quality: Medium	Biological gradient/dose-response: • The risk for ER+ invasive breast cancer was slightly, but significantly, increased in quintile 4 (but not quintile 5) of exposure relative to quintile 1 in the medium-quality study. Magnitude and precision: • The study used quantitative exposure estimates and accounted for covariate information on individual breast cancer risk factors.	Biological gradient/dose-response: • The overall risk for breast cancer (both studies) and ER- invasive breast cancer (medium-quality study) was not significantly increased in 1,2-dichloroethane-exposed women. • Analyses based on quintiles of exposure did not show an exposure-response relationship between 1,2-dichloroethane exposure and ER+ invasive breast cancer. Magnitude and precision: • The significant effect estimate for ER+ invasive breast cancer was small (hazard ratio = 1.17). • Exposure estimates based on modeling of emissions data and/or at the census tract level may have contributed to exposure misclassification.	*Key findings*: In a medium-quality study, an association between 1,2-dichloroethane exposure and ER+ invasive breast cancer was observed, but it was small and did not show a clear exposure-response relationship. *Overall WOSE judgement for cancer effects based on human evidence:* • Indeterminate	
Circulatory system cancer				
• A nested case-control study of male workers from three Union Carbide facilities, for which job assignment and history of departmental use were	Biological gradient/dose-response: • In the medium-quality study, there was a nonsignificant increase in the OR for	Biological gradient/dose-response: • In the medium-quality study, exposure levels of 1,2-	*Key findings*: Significant limitations in the available studies preclude conclusions regarding	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
taken to estimate exposure (ever/never), evaluated the association between 1,2-dichloroethane exposure and the incidence of hematopoietic tissue cancer (Ott et al., 1989; Union Carbide, 1989). Study quality: Medium Study quality ranked as Uninformative: • A retrospective cohort study of male workers [a] from one Union Carbide facility (Ott et al., 1989; Union Carbide, 1989), for which exposure (ever/never) was based on the history and/or duration of work in the chlorohydrin unit (which produced 1,2-dichloroethane as a byproduct), evaluated the association between chemical exposure and the risk of mortality due to lymphopoietic cancers (Benson and Teta, 1993).	nonlymphocytic leukemia (NLL) in 1,2-dichloroethane-exposed workers, which was higher in those working more than 5 years. • In a study ranked as Uninformative owing to lack of an appropriate comparison group and lack of 1,2-dichloroethane exposure levels, work in the chlorohydrin unit was significantly associated with mortality from lymphatic and hematopoietic cancers.	dichloroethane were not provided. Magnitude and precision: • In the medium-quality study, there was potential for confounding because covariates were not considered (race, smoking status, concurrent exposure to other chemicals). • In the medium-quality study, statistical power was limited because cancer case numbers were low (n = 5 for NLL). • In the medium-quality study, statistical methods were not specified and ORs were provided without CIs. Consistency: • In the Uninformative study, analysis was conducted based on work department rather than specific chemicals.	associations between 1,2-dichloroethane exposure in humans and circulatory system cancers. *Overall WOSE judgement for cancer effects based on human evidence:* • Indeterminate	
Pancreatic cancer				
• A case-control study of men and women from 24 states, which estimated intensity and probability of 1,2-dichloroethane exposure (low, medium, high) based on listed occupation and industry (from death certificates) and a job exposure matrix (JEM), evaluated the association between 1,2-Dichloroethane exposure and the risk of pancreatic cancer (Kernan et al., 1999). Study quality: High Study quality ranked as Uninformative: • A retrospective cohort study of male workers [b] from a Union Carbide	Biological gradient/dose-response: • In the high-quality study, 1,2-dichloroethane exposure was associated with a slight, but borderline significant, increased OR for pancreatic cancer among Black females with low estimated exposure intensity. • In a study ranked as Uninformative owing to lack of an appropriate comparison group and lack of 1,2-dichloroethane exposure levels, work in the chlorohydrin unit was significantly associated	Biological gradient/dose-response: • In the high-quality study, the risk for pancreatic cancer in Black females was not increased in groups with medium or high intensity exposure. Consistency: • In the high-quality study, 1,2-dichloroethane exposure was not associated with an increased risk of pancreatic cancer in Black males, White females, or White males. • In the Uninformative study, analysis was conducted based on	*Key findings*: In a high-quality study, a slight, but significant, association between low intensity 1,2-dichloroethane exposure and pancreatic cancer was observed in Black females, but the association did not show an exposure-response relationship, and no association was observed in Black males or White males or females.	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
facility, for which exposure (ever/never) was based on the history and/or duration of work in the chlorohydrin unit (which produced 1,2-dichloroethane as a byproduct), evaluated the association between chemical exposure and the risk of mortality due to pancreatic cancer (Benson and Teta, 1993).	with mortality from pancreatic cancer.	work department rather than specific chemicals. Magnitude and precision: • In the high-quality study, the effect estimate in Black females was small (OR = 1.2, 95% CI 1.0–1.4). • In the high-quality study, there was the potential for exposure misclassification based on the occupation and industry data captured on death certificates.	*Overall WOSE judgement for cancer effects based on human evidence:* • Indeterminate	
Kidney cancer				
• A population-based, case-control study of men and women from the Minnesota Cancer Surveillance System (cases) and the general population of Minnesota or the Health Care Financing administration (controls), for which exposure was estimated based on occupational history and JEMs, evaluated the association between 1,2-dichloroethane exposure and the risk for renal cell carcinoma (Dosemeci et al., 1999). Study quality: Medium	Biological gradient/dose-response: • The risk of renal cell carcinoma was significantly increased in women exposed to all organic solvents combined and all chlorinated aliphatic hydrocarbons combined. Magnitude and precision: • The use of a priori assessment of exposure to solvents (including 1,2-dichloroethane) using JEMs reduced recall bias among men and women and cases and controls.	Biological gradient/dose-response: • No significant increase in the risk of renal cell carcinoma was observed based on exposure to 1,2-dichloroethane among men, women, or all participants. Magnitude and precision: • The number of participants exposed to 1,2-dichloroethane (40 cases and 48 controls) may have been too low to detect effects associated with 1,2-dichloroethane exposure. Quality of the database: • Only one medium-quality study was available to assess risk of renal cancer due to 1,2-dichloroethane exposure.	*Key findings*: In a medium-quality study, no significant association between 1,2-dichloroethane exposure in humans and renal cell carcinoma was observed; however, the number of exposed subjects in the study population was small. *Overall WOSE judgement for cancer effects based on human evidence:* • Indeterminate	
Prostate cancer				
• A retrospective cohort study evaluated cancer incidence in 251 employees of an herbicide manufacturing facility (bentazon unit) between 1979 and 1987, followed	Biological gradient/dose-response: • A statistically significant association was observed between employment in the bentazon unit and prostate	Magnitude and precision: • The study did not directly assess the association between exposure to 1,2-dichloroethane and prostate cancer. Other chemicals	*Key findings*: In a medium-quality study, an association between work in bentazon production and prostate cancer was	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
until 2003. SMRs were calculated using age-, gender-, and race-specific cancer incidence rates in South Louisiana. (BASF, 2005). Study quality: Medium	cancer incidence (SIR = 2.2, 95% CI = 1.1–3.9)	were also used in the bentazon unit.	observed; however, the association with 1,2-dichloroethane was not directly assessed. *Overall WOSE judgement for cancer effects based on human evidence:* Indeterminate	
Evidence from apical endpoints in *in vivo* mammalian animal studies				
Breast cancer				
• A gavage study in male and female mice examined the mammary gland for neoplasms after 78 weeks of exposure (NTP, 1978). Study quality: High • Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) examined the mammary gland for neoplasms after 104 weeks of exposure. Study quality: High • A dermal study in male and female transgenic mice susceptible to cancer examined the mammary gland for neoplasms after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [d] examined the mammary gland for neoplasms after 78 weeks of exposure (NTP, 1978). • An inhalation study in male and female rats and mice[e] examined the mammary gland for neoplasms at	Biological gradient/dose-response: • A significant dose-related trend for increased incidence of mammary gland adenocarcinomas was observed in female mice in the 78-week gavage study using pooled vehicle controls [c] ; pairwise comparisons showed significant increases at both doses. • Significant dose-related trends for increased mammary gland adenomas, fibroadenomas, and/or adenocarcinomas were observed in male and female rats after 104 weeks of inhalation exposure; pairwise comparisons showed significant increases at the highest exposure. • A significant dose-related trend for increased incidence of mammary gland adenocarcinoma was observed in female mice after 104 weeks of inhalation exposure. • In a study ranked as Uninformative due to high mortality from pneumonia,	Consistency: • The incidence of mammary gland tumors was not increased in a 26-week dermal study in transgenic mice. Magnitude and precision: • Pairwise comparisons were not significant for increased incidence of mammary gland adenocarcinoma in female mice after 104 weeks of inhalation exposure.	*Key findings*: Mammary gland tumors were observed in male and female rats and in female mice exposed to 1,2-dichloroethane orally or via inhalation in high-quality studies. *Overall WOSE judgement for breast cancer effects based on animal evidence*: • Robust	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
natural death after 78 weeks of exposure (Maltoni et al., 1980).	significant dose-related trends for increased mammary gland adenocarcinomas or adenocarcinomas and fibroadenomas were observed in female rats in the 78-week study; pairwise comparisons showed a significant increase at the high dose for adenocarcinomas and at both doses for combined tumors. • In a study ranked uninformative due to lack of inhalation exposure details, the incidence of mammary gland fibromas and fibroadenomas was significantly increased in rats after 78 weeks of inhalation exposure. Quality of the database: • Evidence of mammary gland tumors in rats and mice was observed in high-quality studies.			
Liver cancer				
• A gavage study in male and female mice examined the liver for neoplasms after 78 weeks of exposure (NTP, 1978). Study quality: High • Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) examined the liver for neoplasms after 104 weeks of exposure. Study quality: High • A dermal exposure study in male and female transgenic mice susceptible to cancer examined the liver for	Biological gradient/dose-response: • A significant dose-related trend for increased incidence of hepatocellular carcinomas was observed in male (but not female) mice in the 78-week gavage study using pooled and matched vehicle controls [f], and the pairwise comparison to pooled vehicle controls showed a significant increase at the high dose. • A significant dose-related trend for increased incidence of hepatocellular adenomas and	Consistency: • The incidence of liver tumors was not increased in transgenic mice following 26 weeks of dermal exposure. Magnitude and precision: • In female mice, incidences of hepatocellular adenomas and adenomas or carcinomas in the 104-week inhalation study were not significantly increased based on pairwise comparisons to controls.	*Key findings*: In high-quality studies, increased liver tumor incidence was observed in male or female mice following exposure via gavage or inhalation, respectively. *Overall WOSE judgement for liver cancer effects based on animal evidence:* • Slight to Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
neoplasms after 26 weeks of exposure (Suguro et al., 2017). Study quality: High • Nine-week gavage studies in male rats evaluated the potential for tumor initiation and/or promotion in the liver based on numbers of gamma-glutamyltranspeptidase (GGT)-positive foci (Milman et al., 1988; Story et al., 1986). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [g] examined the liver for neoplasms after 78 weeks of exposure (NTP, 1978). • A cancer bioassay and a tumor promotion assay in male mice [h] assessed the incidence of liver adenomas and/or carcinomas after 52 weeks drinking water exposure (Klaunig et al., 1986).An inhalation study in male and female rats and mice[i] examined the liver for neoplasms at natural death after 78 weeks of exposure (Maltoni et al., 1980). • A dermal exposure study in female mice [j] examined the liver for neoplasms after up to 85 weeks of exposure (Van Duuren et al., 1979).	adenomas or carcinomas was observed in female (but not male) mice following 104 weeks of inhalation exposure. Quality of the database: • Evidence of increased liver tumor incidence was observed in high-quality studies.			
Lung cancer				
• A gavage study in male and female mice examined the lung for neoplasms after 78 weeks of exposure (NTP, 1978). Study quality: High	Biological gradient/dose-response: • Significant trends and pairwise comparisons for increased incidence of alveolar/bronchiolar adenomas	Magnitude and precision: • Pairwise comparisons did not show a significant increase in the incidence of lung tumors in	*Key findings*: In high-quality studies, increased lung tumor incidence was observed in male and/or female mice following gavage,	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) examined the lung for neoplasms after 104 weeks of exposure. Study quality: High • A dermal exposure study in male and female transgenic mice susceptible to cancer examined the lung for neoplasms after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [k] examined the lung for neoplasms after 78 weeks of exposure (NTP, 1978). • A cancer bioassay and a tumor promotion assay in male mice [l] assessed the incidence of lung adenomas and/or carcinomas after 52 weeks of drinking water exposure (Klaunig et al., 1986). • An inhalation study in male and female rats and mice [m] examined the lungs for neoplasms at natural death after 78 weeks of exposure (Maltoni et al., 1980). • A dermal exposure study in female mice [n] reported neoplasms in the lung (not routinely examined) after up to 82 weeks of exposure (Van Duuren et al., 1979).	were observed in male and female mice in the 78-week gavage study. • Significant trends for increased incidence of bronchiolo-alveolar carcinomas and carcinomas or adenomas were observed in female mice following 104 weeks of inhalation exposure. • Significant increases in the incidence and multiplicity of bronchiolo-alveolar adenomas and adenocarcinomas were observed in both sexes in the dermal study using transgenic mice. Consistency: • In the dermal study ranked as Uninformative due to the use of methods that did not account for the volatility of 1,2-dichloroethane, a significantly increased incidence of benign lung papillomas was observed in female mice. Quality of the database: • Evidence of lung tumors was observed in three high-quality studies.	female mice in the 104-week study.	inhalation, or dermal exposure. *Overall WOSE judgement for lung cancer effects based on animal evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Mesothelioma of the peritoneum				
• A gavage study in male and female mice conducted comprehensive histopathological examination after 78 weeks of exposure (NTP, 1978). Study quality: High • Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) conducted comprehensive histopathological examination after 104 weeks of exposure. Study quality: High • A dermal exposure study in male and female transgenic mice susceptible to cancer conducted comprehensive histopathological examination after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [o] conducted comprehensive histopathological examination after 78 weeks of exposure (NTP, 1978). • An inhalation study in male and female rats and mice [p] conducted comprehensive histopathological examination at natural death after 78 weeks of exposure (Maltoni et al., 1980).	Biological gradient/dose-response: • A significant trend for increased incidence of mesothelioma of the peritoneum was observed in male rats following 104 weeks of inhalation exposure. Quality of the database: • Evidence of mesothelioma of the peritoneum was observed in a high-quality study.	Magnitude and precision: • Pairwise comparisons did not show a significant increase in the incidence of mesothelioma of the peritoneum in male rats in the 104-week inhalation study. Consistency: • There was no significant increase in incidence of mesothelioma of the peritoneum in female rats following 104 weeks of inhalation exposure. • The incidence of mesothelioma of the peritoneum was not increased in transgenic mice following 26 weeks of dermal exposure.	*Key findings*: In a high-quality study, a trend for increased incidence of mesothelioma of the peritoneum was observed in male mice following inhalation exposure; no significant increase was noted in pairwise comparison, and no increase was seen in female mice. *Overall WOSE judgement for mesothelioma of the peritoneum based on animal evidence:* • Indeterminate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
Endometrial stromal polyps				
• A gavage study in female mice conducted histopathological examination of the uterus after 78 weeks of exposure (NTP, 1978). Study quality: High • Two inhalation studies in female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in female mice (Nagano et al., 2006) conducted histopathological examination of the uterus after 104 weeks of exposure. Study quality: High • A dermal exposure study in female transgenic mice susceptible to cancer conducted histopathological examination of the uterus after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in female rats [q] examined the uterus for neoplasms after 78 weeks of exposure (NTP, 1978).	Biological gradient/dose-response: • A significant trend for increased incidence of endometrial stromal polyps or sarcomas was observed in female mice in the 78-week gavage study using pooled vehicle controls [r], and the pairwise comparison showed a significant increase at both doses. • A significant trend for increased incidence of endometrial stromal polyps was observed in female mice following 104 weeks of inhalation exposure. Quality of the database: • Evidence of endometrial stromal polyps in mice was observed in high-quality oral and inhalation studies.	Biological gradient/dose-response: • The incidence of endometrial stromal polyps in female mice was not significantly increased in a 26-week dermal exposure study in transgenic mice. Magnitude and precision: • Pairwise comparisons using matched controls did not show a significant increase in the incidence of stromal polyps or sarcomas, and the incidence of sarcomas (alone) was not significantly increased in female mice in the 78-week gavage study. • Pairwise comparisons did not show a significant increased incidence in stromal polyps in female mice in the 104-week inhalation study. Biological plausibility and human relevance: The relevance to humans of endometrial stromal polyps in mice is uncertain due to differences in etiology and hormone sensitivity (Davis, 2012)	*Key findings*: In high-quality oral and inhalation studies, the incidence of endometrial stromal polyps was increased in female mice. The relevance of these findings to humans is uncertain due to differences in etiology and hormone sensitivity among rodents and humans. In addition, there is uncertainty within the scientific community whether endometrial stromal polyps should be considered benign tumors or nonneoplastic lesions. *Overall WOSE judgement for uterine cancer effects based on animal evidence:* • Indeterminate	
Circulatory system cancer				
• A gavage study in male and female mice subjected animals to comprehensive histological examinations for neoplasms after 78 weeks of exposure (NTP, 1978). Study quality: High	Biological gradient/dose-response: • Significant pairwise increases in the incidence of hemangiosarcoma in the liver were observed in male mice at the two highest exposure	Biological gradient/dose-response: • There was not a significant dose-related trend for increased hemangiosarcomas of the liver in male mice following 104 weeks of inhalation exposure.	*Key findings*: In medium- and high-quality studies, the incidence of circulatory system tumors (*e.g.*, hemangiosarcomas) was increased in mice	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• A gavage study in female transgenic mice susceptible to cancer subjected animals to histological examinations after 40 weeks of exposure (Storer et al., 1995). Study quality: Medium • Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) subjected animals to comprehensive histological examinations for neoplasms after 104 weeks of exposure. Study quality: High • A dermal study in transgenic mice susceptible to cancer subjected animals to comprehensive histological examinations for neoplasms after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [s] subjected animals to comprehensive histological examinations for neoplasms after 78 weeks of exposure (NTP, 1978).	concentrations following 104 weeks of inhalation exposure. • A significantly increased incidence of malignant lymphoma was observed in female transgenic mice in a 40-week gavage study. • In a study ranked as Uninformative due to high mortality from pneumonia, there was a significant trend for increased hemangiosarcomas in male and female rats in a 78-week gavage study using pooled vehicle controls [t], and the pairwise comparison showed a significant increase at both doses. Quality of the database: • Increased incidences of circulatory system cancers were observed in medium- and high-quality studies.	• The incidence of circulatory system cancers was not increased in mice in a 78-week gavage study. There was a significant trend for *decreased* malignant lymphomas of the hematopoietic system in females using matched vehicle controls. • No hemangiomas or hemangiosarcomas were observed in male or female transgenic mice in a 26-week dermal study. Magnitude and precision: • In the 78-week gavage study ranked Uninformative, the trends for increased hemangiosarcomas in male and female rats were not significant using matched controls.	following inhalation and dermal exposure. *Overall WOSE judgement for circulatory system cancer effects based on animal evidence:* • Slight	
• A gavage study in male transgenic mice [u] susceptible to cancer examined the incidence of malignant lymphomas after 40 weeks of exposure (Storer et al., 1995). • An inhalation study in male and female rats and mice [v] examined animals for neoplasms at natural death after 78 weeks of exposure (Maltoni et al., 1980).				
Gastrointestinal tract cancer				

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
• A gavage study in male and female mice examined the gastrointestinal tract for neoplasms after 78 weeks of exposure (NTP, 1978). Study quality: High • Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) examined the gastrointestinal tract for neoplasms after 104 weeks of exposure. Study quality: High • A dermal exposure study in male and female transgenic mice susceptible to cancer examined the gastrointestinal tract for neoplasms after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [x] examined the gastrointestinal tract for neoplasms after 78 weeks of exposure (NTP, 1978). • An inhalation study in male and female rats and mice [y] examined the stomach and intestines for neoplasms at natural death after 78 weeks of exposure (Maltoni et al., 1980). • A dermal exposure study in female mice [z] examined the stomach for neoplasms after up to 85 weeks of exposure (Van Duuren et al., 1979).	Biological gradient/dose-response: • A significant trend for increased incidence of squamous-cell carcinomas in the stomach was observed in female mice in the 78-week gavage study using pooled vehicle controls. • In a study ranked as Uninformative owing to high mortality from pneumonia, a significant trend for increased incidence of squamous-cell carcinomas in the stomach was observed in male rats in the 78-week gavage study using pooled and matched vehicle controls [w]; the pairwise comparisons showed a significant increase at the highest dose.	Biological gradient/dose-response: • The incidence of gastrointestinal tumors (forestomach tumors) was not increased in rats or mice following 104 weeks of inhalation exposure. • The incidence of gastrointestinal tumors was not increased in two dermal studies, including a study in transgenic male and female mice treated for 26 weeks, and an 85-week study in female mice ranked as Uninformative due to the use of methods that did not account for the volatility of 1,2-dichloroethane. Magnitude and precision: • The trend for increased incidence of squamous-cell carcinomas in female mice in the 78-week gavage study was not significant using matched controls, and the pairwise comparisons using pooled and matched controls were not significant.	*Key findings*: In high-quality and Uninformative gavage studies, increased incidences of gastrointestinal tract tumors were observed in female mice and male rats. The effect appears to be route-specific because several high-quality studies did not identify gastrointestinal tumors following inhalation or dermal exposure. *Overall WOSE judgement for gastrointestinal cancer effects based on animal evidence:* • Indeterminate	
Subcutaneous fibromas				
• A gavage study in male and female mice conducted comprehensive histopathological examination after 78	Biological gradient/dose-response: • A significant trend for increased incidence subcutaneous fibroma was observed in male and	Magnitude and precision: • A significant dose-related trend for increased incidence of subcutaneous fibromas was not	*Key findings*: In a high-quality study, an increased incidence of subcutaneous fibromas in	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
weeks of exposure (NTP, 1978). Study quality: High • Two inhalation studies in male and female rats (Nagano et al., 2006; Cheever et al., 1990) and one inhalation study in male and female mice (Nagano et al., 2006) conducted comprehensive histopathological examination after 104 weeks of exposure. Study quality: High • A dermal exposure study in male and female transgenic mice susceptible to cancer conducted comprehensive histopathological examination after 26 weeks of exposure (Suguro et al., 2017). Study quality: High Study quality ranked as Uninformative: • A gavage study in male and female rats [aa] conducted comprehensive histopathological examination after 78 weeks of exposure (NTP, 1978). • An inhalation study in male and female rats and mice [bb] conducted comprehensive histopathological examination at natural death after 78 weeks of exposure (Maltoni et al., 1980).	female rats following 104 weeks of inhalation exposure; pairwise comparisons showed a significant increase at the high dose in female rats only. • In a study ranked as Uninformative due to high mortality from pneumonia, a significant dose-related trend for increased incidence of subcutaneous fibromas was observed in male rats in the 78-week gavage study using pooled vehicle controls [dd]; pairwise comparisons showed significant increases at both doses. Quality of the database: • Evidence of subcutaneous fibroma was observed in a high-quality study.	observed in male rats in the 78-week gavage study using matched vehicle controls. Consistency: • The incidence of subcutaneous tumors was not increased in transgenic mice following 26 weeks of dermal exposure.	male and female rats was seen following inhalation exposure. *Overall WOSE judgement for subcutaneous fibromas based on animal evidence:* • Indeterminate	
Evidence in mechanistic studies				
Genotoxicity: [cc] • Two recent authoritative reviews (ATSDR, 2022; Gwinn et al., 2011) were the primary sources used to provide an overview of the database of genotoxicity studies available for 11,2 dichloroethane, including numerous studies of gene mutation in *Salmonella typhimurium*; gene mutation in fruit flies; gene mutation,	Consistency: • In most of the available studies, 1,2 dichloroethane induced mutations in *S. typhimurium* in the presence of metabolic activation. Many of these studies also reported positive results without metabolic activation.	Quality of the database: • Alternative modes of action were investigated only for mammary gland tumors and not for other tumor types induced by 1,2-dichloroethane.	*Key findings*: 1,2-dichloroethane has induced mutations, clastogenic effects, DNA damage, and DNA binding/adduct formation *in vitro* and *in vivo*. The preponderance of the substantial database consists of positive results. While	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
micronucleus formation, DNA damage, and DNA binding/adduct formation in mammalian cells/tissue isolates *in vitro*; and clastogenicity, DNA damage, and DNA binding/adduct formation in mammals *in vivo*. Other mechanisms: • A 28-day inhalation exposure experiment in female rats evaluated cell proliferation in mammary tissue and serum prolactin levels (Lebaron et al., 2021).	• 1,2 dichloroethane induced gene mutations in multiple studies of fruit flies. • 1,2 dichloroethane yielded positive results in gene mutation assays in Chinese hamster ovary cells and human lymphoblastoid cells *in vitro*. • 1,2 dichloroethane produced clastogenic effects including micronuclei in human lymphocytes *in vitro* and micronuclei, chromosomal aberrations, and sister chromatid exchanges in rat and mouse bone marrow *in vivo*. • DNA damage was observed in human lymphocytes and rat and mouse hepatocytes exposed to 1,2 dichloroethane *in vitro* and in multiple tissues from rats and mice exposed *in vivo*. • DNA binding/adduct formation after 1,2 dichloroethane exposure was observed *in vitro* and in multiple tissues from rats and mice *in vivo*. Biological plausibility and human relevance: • Several metabolites of 1,2-dichloroethane, particularly those from the glutathione conjugation pathway, have been shown to bind DNA and induce DNA damage *in vivo*, and to induce mutations in *S. typhimurium in vitro*. Quality of the database:		these effects could plausibly be related to formation of tumors, a direct connection between these events and 1,2 dichloroethane induced carcinogenesis has not been conclusively demonstrated. Few mechanistic data examining alternative modes of carcinogenic action are available. *Overall WOSE judgement for cancer effects based on mechanistic evidence:* • Moderate	

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement
	• The genotoxicity database includes numerous *in vitro* and *in vivo* studies evaluating a wide variety of genotoxic endpoints in multiple test systems.			

[a] The study was ranked as Uninformative because SMRs were calculated based on expected deaths from a reference population matched on sex, but not age, and exposure was assessed based on duration of work in the facility; no information was provided on levels of exposure to 1,2-dichlororethane.
[b] The study was ranked as Uninformative because SMRs were calculated based on expected deaths from a reference population matched on sex and exposure was assessed based on duration of work in the facility; no information was provided on levels of exposure to 1,2-dichloroethane.
[c] Pooled controls from several bioassays were used based on data for the same strain, tested by the same laboratory no more than 6 months apart, and diagnosed by the same pathologist.
[d] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[e] Pending evaluation.
[f] Pooled controls from several bioassays were used based on data for the same strain, tested by the same laboratory no more than 6 months apart, and diagnosed by the same pathologist
[g] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[h] The study in male mice was considered Uninformative due to inadequate study duration (52-week cancer bioassay) and a high tumor response rate in the initiation-only control group (tumor promotion assay).
[i] This chronic inhalation study was ranked Uninformative due to lack of information on the inhalation exposure methodology.
[j] The study in female mice was considered Uninformative because methods used to conduct the study did not account for volatility of the test substance.
[k] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[l] The study in male mice was considered Uninformative due to inadequate study duration (52-week cancer bioassay) or a high tumor response rate in the initiation-only control group (tumor promotion assay).
[m] This chronic inhalation study was ranked Uninformative due to lack of information on the inhalation exposure methodology.
[n] The study in female mice was considered Uninformative because methods used to conduct the study did not account for volatility of the test substance.
[o] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[p] This chronic inhalation study was ranked Uninformative due to lack of information on the inhalation exposure methodology.
[q] The study in female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[r] Pooled controls from several bioassays were used based on data for the same strain, tested by the same laboratory no more than 6 months apart, and diagnosed by the same pathologist.
[s] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[t] Pooled controls from several bioassays were used based on data for the same strain, tested by the same laboratory no more than 6 months apart, and diagnosed by the same pathologist.
[u] The study in male transgenic mice was considered Uninformative because the duration of the study was potentially inadequate for tumor development and no tumors were observed (the same study in female transgenic mice was considered Informative because tumors were observed).
[v] This chronic inhalation study was ranked Uninformative due to lack of information on the inhalation exposure methodology.
[w] Pooled controls from several bioassays were used based on data for the same strain, tested by the same laboratory no more than 6 months apart, and diagnosed by the same pathologist.

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and within-Stream Strength of the Evidence Judgement	Inferences across Evidence Streams and Overall WOSE Judgement

[x] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[y] Pending evaluation.
[z] The study in female mice was considered Uninformative due to the use of methods that did not account for the volatility of 1,2-dichloroethane.
[aa] The study in male and female rats was considered Uninformative due to high mortality from pneumonia in all groups (including controls).
[bb] This chronic inhalation study was ranked Uninformative due to lack of information on the inhalation exposure methodology.
[cc] Including experiments reviewed by Gwinn et al. (2011), and/or ATSDR (2022) that were not flagged as inconsistent with OECD guidance on genotoxicity testing, as well as the one study published subsequently (Lone et al., 2016).
[dd] Pooled controls from several bioassays were used based on data for the same strain, tested by the same laboratory no more than 6 months apart, and diagnosed by the same pathologist.

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Appendix D LIST OF SUPPLEMENTAL DOCUMENTS

Appendix D incudes a list and citations for all supplemental documents included in this Draft Human Health Hazard Assessment for 1,2-Dichloroethane. See Docket EPA-HQ-OPPT-2024-0114 for all publicly released files associated with peer review and public comments.

Associated **Systematic Review Protocol and Data Quality Evaluation and Data Extraction** Documents – Provide additional detail and information on systematic review methodologies used as well as the data quality evaluations and extractions criteria and results.

Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Protocol (U.S. EPA, 2024b) – In lieu of an update to the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances*, also referred to as the "2021 Draft Systematic Review Protocol" (U.S. EPA, 2021), this systematic review protocol for the Draft Risk Evaluation for 1,1-Dichloroethane describes some clarifications and different approaches that were implemented than those described in the 2021 Draft Systematic Review Protocol in response to (1) SACC comments, (2) public comments, or (3) to reflect chemical-specific risk evaluation needs. This supplemental file may also be referred to as the "1,1-Dichloroethane Systematic Review Protocol."

Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Supplemental File: Data Quality Evaluation Information for Human Health Hazard Epidemiology (U.S. EPA, 2024e) – Provides a compilation of tables for the data quality evaluation information for 1,2-dichloroethane. Each table shows the data point, set, or information element that was evaluated from a data source that has information relevant for the evaluation of epidemiological information. This supplemental file may also be referred to as the "1,1-Dichloroethane Data Quality Evaluation Information for Human Health Hazard Epidemiology."

Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Supplemental File: Data Quality Evaluation Information for Human Health Hazard Animal Toxicology (U.S. EPA, 2024d) – Provides a compilation of tables for the data quality evaluation information for 1,2-dichloroethane. Each table shows the data point, set, or information element that was evaluated from a data source that has information relevant for the evaluation of human health hazard animal toxicity information. This supplemental file may also be referred to as the "1,1-Dichloroethane Data Quality Evaluation Information for Human Health Hazard Animal Toxicology."

Draft Risk Evaluation for 1,1-Dichloroethane – Systematic Review Supplemental File: Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology (U.S. EPA, 2024c) – Provides a compilation of tables for the data extraction for 1,2-dichloroethane. Each table shows the data point, set, or information element that was extracted from a data source that has information relevant for the evaluation of environmental hazard and human health hazard animal toxicology and epidemiology information. This supplemental file may also be referred to as the "1,1-Dichloroethane Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology."

Associated **Supplemental Information Documents** – Provide additional details and information on exposure, hazard, and risk assessments.

Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling (U.S. EPA, 2024a).

Appendix E HUMAN HEALTH HAZARD VALUES USED BY EPA OFFICES AND OTHER AGENCIES

Historically, offices across EPA and other agencies (ATSDR), have developed their own assessments for 1,2-dichloroethane. A comparison of these assessments is outlined in Table_Apx E-1 for non-cancer based on exposure duration and route.

E.1 Summary of Non-cancer Assessments of EPA Offices and Other Agencies

EPA first reviewed existing assessments of 1,2-dichloroethane conducted by regulatory and authoritative agencies such as ATSDR (2022), as well as several systematic reviews of studies of 1,2-dichloroethane published by U.S. EPA Integrated Risk Information System (IRIS) program(U.S. EPA, 1987b) and U.S. EPA Provisional Peer-Reviewed Toxicity Values (U.S. EPA, 2010).

Upon evaluation of the ATSDR (2022) *Toxicological Profile for 1,2-Dichloroethane* and U.S. EPA *Provisional Peer-Reviewed Toxicity Values for 1,2-Dichloroethane* (U.S. EPA, 2010), the studies identified for minimal risk level (MRL) and provisional values, respectively, by these assessments were evaluated by the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (U.S. EPA, 2021). While there are many areas of agreement with these assessments, both the ATSDR (2022) and (U.S. EPA, 2010) assessments used studies that were identified as "Uninformative" based on systematic review for the subchronic duration scenarios.

More specifically for both ATSDR (2022) and (U.S. EPA, 2010), the 13-week study by (NTP, 1991) in male and female F344/N, Sprague Dawley, and Osborne-Mendel rats as well as B6C3F1 mice exposed to 1,2-dichloroethane in drinking water was used. A significant dose-related increase in kidney weight and the kidney-body-ratio of female F344 rats was identified at 58 mg/kg/day among the three rat strains. This study was considered as a potential candidate for POD derivation, however, the daily intake doses were estimated on a mg/kg body weight basis and not measured throughout the duration of exposure. The means by which the dosage estimates were calculated was by dividing the mean water consumption over the 13-week study by the initial and final body weights of ten animals. Additionally, weight gain depression was seen in males and females in the two higher dose groups throughout the study and was likely caused by dehydration due to poor palatability of the formulated drinking water. The study also indicated that water consumption was substantially decreased with increasing dose. According to the study, a decrease of as much as 60 percent in water intake was also seen in both male and female Osborne-Mendel rats at the highest concentration of 8000 ppm (a range of 500 -725 mg/kg/day) that indicates that the dose received by all exposed animals was less than the target dose. The authors indicate that as water intake was reduced at most exposure levels, equivalent exposure did not, however, occur at different dose levels within a strain. Due to the uncertainty regarding the delivered dose and the inherit volatility associated with 1,2-dichloroethane, it was not recommended using this drinking water study for this dose-response assessment.

(NTP, 1991), however, also included a 13-week gavage study that was rated high by systematic review and considered for a POD for subchronic exposures based on kidney weight (30 mg/kg/day LOAEL males; 75 mg/kg/day LOAEL females), however, the study had a higher POD via oral gavage, and was not ultimately selected as the use of the most sensitive endpoint, immunosuppression, from Munson et al. (1982) (LOAEL 4.9 mg/kg-day), was considered instead. In support, the 1,2-dichloroethane ATSDR (2022) authoritative document also concluded that "the immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice."

With regard to identification of a subchronic provisional reference concentration (p-RfC) in (U.S. EPA, 2010) for 1,-2-dichloroethane, the occupational (Kozik, 1957) study used identified in this assessment was rated "Uninformative" by systematic review based on a number of limitations (poor data and test method reporting, lack of description of the analytical methodology, limited quantitative data and statistical analyses, unstated criteria for diagnosis of disease, limited number of study participants and no matched control group, lack of control for potential confounding, lack of exposure duration information). Furthermore, (Kozik, 1957) did not report any data that could be used for BMD modeling. Additionally, PPRTV also commented on the confidence of the study as well as confidence in the calculated p-RfC as being very low. This study was also used for the chronic p-RfC irrespective of this low confidence with additional uncertainty factor of 10 for the duration adjustment.

Therefore, studies only studies that received a rating of high and medium by systematic review were considered for POD as outlined in Section 6.1 with study evaluation and selection rationale.

Table_Apx E-1. Non-cancer Human Health Hazard Values based on Exposure Duration and Route for 1,2-Dichloroethane

Exposure	Solvent	Oral	Inhalation	Dermal	Comments
Acute	1,2-Dichloroethane	POD $BMDL_{10}$ = 153 mg/kg based on increased kidney weight via gavage (Storer et al., 1984). UF = 30	POD BMC_{10} = 48.9 mg/m^3 or 12.1 ppm based on olfactory necrosis (Dow Chemical, 2006b). UF = 30	POD $BMDL_{10}$ = 153 mg/kg based on increased kidney weight ((Storer et al., 1984). UF = 30	
Subchronic	1,2-Dichloroethane	POD = $LOAEL_{adj}$ = 4.89 mg/kg based on immunosuppression in a 14-day gavage study (Munson et al., 1982). UF = 100	POD = $BMCL_5$ = 21.2 mg/m^3 based on decreases in sperm concentration (Zhang et al., 2017). UF = 30	POD = $LOAEL_{adj}$ = 4.89 mg/kg based on immunosuppression in a 14-day gavage study (Munson et al., 1982). UF = 100	(ATSDR, 2022) identified immunosuppression as the most sensitive endpoint – however, ATSDR characterized the Munson et al. (1982) study as an acute study and therefore it was excluded from derivation of MRLs for subchronic and chronic exposures.
Chronic	1,2-Dichloroethane	POD = $LOAEL_{adj}$ = 4.89 mg/kg based on immunosuppression in a 14-day gavage study (Munson et al., 1982). UF = 1,000 [a]	POD = $BMCL_5$ = 21.2 mg/m^3 based on decreases in sperm concentration (Zhang et al., 2017). UF = 300	POD = $LOAEL_{adj}$ = 4.89 mg/kg based on immunosuppression in a 14-day gavage study (Munson et al., 1982). UF = 1,000	A standard default of a UF_s of 10 was added for use of subchronic data for chronic duration. (ATSDR, 2022) identified immunosuppression as the most sensitive endpoint – however, ATSDR characterized the Munson et al. (1982) study as an acute study and therefore it was excluded from derivation of MRLs for subchronic and chronic exposures.
IRIS (U.S. EPA, 1990, 1987b)					
Acute	1,2-Dichloroethane	Not assessed under IRIS	Not assessed under IRIS	Not assessed under IRIS	
Subchronic	1,2-Dichloroethane	Not assessed under IRIS	Not assessed under IRIS	Not assessed under IRIS	
Chronic	1,2-Dichloroethane	Not assessed under IRIS	Not assessed under IRIS	Not assessed under IRIS	
PPRTV (U.S. EPA, 2010, 2006)					
Acute	1,2-Dichloroethane	Did not derive a provisional value	Did not derive a provisional value	Did not derive a provisional value	Database considered inadequate

Exposure	Solvent	Oral	Inhalation	Dermal	Comments
Subchronic	1,2-Dichloroethane	1,2-Dichloroethane animal data was used. Database is lacking human data by the oral route. RfD = 0.02 mg/kg-day based on increased kidney weights (NTP, 1991); (Morgan et al., 1990), 90-day drinking water (DW) UF = 3000 In context, the OPPT MRL is 0.049 mg/kg/day based on the Munson et al. (1982) immunotoxicity POD of 4.89 mg/kg/day and a total UF of 100.	1,2-Dichlorothane animal data was not used – human data was selected as the only feasible study for subchronic durations. RfC = 0.07 mg/m^3 based on neurobehavioral impairment (Kozik, 1957) UF = 300 In context, based on decreased sperm count in the Zhang et al. (2017) study with the UF of 30, the OPPT RfC = 0.71 mg/m^3.	Did not derive a provisional value	For the oral route: PPRTV used a UF_D of 3 to account for database inadequacies. OPPT/ECRAD did not use the (NTP, 1991)/(Morgan et al., 1990) DW study as it rated "Uninformative" in our SR due to a reported 59% decrease in dose at the end of each day, as well as noted dehydration due to decreased water consumption. Kidney effects could be due to dehydration and not direct result of chemical exposure. PPRTV made no mention of the limitations of the DW study. PPRTV makes no mention of the gavage portion of the (NTP, 1991)/ (Morgan et al., 1990). Note: OPPT/ECRAD [b] PPRTV commented [c] For the inhalation route: OPPT/ECRAD did not use the (Kozik, 1957) study because it rated as "Uninformative" in our SR based on a number of limitations (poor data and test method reporting, lack of description of the analytical methodology, limited quantitative data and statistical analyses, unstated criteria for diagnosis of disease, limited number of study participants and no matched control group, lack of control for potential confounding, lack of exposure duration information). (Kozik, 1957) did not report any data that could be used for BMD modeling. PPRTV commented [d]
Chronic	1,2-Dichloroethane	Did not derive a provisional value.	RfC = 0.007 mg/m^3 based on neurobehavioral impairment (Kozik, 1957) UF = 3,000	Did not derive a provisional value.	For the RfD: PPRTV commented [e]: For the RfC: Same study and conclusions as for the subchronic duration only added an additional

Exposure	Solvent	Oral	Inhalation	Dermal	Comments
			In context, based on decreased sperm count in the Zhang et al. (2017) study with the UF of 300, the OPPT RfC = 0.071 mg/m^3		UF of 10 for use of subchronic study for chronic duration to yield a total UF = 3,000.
ATSDR (ATSDR, 2022, 2015)					
Acute	1,2-Dichloroethane	Did not derive an MRL	0.3 ppm based on Degeneration, with necrosis, olfactory epithelium in rats (Dow Chemical, 2006b);(Hotchkiss et al., 2010) $BMCL_{10}$ = 57 ($BMCL_{HEC}$ = 9.2) UF = 30 In context, OPPT determined an MRL of 0.3 ppm	Did not derive an MRL	ATSDR did not use the Munson et al. (1982) gavage study because of a difference in classification of acute and subchronic between ATSDR and EPA. ATSDR classifies a 14-day study as "acute," and therefore it was not used by them for subchronic or chronic POD derivation.
Subchronic	1,2-Dichloroethane	0.2 mg/kg/day based on kidney weight in rats (NTP, 1991)/ (Morgan et al., 1990), 90-day drinking water (DW) LOAEL = 58 UF = 300 In context, the OPPT MRL is 0.049 mg/kg/day based on the Munson immunotoxicity POD of 4.89 mg/kg/day and a total UF of 100	Did not derive an MRL	Did not derive an MRL	OPPT/ECRAD did not use the drinking water portion of either the Munson et al. (1982) or (NTP, 1991)/(Morgan et al., 1990) studies for identification of a POD. The (NTP, 1991)/(Morgan et al., 1990) study identified kidney weight as a POD via DW (58 mg/kg). The DW portion of the study rated "Uninformative" in our SR. The rationale for that rating is based on up to a 59% loss of concentration at the end of each day, with a 60% decrease in water consumption which lead to dehydration and therefore the kidney effects could likely be artifacts of dehydration.
Chronic	1,2-Dichloroethane	Did not derive an MRL	Did not derive an MRL	Did not derive an MRL	According to ATSDR, data were insufficient to derive an acute-duration provisional oral MRL due to uncertainty about the validity of results at the lowest effect level based on differences in effect between gavage doses

Exposure	Solvent	Oral	Inhalation	Dermal	Comments
					and drinking water doses. Data were insufficient for the derivation of a chronic-duration provisional oral MRL as the most sensitive endpoint was represented by a serious effect (such as death). ATSDR concluded that the inhalation database was inadequate for derivation of intermediate- and chronic-duration inhalation MRLs.

[a] Per EPA RfC/RfD Guidance Document (U.S. EPA, 2002), UF's of up to 3,000 are acceptable. In the case of the RfC, the maximum UF would be 3,000, whereas the maximum would be 10,000 for the RfD.
[b] OPPT/ECRAD used the gavage portion of the Munson et al. (1982) study to derive an oral POD for subchronic duration, as opposed to the gavage portion of the (NTP, 1991)/ (Morgan et al., 1990) study, as it represented a more biologically relevant and sensitive POD. PPRTV briefly mentions the Munson et al. (1982) study.
[c] PPRTV commented confidence in the study (NTP, 1991)/ (Morgan et al., 1990) is medium (a UFD of 3 was used in their total UF calculation), and overall confidence in the calculation of the provisional RfD is medium.
[d] PPRTV commented confidence in the study (Kozik, 1957) is very low (and a UFD of 3 was used in their total UF calculation), and overall confidence in the calculation of the provisional RfC is low.
[e] PPRTV commented "In the absence of suitable chronic data, the POD from the subchronic (NTP, 1991) p-RfD could be used to derive the chronic p-RfD; however, the composite UF would include the additional UFs of 10 for applying data from a subchronic study to assess potential effects from chronic exposure. This would result in the large composite UF of greater than 3,000, thereby relegating this derivation of the chronic p-RfD to an appendix screening value."

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E.2 Summary of Cancer Assessments of EPA Offices and Other Agencies

Historically, offices across EPA and other agencies (OW, OLEM, CalEPA), have developed their own cancer assessments for 1,2-dichloroethane. The IRIS assessment of carcinogenic potential of 1,2-dichloroethane was considered to be 'supportive' of 1,2-dichloroethane carcinogenic potential. A comparison of the cancer slope factors across other program offices for 1,2-dichloroethane can be seen in Table_Apx E-2.

Table_Apx E-2. 1,2-Dichloroethane Cancer Slope Factors and Inhalation Unit Risk of EPA Offices and Other Agencies

EPA Program	Oral Slope Factor	Inhalation Unit Risk
OPPT RE Continuous Exposure	• 0.062 per mg/kg/day • Mouse (NTP, 1978) • Hepatocellular carcinoma data • **High OPPT SR rating**	• 7.1E−06 per µg/m^3 • Rat inhalation (Nagano et al., 2006) • Combined tumors in females • **High OPPT SR rating**
IRIS 1987 Assessment U.S. EPA (1987a)	• 0.091 per mg/kg/day • Rat hemangiosarcoma data (using a time to death analysis) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**	• 2.6E−5 per µg/m^3 • Rat oral hemangiosarcoma data (using a time to death analysis) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**
OW	• 0.091 per mg/kg/day **based on (**U.S. EPA, 1987a**)** • Rat hemangiosarcoma data (using a time to death analysis) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**	• Not reported
OAR	• Not reported	• 2.6E−5 per µg/m^3 **based on (**U.S. EPA, 1987a**)** • Rat oral hemangiosarcoma data (using a time to death analysis) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**
OLEM	• 0.091 per mg/kg/day **based on (**U.S. EPA, 1987a**)** • Rat oral hemangiosarcoma data (using a time to death analysis) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**	• 2.6E−5 per µg/m^3 **based on (**U.S. EPA, 1987a**)** • Rat oral hemangiosarcoma data (using a time to death analysis) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**
Cal EPA	• 0.072 per mg/kg/day • Rat oral hemangiosarcoma data (using a Weibull model) (NTP, 1978) • **Rat study rated Uninformative OPPT SR**	• 2.1E−05 per µg/m^3 • Derived from oral rat data • **Rat study rated Uninformative OPPT SR**

Appendix F BENCHMARK DOSE ANALYSIS

As described in the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling* (U.S. EPA, 2024a), all studies that were identified and considered as candidate non-cancer PODs are indicated for each exposure duration and route. Those specific to 1,2-dichloroethane can be found in Section 2.1 of U.S. EPA (2024a). Appendix F provides a summary of those studies that were identified as the non-cancer PODs for 1,2-dichloroethane and used for HED/HEC calculations. Section 2.2 in U.S. EPA (2024a) provides all studies that were identified and considered for cancer dose-response.

F.1 Non-cancer PODs for Acute Exposures for 1,2-Dichloroethane

Oral

The acute-duration oral POD for 1,2-dichloroethane was based on increased relative kidney weight in male mice given a single gavage dose of 1,2-dichloroethane (Storer et al., 1984). For this study, a NOAEL of 200 mg/kg-bw/day and a LOAEL of 300 mg/kg-bw/day were identified for kidney weight effects. To obtain a POD, BMD modeling was conducted on the relative kidney weight data using U.S. EPA's Benchmark Dose Software (BMDS; v. 3.3). Table_Apx F-1 shows the relative kidney weights corresponding to each dose. BMD modeling was conducted using a benchmark response (BMR) of 10 percent relative deviation from the control mean (U.S. EPA, 2012b).

Table_Apx F-1. Relative Kidney Weights in Male Mice Exposed to 1,2-Dichloroethane Once by Gavage

Dose (mg/kg-day)	Number of Mice	Mean (g/100 g body weight)	Standard Deviation
0	5	1.50	0.09
200	5	1.58	0.19
300	5	1.69	0.09
400	3	1.75	0.08
500	1[a]	1.82	N/A
600	1[a]	1.61	N/A

Source: Storer et al. (1984)
[a] 4/5 mice died in this group.

Following (U.S. EPA, 2012b) guidance, the polynomial 2-degree model with constant variance was selected for these data. The $BMD_{10\%}$ and $BMDL_{10}$ values for this model were 270 and 153 mg/kg-bw/day, respectively. The $BMDL_{10}$ of 153 mg/kg-bw/day was selected as the POD.

The $BMDL_{10}$ of 153 mg/kg-bw/day was converted to a HED of 19.9 mg/kg-bw/day using the DAF of 0.13 for mice (see Appendix A.1.3) and Equation_Apx F-1, as shown below:

Equation_Apx F-1.

$$HED = 153\ mg/kg \times 0.13 = 19.9\ mg/kg$$

The HED of 19.9 mg/kg-bw/day does not need to be adjusted for occupational exposure. The benchmark MOE for this POD is 30 (3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability).

Inhalation

The acute-duration inhalation POD for 1,2-dichloroethane was based on nasal lesions in rats exposed once by inhalation for 8 hours (Dow Chemical, 2006b). For this study, a NOAEL of 71.3 mg/m^3 and LOAEL of 145 mg/m^3 were identified for increased incidences of degeneration with necrosis in the olfactory mucosa of the nasal passages in male and female rats. To obtain a POD, BMD modeling was conducted using EPA's BMDS (v. 3.3.2) on the incidence of these nasal lesions in male and female rats (combined). The male and female data were combined for modeling because incidences were similar in both sexes and the combined data set provided increased statistical power relative to the sex-specific data sets. Prior to modeling, the exposure concentrations in the (Dow Chemical, 2006b) rat 8-hour study were adjusted from the exposure scenario of the original study to continuous (24 hours/day) exposure using Equation_Apx A-4. Table_Apx F-2 shows the nasal lesion incidences corresponding to each exposure concentration. BMD modeling was conducted on the incidences using the continuous equivalent concentrations and the default BMR for quantal data of 10 percent extra risk (U.S. EPA, 2012b).

Table_Apx F-2. Incidence of Nasal Lesions in Male and Female Rats (Combined) Exposed to 1,2-Dichloroethane for 8 Hours

Unadjusted Exposure Concentration (mg/m^3)	Adjusted (Continuous) Exposure Concentration (mg/m^3)	Incidence of Degeneration with Necrosis of the Olfactory Mucosa
0	0	0/10
214	71.3	0/10
435.1	145.0	4/10
630.6	210.2	9/10
Source: Dow Chemical (2006b)		

Following U.S. EPA (2012b) guidance, the multistage 3-degree model was selected for these data. The BMC_{10} and $BMCL_{10}$ for this model were 81.4 and 48.9 mg/m^3, respectively. The $BMCL_{10}$ of 48.9 mg/m^3 was selected as the POD.

U.S. EPA (1994) guidance was used to convert the $BMCL_{10}$ of 48.9 mg/m^3 to a HEC. For nasal lesions, the $RGDR_{ET}$ in rats is used. The $RGDR_{ET}$ of 0.2 was calculated using Equation_Apx A-8 (U.S. EPA, 1994).

The $BMCL_{10}$ (48.9 mg/m^3) was multiplied by the $RGDR_{ET}$ (0.2) to calculate the HEC, as shown in the Equation_Apx A-9.

The resulting HEC is 9.78 mg/m^3 for continuous exposure. The continuous HEC of 9.78 mg/m^3 is converted to an equivalent worker HEC using Equation_Apx A-12. The resulting POD for workers is 41.1 mg/m^3. The benchmark MOE for this POD is 30 (3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability).

EPA presents all inhalation PODs in equivalents of both mg/m^3 and ppm to avoid confusion and errors. Equation_Apx A-2 was used with the molecular weight of 1,2-dichloroethane (98.96 mg/mmol) to convert the continuous and worker PODs (9.78 and 41.1 mg/m^3, respectively) to 2.42 and 10.2 ppm, respectively.

Dermal

No PODs were identified from acute studies of dermal exposure to 1,2-dichloroethane. Therefore, the acute oral HED of 19.9 mg/kg-bw/day with benchmark MOE of 30 was used for risk assessment of acute dermal exposure for both continuous and worker exposure scenarios. As noted in Section M.3.1.4, when extrapolating from oral data that incorporated $BW^{3/4}$ scaling to obtain the oral HED, EPA uses the same HED for the dermal route of exposure. The same uncertainty factors are used in the benchmark MOE for both oral and dermal scenarios.

F.2 Non-cancer PODs for Short/Intermediate-Term Exposures for 1,2-Dichloroethane

Oral

The short-term/subchronic-duration oral POD for 1,2-dichloroethane was based on decreased immune response in mice exposed to 1,2-dichloroethane by gavage for 14 days (Munson et al., 1982). In this study, a dose-related significant decrease in the number of antibody-forming cells per spleen (AFC/spleen) was observed at all doses; the LOAEL was 4.89 mg/kg-bw/day. Using EPA's BMDS (v. 3.3), BMD modeling was conducted on the AFC/spleen data. The mice in the study by Munson et al. (1982) were exposed 7 days/week, so no adjustment for continuous exposure was needed. Table_Apx F-3 shows the AFC/spleen corresponding to each dose.

Table_Apx F-3. Antibody-forming Cells per Spleen in Male Mice Exposed to 1,2-Dichloroethane by Daily Gavage for 14 Days

Dose (mg/kg-bw/day)	Number of Mice	Mean Number AFC/Spleen ($\times 10^5$)	Standard Error
0	12	3.00	0.3
4.89	10	2.20	0.2
48.9	10	1.80	0.1
Source: Munson et al. (1982)			

None of the models provided adequate fits to the means either assuming constant or non-constant variance. Therefore, the LOAEL (lowest dose tested) was used as the POD.

The LOAEL of 4.89 mg/kg-bw/day was converted to a HED of 0.636 mg/kg-bw/day using the DAF of 0.13 for mice (see Section A.1.3) and Equation_Apx A-5.

The continuous HED of 0.636 mg/kg-bw/day was converted to a worker HED of 0.890 mg/kg-bw/day using Equation_Apx A-11. The benchmark MOE for this POD is 100 based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, and 3 for use of a LOAEL to extrapolate a NOAEL (based on the dose-response) for short-term and subchronic exposures.

Inhalation

The short-term/subchronic-duration inhalation POD for 1,2-dichloroethane was based on decreased sperm concentration in mice exposed to 1,2-dichloroethane by inhalation for 4 weeks (Zhang et al., 2017). In this study, a concentration-related decrease in sperm concentration was observed, reaching statistical significance (relative to controls) at 707.01 mg/m^3. Using EPA's BMDS (v. 3.3.2), BMD modeling was conducted on the sperm concentrations using mouse exposure concentrations. The mice in the study by Zhang et al. (2017) were exposed for 6 hours/day, 7 days/week. Prior to BMD modeling, the exposure concentrations in the Zhang et al. (2017) study were adjusted from the exposure scenario of

the original study to equivalent continuous (24 hours/day) exposure concentrations using Equation_Apx A-4. Table_Apx F-4 shows the sperm concentrations corresponding to each exposure concentration. BMD modeling was conducted on these data using a BMR of 5 percent relative deviation from controls.

Table_Apx F-4. Sperm Concentration in Male Mice Exposed to 1,2-Dichloroethane for 4 Weeks

Unadjusted Exposure Concentration (mg/m^3)	Adjusted (Continuous) Exposure Concentration (mg/m^3)	Number of Animals	Mean Sperm Concentration (M/g)	SD (M/g)
0.30	0.075	10	4.65	0.52
102.70	25.675	10	4.36	0.40
356.04	89.010	10	3.89	0.47
707.01	176.75	10	3.30	0.57
Source: Zhang et al. (2017)				

Following U.S. EPA (2012b) guidance, the exponential 3 model with constant variance was selected for these data. The BMC_5 and $BMCL_5$ for this model were 26.735 and 21.240 mg/m^3, respectively. The $BMCL_5$ of 21.240 mg/m^3 was selected as the POD.

U.S. EPA (1994) guidance was used to convert animal inhalation PODs to HECs. For systemic (extrarespiratory) effects, the HEC is calculated by multiplying the animal POD by the ratio of the blood/gas partition coefficients in animals and humans, as shown in Equation_Apx A-7.

A human blood/air partition coefficient of 19.5 ± 0.7 has been reported for 1,2-dichloroethane (Gargas et al., 1989). No blood/air partition coefficient for mice was identified in the literature reviewed. In the absence of a blood/air partition coefficient for mice, the default ratio of 1 is used in the calculation, in accordance with U.S. EPA (1994) guidance. Therefore, the POD of 21.240 mg/m^3 is multiplied by 1 to give the HEC.

The resulting POD is 21.240 mg/m^3 for continuous exposure. The continuous POD of 21.240 mg/m^3 is converted to an equivalent worker POD using Equation_Apx A-13. The resulting POD for workers is 89.208 mg/m^3. The benchmark MOE for this POD is 30 based on a combination of uncertainty factors: 3 for interspecies extrapolation when a dosimetric adjustment is used and 10 for human variability for short-term and subchronic exposures.

Dermal

No PODs were identified from short-term or subchronic studies of dermal exposure to 1,2-dichloroethane. Therefore, the short-term/subchronic oral HED of 0.636 mg/kg-bw/day and worker HED of 0.890 mg/kg-bw/day with benchmark MOE of 100 were used for risk assessment of short/intermediate-term dermal exposure. As noted in Appendix M.3.1.4, when extrapolating from oral data that incorporated $BW^{3/4}$ scaling to obtain the oral HED, EPA uses the same HED for the dermal route of exposure. The same uncertainty factors are used in the benchmark MOE for both oral and dermal scenarios.

F.3 Non-cancer PODs for Chronic Exposures for 1,2-Dichloroethane

Oral

No studies of chronic oral exposure in laboratory animals were considered suitable for POD determination (see Table 6-7). Therefore, the short-term/subchronic POD was also used for chronic exposure. The short-term/subchronic continuous HED was 0.636 mg/kg-bw/day and the worker HED

was 0.890 mg/kg-bw/day (see Appendix F.2). The benchmark MOE for this POD is 1,000 based on 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, 3 for the use of a LOAEL to extrapolate a NOAEL (based on the dose-response), and 10 for extrapolating from a subchronic study duration to a chronic study duration for chronic exposures.

Inhalation

Only one study of chronic inhalation exposure in laboratory animals (IRFMN, 1978) was considered suitable for POD determination (see Table 6-10). However, the 12-month study by IRFMN (1978) evaluated limited endpoints (serum chemistry changes only) and identified a higher LOAEL than the study of sperm parameters by Zhang et al. (2017) that was used as the basis for the short-term/subchronic POD. Therefore, the POD from Zhang et al. (2017) was also used for chronic exposure. The resulting POD is 21.240 mg/m^3 for continuous exposure. The continuous POD of 21.240 mg/m^3 is converted to an equivalent worker POD using Equation_Apx A-12. Equation_Apx A-2 was used with the molecular weight of 1,2-dichloroethane (98.96 mg/mmol) to convert the continuous and worker short-term/subchronic/chronic PODs (21.240 and 89.208 mg/m^3, respectively) to 5.2478 and 22.041 ppm, respectively. The resulting POD for workers is 89.208 mg/m^3 (see Table_Apx A-1). The benchmark MOE for this POD is 300 based on 3 for interspecies extrapolation when a dosimetric adjustment is used, 10 for human variability, and 10 for extrapolation from a 4-week study to chronic exposure duration for chronic exposures.

Dermal

No PODs were identified from chronic-duration studies of dermal exposure to 1,2-dichloroethane. Therefore, the oral HEDs of 0.636 mg/kg-bw/day (continuous) and 0.890 mg/kg-bw/day (for workers) with benchmark MOE of 1,000 were used for risk assessment of chronic-duration dermal exposure. As noted in Section A.1.3, when extrapolating from oral data that incorporated BW$^{3/4}$ scaling to obtain the oral HED, EPA uses the same HED for the dermal route of exposure. The same uncertainty factors are used in the benchmark MOE for both oral and dermal scenarios.