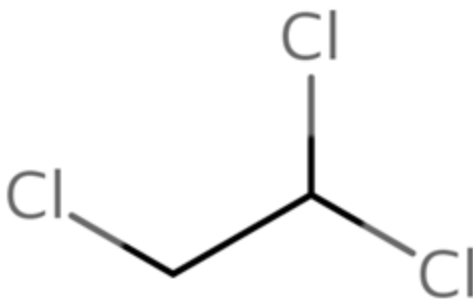




Draft Human Health and Environmental Hazard Assessment for 1,1,2-Trichloroethane

Technical Support Document for the Draft Risk Evaluation

CASRN 79-00-5



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358 **KEY ABBREVIATIONS AND ACRONYMS**

359	ADME	Absorption, distribution, metabolism, and excretion
360	AF	Assessment factor
361	AFC	Antibody forming cell(s)
362	ALT	Alanine aminotransferase
363	AST	Aspartate aminotransferase
364	ATSDR	Agency for Toxic Substances and Disease Registry
365	BMD	Benchmark dose
366	BMDL	Benchmark dose lower confidence limit
367	CASRN	Chemical Abstracts Service Registry Number
368	ChV	Chronic value
369	COC	Concentration(s) of concern
370	CSF	Cancer slope factor
371	DAF	Dosimetric adjustment factors
372	EPA	Environmental Protection Agency (U.S.)
373	FOB	Functional observational battery
374	HEC	Human equivalent concentration
375	HED	Human equivalent dose
376	IRIS	Integrated Risk Information System
377	IUR	Inhalation unit risk
378	LO[A]EC	Lowest-observed-[adverse]-effect concentration
379	LO[A]EL	Lowest-observed-[adverse]-effect level
380	MOA	Mode of action
381	NO[A]EC	No-observed-[adverse]-effect concentration
382	NO[A]EL	No-observed-[adverse]-effect level
383	OCSP	Office of Chemical Safety and Pollution Prevention (EPA)
384	OECD	Organisation for Economic Co-operation and Development
385	OPPT	Office of Pollution Prevention and Toxics (EPA)
386	PBPK	Physiologically based pharmacokinetic
387	PESS	Potentially exposed or susceptible subpopulations
388	POD	Point of departure
389	PPRT	Provisional Peer-Reviewed Toxicity Values (PPRTV) Report (EPA)
390	OCSP	Office of Chemical Safety and Pollution Prevention (EPA)
391	OPPT	Office of Pollution Prevention and Toxics (EPA)
392	PBPK	Physiologically-based pharmacokinetic
393	RMSLE	Root mean squared logarithmic error
394	SSD	Species sensitivity distribution
395	TDAR	T-cell dependent antigen response
396	TSCA	Toxic Substances Control Act
397	TWA	Time-weighted average
398	U.S.	United States
399		

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Docket

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SUMMARY

This technical summary document (TSD) is part of the Toxic Substances Control Act (TSCA) *Draft Risk Evaluation for 1,1,2-Trichloroethane* ([U.S. EPA, 2026f](#)) (CASRN 79-00-5).

Human Health Hazard

EPA considered all information that was reasonably available for 1,1,2-trichloroethane identified through the OPPT systematic review process under the Toxic Substances Control Act (TSCA) to characterize human health hazard endpoints and points of departure (PODs). The 1,1,2-trichloroethane human health toxicology database includes medium- and high-quality literature studies and standard guideline studies for risk evaluation up to April 2025, and the best available science was utilized for endpoint and POD derivation. Although EPA conducted an independent analysis of the toxicology database, there is consistency in the endpoints and PODs selected with the 2021 Agency for Toxic Substances and Disease Registry (ATSDR) evaluation ([ATSDR, 2021](#)), U.S. EPA Integrated Risk Information System (IRIS) ([U.S. EPA, 1987](#)), and the 2011 U.S. EPA Provisional Peer-Reviewed Toxicity Values (PPRTV) report ([U.S. EPA, 2011a](#)): Table 2-3 provides a cross-reference comparison of these resources in Section 2.3.

Overall, there is confidence that the endpoint and POD selections are human health protective for all hazards identified from the best science available. The endpoints identified for 1,1,2-trichloroethane were neurotoxicity, respiratory tract pathology, immunotoxicity, liver pathology, irritation, genotoxicity, tumors, male reproductive toxicity, body weight changes, and mortality. 1,1,2-Trichloroethane is used as a solvent and a reactive intermediate for synthesis of other chemicals. The metabolism of 1,1,2-trichloroethane produces reactive metabolites such as a free radical, a chlorinated aldehyde, an acyl chloride, and hydrochloric acid. Upon evaluating the reasonably available information for the oral, dermal, and inhalation scenarios, human hazard endpoints and PODs were derived for acute, intermediate, and chronic exposure durations to the general population (Table S-1 and Table S-2). Oral, dermal, and inhalation cancer slope values were also derived (Table S-3 and Table S-4). The confidence conclusion is the weight of scientific evidence based on the study quality and the best available science. The acute duration is 0 to 24 hours, the intermediate duration is 24 hours to 90 days, and chronic duration is over 90 days.

459 **Table S-1. Oral and Dermal Scenario Endpoints and PODs for 1,1,2-Trichloroethane**

Duration	Effect	Study POD	NOAEL HED	Uncertainty Factors	Reference, Species, Duration, Route, Data Evaluation Rating	POD Confidence Conclusion
Acute	Neurotoxicity, decreased acute motor activity in rats	LOAEL = 95 mg/kg NOAEL = 55 mg/kg	NOAEL HED = 12.6 mg/kg	UF _A = 3 UF _H = 10 Total = 30	(WIL Research, 2004) Sprague-Dawley Rats Oral, Acute Neurotoxicity Guideline Study OECD 424 High	Oral – Robust
				Dermal – Moderate-to-Robust		
Intermediate	Immunotoxicity, decreased hemagglutination titers in mice, 90 days	LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10 Total = 30	(Sanders et al., 1985) CD-1 Mice Oral High	Oral – Robust
				Dermal – Moderate-to-Robust		
Chronic	Immunotoxicity, decreased hemagglutination titers in mice, 90 days	LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10 UF _S = 10 Total = 300	(Sanders et al., 1985) CD-1 Mice Oral High	Oral – Moderate-to-Robust
				Dermal – Moderate		
HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; UF _S = subchronic-to-chronic uncertainty factor						

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Table S-2. Inhalation Scenarios Endpoints and PODs for 1,1,2-Trichloroethane

Duration	Hazard Effect	Study POD	Continuous POD	Uncertainty Factors	Reference, Species, Duration, Route, Systematic Review Rating	POD Confidence Conclusion
Acute	Olfactory epithelium necrosis, 4 hours whole body	LOAEC = 316 mg/m ³ (58 ppm) in 4 hours	LOAECadj = 52.7 mg/m ³ (9.7 ppm) LOAECadj HEC = 6.1 mg/m ³ (1.1 ppm)	UF _A = 3 UF _H = 10 UF _L = 3 Total = 100	(WIL Research, 2001) F-344 Rats Inhalation, Guideline Study TSCA 799.9135, High	Robust
Intermediate	Lesions in the olfactory epithelium, 13 weeks, 6 hours/day, 5 days/week	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm) BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm) BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm)	UF _A = 3 UF _H = 10 Total = 30	(WIL Research, 2002) F-344 Rats Whole body Inhalation, Guideline Study TSCA 799.9346, High	Robust

Duration	Hazard Effect	Study POD	Continuous POD	Uncertainty Factors	Reference, Species, Duration, Route, Systematic Review Rating	POD Confidence Conclusion
Chronic	Lesions in the olfactory epithelium, 13 weeks, 6 hours/day, 5 days/week	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm) BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm) BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm)	UF _A = 3 UF _H = 10 UF _S = 10 Total = 300	(WIL Research, 2002) F-344 Rats Whole body Inhalation, Guideline Study TSCA 799.9346, High	Moderate-to-Robust
BMC = benchmark concentration; BMCL = benchmark concentration lower bound; ppm = parts per million; HEC = human equivalent concentration; LOAEC = lowest observed adverse effect concentration; POD = point of departure; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; UF _S = subchronic-to-chronic uncertainty factor;						

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Table S-3. Oral and Dermal Cancer Slope Factors for 1,1,2-Trichloroethane

Mouse Tumor	BMD	BMDL	Oral and Dermal Slope Factor	Confidence Conclusion
Male liver, HED input	3.72 mg/kg/day	2.87 mg/kg/day	0.0348 per mg/kg/day	Oral – Moderate
				Dermal – Low-to-Moderate
BMD = benchmark dose; BMDL = benchmark dose lower bound; HED = human equivalent dose (NCL, 1978), Medium systematic review rating				

Table S-4. Inhalation Unit Risk Values for 1,1,2-Trichloroethane

Mouse Tumor	BMC	BMCL	IUR	Confidence Conclusion
Male liver, PBPK HEC input in mg/m ³ from oral data	2 73.30 mg/m ³	33.54 mg/m ³	2.98×10 ⁻⁶ per ug/m ³	Moderate
Male liver, PBPK HEC input in ppm from oral data	0 13.48 ppm	6.14 ppm	0.0163 per ppm	
BMC = benchmark concentration; BMCL = benchmark concentration lower bound; IUR = inhalation unit risk; PBPK = physiologically-based pharmacokinetic modeling (NCL, 1978), Medium systematic review rating				

Environmental Hazard

EPA considered all reasonably available information identified through the systematic review process under TSCA to characterize environmental hazard endpoints for 1,1,2-trichloroethane. EPA also incorporated hazard data received from a TSCA section 4(a)(2) test order for sediment-dwelling (benthic) animals. Upon evaluating the reasonably available information, environmental hazard thresholds were derived for acute exposures to aquatic species and chronic exposures to aquatic vertebrates, aquatic invertebrates, and sediment-dwelling invertebrates and algae (Table S-5). Hazard thresholds were also derived for inhalation hazard to terrestrial vertebrates using human health hazard rodent models and for terrestrial invertebrates and plants. EPA's rationale for selecting these hazard thresholds, as well as the level of confidence based on the weight of scientific evidence, are described in Section 3.

Overall, the Agency has robust confidence in hazard thresholds for acute exposures to aquatic vertebrates and invertebrates and chronic exposures to aquatic invertebrates based on the quality of the database, consistency, strength and precision, dose-response, and relevance of the available data for each ecological receptor group. EPA has moderate confidence in chronic exposures to aquatic vertebrates, terrestrial invertebrates, and terrestrial plants. EPA has slight-to-moderate confidence that the COCs for sediment-dwelling invertebrates represent relevant exposure concentration duration and magnitude based on one dose-response study that reports rapid decreases in 1,1,2-trichloroethane concentrations in sediment, pore water, and the water column. EPA also has slight-to-moderate confidence that the inhalation hazard threshold of terrestrial mammals represents relevant wildlife exposure concentrations because it is based on one available study.

492 **Table S-5. Environmental Hazard Thresholds for 1,1,2-Trichloroethane**

Receptor Group	Exposure Duration	Hazard Threshold (COC or HV)	Assessment Medium	Confidence in COC or HV	Citation (Study Quality)
Aquatic vertebrates and invertebrates	Acute	25.3 mg/L	Water column	Robust (Section 3.2.1.2)	From SSD; see Section 3.2.1
Aquatic vertebrates	Chronic (32-days)	2.67 mg/L	Water column	Moderate (Section 3.2.2.2)	(Ahmad et al., 1984) (High)
Aquatic invertebrates	Chronic (28-days)	3.3 mg/L	Water column	Robust (Section 3.2.3.2)	(Richter et al., 1983) (High)
Sediment-dwelling invertebrate sediment exposure	56-days with multiple acute exposures	2.89 mg/kg	Sediment	Slight-to-Moderate (Section 3.2.4.2)	(Smithers, 2023) (High)
Sediment-dwelling invertebrate sediment pore water exposure	56-days with multiple acute exposures	93 mg/L	Sediment pore water	Slight-to-Moderate (Section 3.2.4.2)	(Smithers, 2023) (High)
Algae	72-hour	26.3 mg/L	Water column	Moderate (Section 3.2.5.2)	(Brack and Rottler, 1994) (High)
Terrestrial mammals	4-hour acute inhalation converted to chronic inhalation exposure	2,126 mg/m ³	Air inhalation	Slight-to-Moderate (Section 3.3.1.1.2)	(WIL Research, 2001) (High)
Terrestrial invertebrates	Chronic	42 ug/cm ² (1.05 mg/kg)	Soil	Moderate (Section 3.3.2.2)	(Neuhauser et al., 1985) (High)
Terrestrial plants	Chronic	306.9 mg/L	Soil	Moderate (Section 3.3.3.2)	(Dietz and Schnoor, 2001) (Medium)
COC = concentration of concern; HV = hazard value; SSD = species sensitivity distribution					

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1 INTRODUCTION

1,1,2-Trichloroethane (CASRN 79-00-5) is a colorless liquid that is generally nonflammable, can be dissolved in water, and evaporates easily. It is used as a solvent and as a reactive intermediate in the production of other chemicals.

This draft TSD presents the draft human health and environmental hazard assessment in support of the TSCA *Draft Risk Evaluation for 1,1,2-Trichloroethane* (also referred to as the “draft risk evaluation”) ([U.S. EPA, 2026f](#)) that was conducted under the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which amended TSCA on June 22, 2016. The new law and implementing regulations include statutory requirements for actions related to conducting risk evaluations of existing chemicals.

2 HUMAN HEALTH HAZARD ASSESSMENT

2.1 Approach and Methodology

EPA conducted an independent systematic review of the literature up to 2025 to identify hazards and PODs for 1,1,2-trichloroethane. Existing assessments were also considered, such as the 2021 ATSDR assessment ([ATSDR, 2021](#)), U.S. EPA IRIS ([U.S. EPA, 1987](#)), and the 2011 U.S. EPA PPRTV report ([U.S. EPA, 2011a](#)). EPA considered studies of various data quality (*e.g.*, considered high and medium quality data) for dose-response POD selection, but discussed lower quality or uninformative studies for dose-response as needed to support weight of the scientific evidence and qualitative hazard narratives. An overview of hazard identification and evidence integration steps are summarized in Figure 2-1 with references to specific documents presented in Section 2.1.1. For 1,1,2-trichloroethane, medium- and high-quality animal data were used for POD selection. No epidemiology studies were suitable for dose-response. For the dermal route, data were extrapolated from the oral route utilizing the dermal absorption data from the OECD 428 dermal absorption data utilizing human skin ([Labcorp Early Development, 2023](#)). Benchmark dose (BMD) analysis was conducted as feasible. For the inhalation unit risk cancer calculation, a peer-reviewed physiologically-based pharmacokinetic (PBPK) model from the Sapphire Group ([2002](#)) was utilized for the oral to inhalation route extrapolation refinement using data from a medium quality oral exposure cancer study.

EPA utilized systematic review processes to search, screen, evaluate, extract, and integrate reasonably available information to make conclusions about relevant adverse health effects from 1,1,2-trichloroethane exposure. Following evidence integration, EPA performed dose-response analysis to derive hazard values for use in risk characterization. The Agency then evaluated the weight of scientific evidence for each aspect of the assessment and determined overall confidence ratings for each critical hazard outcome utilizing the best available science. The generalized process for conducting human health hazard assessments under TSCA is presented in Figure 2-1.

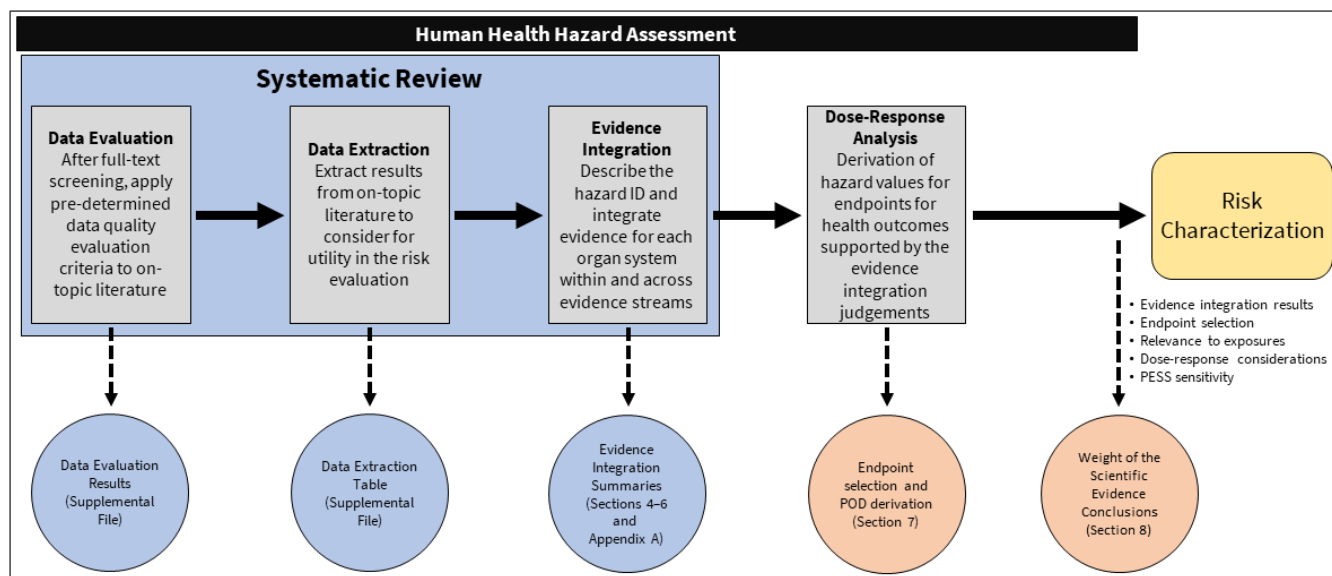


Figure 2-1. EPA Approach to Hazard Identification, Evidence Integration, and Dose-Response Analysis for 1,1,2-Trichloroethane

2.1.1 Systematic Review

The searching and screening steps of the systematic review process for 1,1,2-trichloroethane generally followed the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Version 1.0: A Generic TSCA Systematic Review Protocol with Chemical-Specific Methodologies* (also called the “[2021] Draft Systematic Review Protocol”) ([U.S. EPA, 2021a](#)) covering all reasonably available literature published through up to April 2025. Full details and screening results for all the identified studies are described in the *Draft Systematic Review Protocol for 1,1,2-Trichloroethane* ([U.S. EPA, 2026g](#)). The data quality results are listed in the *Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for 1,1,2-Trichloroethane* ([U.S. EPA, 2026d](#)), *Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for 1,1,2-Trichloroethane* ([U.S. EPA, 2026c](#)), and the *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for 1,1,2-Trichloroethane* ([U.S. EPA, 2026b](#)) documents.

2.1.2 Enforceable Consent Agreement for 1,1,2-Trichloroethane

Under section 4 of TSCA, in 2000, EPA issued a testing consent order (Order) that incorporates an Enforceable Consent Agreement (ECA) (Federal Register 65 FR 37550) ([U.S. EPA, 2000](#)). The objective of the ECA was to develop toxicity testing and PBPK and mechanistic testing that is intended to satisfy the toxicological data needs identified in the consent order for acute toxicity, subchronic toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, carcinogenicity, *in vivo* cytogenetics, and immunotoxicity effects of 1,1,2-trichloroethane.

2.1.3 Problem Formulation and Focus of Analysis

The human health assessment for 1,1,2-trichloroethane focused on the oral, dermal, and inhalation exposures to the general population for acute, intermediate, and chronic durations. The systematic review covered studies up to April 2025 from the literature and OPPT Test Order data, as well as assessments from ATSDR, U.S. EPA IRIS, and U.S. EPA PPRTV. There is consistency in this evaluation with ATSDR, PPRTV reports, and IRIS ([U.S. EPA, 1987](#)) (see also Table 2-3).

2.2 Toxicokinetics and Physiologically-Based Pharmacokinetic (PBPK) Models

In vivo and *in vitro* ADME (absorption, distribution, metabolism, and excretion) studies are available in the rat, guinea pig, and mouse species via the oral, dermal, and inhalation routes. A guideline *in vitro* OECD 428 dermal absorption study ([Labcorp Early Development, 2023](#)) utilizing human skin provided dermal absorption data to utilize oral data for extrapolation to assess the dermal route. A PBPK model was initially developed by ([Sapphire Group, 2002](#)) under the Final Enforceable Consent Agreement for 1,1,2-Trichloroethane and Accompanying Testing Consent Order, signed by EPA on June 7, 2000. EPA revalidated and reconstructed the Sapphire Group PBPK Model ([2002](#)) from its original obsolete ACSLx software into the R/MCSim software environment, and utilized it for oral-to-inhalation route extrapolation, for non-cancer hazards, and made possible the inhalation unit risk cancer evaluation for 1,1,2-trichloroethane.

2.2.1 Absorption

Oral

1,1,2-Trichloroethane is lipophilic and fat-soluble, indicating that it can be readily absorbed ([Reed et al., 1988](#)). Oral administration studies demonstrate uptake in the gastrointestinal tract from this route of exposure. Rats orally exposed to 70 mg/kg and mice orally exposed to 300 mg/kg absorbed more than half of the oral dose ([Mitoma et al., 1985b](#)). In another study, oral exposures were either corn oil gavage or in drinking water, which was consumed periodically. Rats were administered oral doses of 92 mg/kg/d in corn oil gavage or 1.7 mg/kg/d in their drinking water for 5 days, and mice were administered 390 mg/kg/d in corn oil gavage or 10 mg/kg/d in their drinking water for 5 days. Peak blood concentrations in rats were observed on day 1 (up to 17 µg/g) and between days 3 and 5 for mice (8.5–25 µg/g) ([Sapphire Group, 2002](#); [Battelle, 2001](#)). For the exposure in periodic drinking water, the absorption rate for mice was almost double that than the absorption rate for rats; however, rats were shown to absorb 1,1,2-trichloroethane faster than mice when exposed via corn oil gavage ([Sapphire Group, 2002](#)). Metabolism studies ([Mitoma et al., 1985b](#)) also suggest uptake from oral exposure. Over 80% of the dose was shown to be metabolized at the near-maximal tolerated oral doses (300 mg/kg in mice and 70 mg/kg in rats).

Inhalation

Human studies suggest that 1,1,2-trichloroethane is rapidly absorbed following inhalation. In one experiment, 2 to 3% of the dose was exhaled within 12 seconds after the subject inhaled a single breath of radiolabeled 1,1,2-trichloroethane ([Morgan et al., 1972, 1970](#)) as cited in ([ATSDR, 2021](#)).

Human data also show that 1,1,2-trichloroethane is absorbed after inhalation with more than 90% of dose retained in the body within 50 minutes ([Morgan et al., 1972, 1970](#)). This high degree of absorption is consistent with the calculated human blood-to-air partition coefficient (describing how readily a chemical dissolves in blood and in air at equilibrium) of 44.2 and serum-to-air partition coefficient of 37.1. These values indicate that 1,1,2-trichloroethane is highly blood soluble, dissolving into blood at approximately 40 times the concentration found in air. ([Gargas et al., 1989](#)) reports a similar value of 35.7. Because it partitions relatively preferentially into the blood, uptake is efficient, as the blood acts as a reservoir.

Animal studies support these findings. Rats and mice exposed to 100 ppm 1,1,2-trichloroethane for 6 hours/day, 5 days/week over 4 weeks retained concentrations in blood ([Sapphire Group, 2002](#)). Reported blood-to-air partition coefficients include 58.0 in rats ([Gargas et al., 1989](#)). In one study, maximum

blood concentrations after 4 weeks were 2.2 µg/mL in rats and 2.1 µg/mL in mice, though data are limited by small sample sizes and restricted time points ([Battelle, 2001](#)).

Dermal

Dermal studies show that 1,1,2-trichloroethane can also penetrate the skin. In guinea pigs, a single 1.0 mL topical application (1.43 g) produced peak blood concentration of approximately 3.7 µg/mL within 30 minutes. Levels then decreased to approximately 2.5 µg/mL at 1 hour, followed by a plateau period, and then rose to 3.7 µg/mL by 6 hours ([Jakobson et al., 1977](#)). This complex absorption profile may reflect an initial barrier effect due to delayed penetration or retention within skin lipids. In mice, 15 minutes after dermal exposure to 0.5 mL, 99.7% of the dose remained in the body and 0.3% was exhaled, resulting in a calculated absorption rate of 130 nmoles/min/cm² ([Tsuruta, 1975](#)). Rapid uptake is attributed to high lipid solubility ([Kronevi et al., 1977](#)).

A guideline dermal absorption OECD (Organisation for Economic Co-operation and Development) 428 *in vitro* study ([Labcorp Early Development, 2023](#)) was performed utilizing human skin biopsies with the results listed in Table 2-1. The percent absorption values, noted with bold font, are recommended to be utilized in the risk evaluation. The results in the 1,2-dichloroethane as a COU vehicle ranged from 0.5 to 1.0% absorption. Data with percent coefficient of variation over 25% were corrected for high variability and low N by the Excel T Test 95% upper confidence limit and the mean + k × SD method, which have very similar results. The k values for N at 4, 5, and 6 replicates are 1.6, 1.2, and 1.0, respectively. Data with dermal absorption recovery values less than 95% or greater than 100% mass balance were also normalized to the 100% basis—because the absorption values were less than 5% (*i.e.*, the absorption signal is of similar magnitude to the missing mass amount). Both of these data corrections are recommended in the 2022 OECD GD156 and 2017 EFSA dermal guidances. For comparison, the IHSkin Perm model had results in the range of 1.4 to 1.6% absorption for neat 1,1,2-trichloroethane, indicating general concordance between the *in vitro* experimental data and *in silico* predictions, with IHSkinPerm results reflecting the upper bound of the *in vitro* absorption values.

The neat 1,1,2-trichloroethane OECD 428 dermal absorption testing had six testing replicates. The replicate with 9.72% absorption could be excluded from the final mean and stand deviation (SD) calculations because that skin sample failed the skin QC (quality control) step (trans epidermal water loss or TEWL). However, the dermal absorption replicate with 1.02% absorption was included in the analysis for a total of five replicates.

Two dermal exposure studies of 1,1,2-trichloroethane in humans found that short-term dermal exposure to 0.1 mL neat concentrations of 1,1,2-trichloroethane showed no evidence of erythema, whitening, edema, scaling, or skin-fold thickness increases, but a short-term dermal exposures of 1.5 mL over 3.2 cm² of the volar forearm led to increased blood flow and a stinging and/or burning sensation ([Wahlberg, 1984a, b](#)).

646 **Table 2-1. 1,1,2-Trichloroethane OECD 428 Dermal Absorption Results**

1,1,2-Trichloroethane Sample	Low	High	Mean	SD	%CV	Mass Balance Fraction ^a	Mass Balance Corrected Mean ^a	Excel T Test Confidence Interval ^{a b c}	Excel T Test 95% UCL ^{a b c}	Mass Balance Corrected Excel T Test 95% UCL ^{a b c}	Mean + k × D Method ^{a b c}	Mass Balance Corrected Mean + k × SD ^{a b c}	Ratio of Missing Mass to Mean Value Ratio
1% in IPM, N = 4	ND	ND	ND	N/A	N/A	1.05	N/A	N/A	N/A	N/A	N/A	N/A	N/A
10% in IPM, N = 6	ND	0.26	7.0E-02	0.10	142.9	0.947	7.4E-02	0.105	0.175	0.185	0.170	0.18	N/A
50% in IPM, N = 6	0.11	0.51	0.29	0.16	55.2	0.964	0.301	0.168	0.458	0.475	0.450	0.467	N/A
1% in 1,2-DCA, N=6	0.18	0.69	0.34	0.24	70.6	0.923	0.369	0.252	0.592	0.642	0.580	0.629^d	22.79
10% in 1,2-DCA, N = 6	0.31	0.59	0.43	0.10	23.3	0.916	0.469^e	0.105	0.535	0.584	0.530	0.578	19.44
50% in 1,2-DCA, N = 6	0.33	0.89	0.59	0.20	33.9	0.935	0.631	0.210	0.8	0.855	0.790	0.844^d	10.95
Neat, 100% 1,1,2-trichloroethane, N = 5	0.36	1.02	0.57	0.26	45.61	0.923	0.618	0.323	0.893	0.968	0.882	0.956^d	13.58
1,2-DCA = 1,2-dichloroethane; %CV = percent coefficient of variation; IPM = isopropyl myristate; SD = standard deviation; ND = not detected; UCL = upper confidence level ^a Mass balance corrected = value/mass balance fraction. Consistent with the 1,1-dichloroethane risk evaluation (U.S. EPA, 2025b). ^b Excel T test 95% UCL is based on the Excel T test confidence interval function ^c Excel T test 95% UCL = mean + Excel T test confidence interval ^d Used mass balance corrected mean + k × SD value: mass balance is less than 95% and absorption is less than 5%, high %CV. ^e Used mass balance corrected mean: mass balance is less than 95% and absorption is less than 5%, low %CV. Low and high values indicate minimum and maximum of measured samples, respectively. For 1% in IPM, most cells were ND with 2 cells having high water loss Bolded values indicate which method was used in this assessment to estimate dermal absorption.													

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2.2.2 Distribution

Inhalation exposures in mice showed that 1,1,2-trichloroethane has lipid affinity and preferentially distributes into fat, followed by liver and kidney, blood and brain, and other tissues (spleen, lungs) (Battelle, 2001; Gargas et al., 1989). Approximate tissue distributions in mice exposed to 1,000 ppm 1,1,2-trichloroethane for 1 hour were, 600 µg/g distributed in fat; 80 µg/g in kidney and liver; 45 to 60 µg/g in the blood and brain; and 20 to 35 µg/g in the heart, lung, and spleen, each quantified separately (Takahara, 1986). 1,1,2-Trichloroethane is highly lipid-soluble and has a strong affinity for fat- and lipid-rich tissues (Sato and Nakajima, 1979; Morgan et al., 1972), as evidenced by a fat-to-air partition coefficient of 1,438 (Gargas et al., 1989). Using the vial equilibrium method described in (Gargas et al., 1989) (comparison of headspace 1,1,2-trichloroethane concentrations to vials of 1,1,2-trichloroethane vapor for blood or vials of 0.75 mL saline for the tissues), liquid-to-air and tissue-to-air partition coefficients for mouse blood, rat brain, and rat spleen were determined as 71 (mouse blood-to-air), 56 (rat brain-to-air), and 43 (rat spleen-to-air) (Sapphire Group, 2002; WIL Research, 2002; Battelle, 2001). Gargas (1989) also reported a rat liver-to-air partition coefficient of 73.1. These data indicate preferential distribution and retention in fat, liver, and brain in both animals. Data on oral exposure is more limited. In one study, detectable levels of the compound were found in liver of rats and mice exposed to single oral doses of 70 mg/kg and 300 mg/kg 1,1,2-trichloroethane, respectively (Mitoma et al., 1985b). 1,1,2-Trichloroethane was found localized in the liver and shown to bind to hepatic proteins (Mitoma et al., 1985b), suggesting liver is the primary site for metabolism to reactive metabolites in animals and likely humans. Due to its lipophilic nature in conjunction with animal studies, 1,1,2-trichloroethane can diffuse into the bloodstream distribute preferentially to organs and tissues with high fat content (Reed et al., 1988).

2.2.3 Metabolism

High performance liquid chromatography identified chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid as primary metabolites in rats and mice given 1,1,2-trichloroethane by oral gavage (Mitoma et al., 1985b). These metabolites were also reported following intraperitoneal injection in mice (Yllner, 1971). Formation of S-carboxymethylcysteine and thiodiacetic acid occurs through glutathione conjugation of reactive intermediates, while chloroacetic acid is generated by hepatic cytochrome P450 (CYP450) via oxidative dechlorination (Yllner, 1971). CYP450 metabolism may produce reactive free radical intermediates like acyl chlorides and free radicals, which bind to proteins and nucleic acids and are considered potential mediators of cytotoxic, mutagenic, and carcinogenic effects (Mazzullo et al., 1986; Ivanetich and Van den Honert, 1981). Acyl chloride intermediates that conjugate with endogenous glutathione form the major urinary metabolites of 1,1,2-trichloroethane, S-carboxymethylcysteine and thiodiacetic acid (Yllner, 1971) as cited in ATSDR (2021).

Metabolic capacity differs between species. Rats and mice metabolized identical proportions (81%) of an oral dose; the absolute amount was higher in mice because their maximum tolerated dose was 4.3% times higher than that of rats (Mitoma et al., 1985b). Because the primary metabolites are mediators of toxicity, interspecies metabolism differences may affect susceptibility to toxicity. Mice metabolize 1,1,2-trichloroethane at a higher rate than rats, consistent with findings that mice have increased sensitivity to 1,1,2-trichloroethane for some endpoints (Mazzullo et al., 1986; Mitoma et al., 1985b) and this higher metabolic capacity may increase susceptibility of mice to 1,1,2-trichloroethane-induced carcinogenicity (Mazzullo et al., 1986; Ivanetich and Van den Honert, 1981) as cited in (ATSDR, 2021). Studies in mice demonstrated suicide inhibition of cytochrome P450 metabolism (a form of enzyme inactivation in which the compound inhibits its own metabolism) in female mice but not male mice, which may explain why some results in male mice supported higher toxicity (*i.e.*, higher cancer slope

factors). The human metabolic rate relative to rodents is unknown, but pathways are considered to be similar.

2.2.4 Excretion

In female mice exposed to 250 to 500 ppm 1,1,2-trichloroethane for 4 to 6 hours, breath analysis confirmed pulmonary elimination ([Battelle, 2001](#)). Using gas chromatography, tissue concentrations were measured and tissue half-lives post 1 hour exposure to 1,000 ppm 1,1,2-trichloroethane were 625, 203, 147, 127, 122, 43, 39, and 19 minutes in heart, fat, brain, spleen, lungs, kidneys, blood, and liver, respectively. Whole body half-life of 1,1,2-trichloroethane was estimated at 49.3 minutes ([Takahara, 1986](#)) as cited in ATSDR ([2021](#)). Studies in rodents show excretion pathways in both oral and intraperitoneal administration ([Mitoma et al., 1985b](#); [Yllner, 1971](#)). 48 hours after mice and rats were dosed with radiolabeled compound either orally or intraperitoneally, 7 to 10% of 1,1,2-trichloroethane was exhaled unchanged, 3 to 7% was exhaled as CO₂ (gas), 72 to 87% was excreted as urinary metabolites, approximately 1% was in feces, and 1 to 3% remained in the carcass. The predominant elimination pathway in humans is expected to be urinary metabolites. Humans exposed to approximately 5 mg vaporized 1,1,2-trichloroethane via inhalation eliminated 2.9% of the dose in exhaled breath within the first hour after administration ([Morgan et al., 1970](#)). The retention slope of the compound per unit time was measured to be 0.006. Less than 0.01% of administered radioactivity per minute was excreted in urine within 1 hour after exposure, corresponding to an estimated urinary half-life of approximately 70 minutes ([Morgan et al., 1970](#)). Overall, despite its preference to distribute into lipid-rich tissues, 1,1,2-trichloroethane is rapidly cleared and not expected to accumulate in tissues.

2.2.5 PBPK Modeling Approach

In 2000, EPA required toxicology and ADME testing for 1,1,2-trichloroethane under a testing consent order that incorporated an Enforceable Consent Agreement (Federal Register 65 FR 37550). These studies, performed by the HAP Task Force, allowed the development of a PBPK Model by the Sapphire Group to utilize oral data for the inhalation route and to predict internal tissue levels from oral and inhalation exposures. The PBPK model is described in ([Sapphire Group, 2002](#)). The model was originally used to quantify the pharmacokinetics of 1,1,2-trichloroethane in mice and rats and then to extrapolate inhaled concentrations PODs from oral PODs (route-to-route extrapolation) that were associated with various hazardous endpoints from rodent studies: immunotoxicity in mice ([Sapphire Group, 2004c](#)), acute neurotoxicity in rats ([Sapphire Group, 2004a](#)), developmental endpoints in rats ([Sapphire Group, 2005](#)), and carcinogenicity in rats and mice ([Sapphire Group, 2004b](#)). The purpose of the 1,1,2-Trichloroethane PBPK Model is to conduct route-to-route extrapolation for rodents, *i.e.*, to predict the inhalation exposure necessary to reach internal doses resulting from the oral exposure for each toxicity study.

Route-to-route extrapolation assumes that systemic toxicity is driven by internal dose, and that equivalent internal doses will produce comparable toxic effects regardless of exposure route. PBPK modeling relies on internal dose metrics which are directly linked to toxic effects. For 1,1,2-trichloroethane, toxicity might be due to metabolic activation in the liver (discussed in Section 2.3.1.1.4). Furthermore, suicide inhibition of metabolism in mice occurs only in females, resulting in higher blood and tissue concentrations of 1,1,2-trichloroethane in female mice than in male mice ([Sapphire Group, 2005](#)); however, the overall amount of 1,1,2-trichloroethane metabolized was similar in both sexes and was directly correlated to the observed hazardous effects. As such, the amount of 1,1,2-trichloroethane metabolized in the liver per liter liver per day was selected as the applicable internal dose metric for route-to-route extrapolation ([Sapphire Group, 2005](#)).

First, oral PODs (*i.e.*, no-observed-adverse-effect level [NOAEL]; lowest-observed-adverse-effect level [LOAEL]) were selected from toxicity studies and internal dose metrics were determined that could be linked to toxic effects. The following toxicity studies are described in more detail in Sections 2.3.1.3 and 2.4.4. A 90-day drinking water dosing study ([Sanders et al., 1985](#)) indicated immunosuppression in mice at a LOAEL of 44 mg/kg/d. Acute neurotoxicity through gait impairment in rats was observed at a LOAEL of 95 mg/kg/day (NOAEL of 55 mg/kg/day) ([WIL Research, 2004](#)). The carcinogenic effects of 1,1,2-trichloroethane on rats and mice exposed by gavage administration ([NCI, 1978](#)) where rats had a NOAEL of 92 mg/kg/day for 5 days a week (corresponding to 65.7 mg/kg/day on a 7-day per week continuous basis) and the LOAEL for male and female mice was 195 mg/kg/day for 5 days/week (corresponding to 139.3 mg/kg/day on a 7-day per week continuous basis). A developmental study in rats dosed with a NOAEL of 111 mg/kg/day ([WIL Research, 2005](#)) was considered for route-to-route extrapolation, but was ultimately determined to be an uninformative study. See *Draft PBPK Model Review for 1,1,2-trichloroethane* ([U.S. EPA, 2026e](#)) for details of other dose metrics considered for each endpoint.

The PBPK model was then used for forward dosimetry (*i.e.*, to predict the amount of 1,1,2-trichloroethane metabolized in the liver from the reported oral dose and exposures from each toxicity study) and reverse dosimetry (*i.e.*, to predict the external inhaled concentration needed to generate the same amount metabolized in the liver dose metric associated with hazard). By representing physiological and biological processes explicitly, the PBPK models allow for extrapolations to be addressed using chemical-specific and biology-based data. This approach differs from default route-to-route extrapolation which would convert oral PODs to inhaled concentrations with default adjustment factors. Note that because no human parameter data were available to extrapolate animal doses to human doses, this model is only applicable to rodents for intra-species route extrapolation.

2.2.5.1 1,1,2-Trichloroethane PBPK Model Description

Built upon the previously described 1,1,2-trichloroethane model, ([Sapphire Group, 2002](#)) developed a PBPK model to extrapolate from the oral route of exposure to the inhalation route of exposure for rats and mice. The 1,1,2-Trichloroethane PBPK Model contains the basic set of equations for a volatile organic compound (VOC) inhalation model as originally described in the ([Ramsey and Andersen, 1984](#)) Styrene PBPK Model. This common approach describes the movement of a compound through a mammalian body using sets of mass-balance differential equations to explain the disposition of the compound entering and exiting organs within the body. The ([Ramsey and Andersen, 1984](#)) model is composed of lung, fat, muscle tissues (or other slowly perfused tissues), richly perfused tissues, and liver. Saturable metabolism using Michaelis-Menten kinetics removes the chemical from the liver. Arteries and veins deliver the concentration of compound into and from each tissue. Inhalation of the chemical is represented by a gas exchange compartment. This model was then incorporated by ([Gargas and Andersen, 1989](#)) into a PBPK model for disposition of 1,1,2-trichloroethane and other chlorinated ethanes in male F344 rats. The ([Gargas and Andersen, 1989](#)) rendition incorporated an exhaled breath gas uptake method into their model to be able to determine kinetic constants for chemical metabolism. ([Sapphire Group, 2002](#)) then expanded and refined the model to include a spleen compartment to accommodate immunotoxicity endpoints and a brain compartment for neurotoxic effects. A stomach compartment was also included to account for oral exposure, either by water as the vehicle or corn oil gavage (see Figure 2-2 for the model schematic). See also the *Draft PBPK Model Review for 1,1,2-Trichloroethane* ([U.S. EPA, 2026e](#)) for a thorough description and analysis of the model.

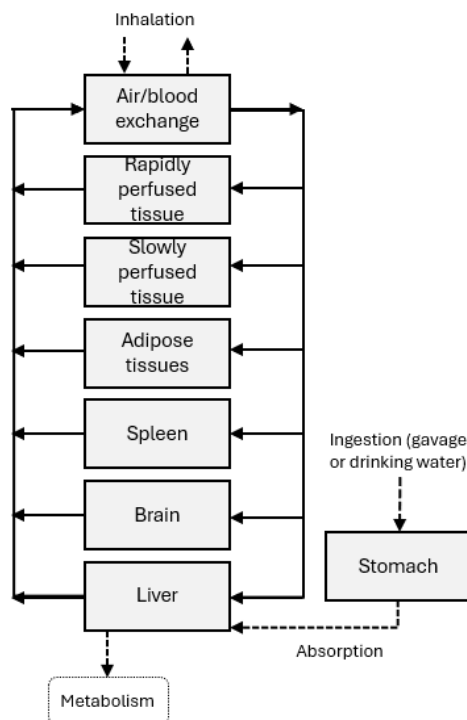


Figure 2-2. PBPK Model Diagram for Rat and Mouse Adapted from Sapphire Group (2002).

1,1,2-Trichloroethane PBPK Model schematic. Solid lines and arrows to the tissues represent arterial blood and arrows from the tissues represent venous blood. Dashed lines represent routes in or out of the body. The oral route of exposure deposits an oral dose into the stomach compartment, which is absorbed into the liver and then distributed in blood. The inhalation route of exposure goes into a gas blood exchange compartment. The chemical is eliminated from the body through exhalation from the air/blood exchange compartment and through hepatic metabolism.

Average anatomical and physiological parameters for rats and mice (body weight, tissue weights, blood flows, respiration rates) were taken from (Brown et al., 1997). Tissue-to-blood partition coefficients were calculated from blood-to-air partition coefficients and tissue-to-air partition coefficients, which were either measured from experimental data (Battelle, 2001) or taken from literature (Gargas et al., 1989). The model can be used for both mice and rats with species-specific parameters. (Sapphire Group, 2002) determined species-specific enzyme affinity, maximum metabolic rate, and absorption rate parameters using optimization fit (a common mathematical method that minimizes errors between a model and data) to mouse and rat data sets. This model allows for oral and inhalation routes of exposure. Oral dosing was modeled as corn oil gavage or with a periodic water drinking exposure (assuming a 12-hour light/dark schedule, where rats consume 80% of their water consumption during the dark period in evenly spaced timepoints).

Absorption studies suggest comparable absorption mechanisms across mice and rat species (similar blood concentrations were reported in both rats and mice following 4 weeks of inhalation exposure in a study conducted by (Battelle, 2001)). Starting values for stomach absorption rates for corn oil were taken from the (Clewett et al., 2000) for another chlorinated solvent trichloroethylene model and assumed to be similar. Absorption rates were determined for water or corn oil dosing. 1,1,2-Trichloroethane in water was estimated to be absorbed from the stomach with first order rate constants of 2.5 h^{-1} and 1.3 h^{-1} for mice and rats, respectively; 1,1,2-trichloroethane in corn oil was estimated to be absorbed slower at rates of 0.2 h^{-1} and 0.45 h^{-1} for mice and rats, respectively. These data reflect the

lipophilic nature of 1,1,2-trichloroethane and reflect the altered absorption kinetics from hydrophobic corn oil, leading to slower uptake and more dependence on systemic perfusion for distribution.

Species differences in metabolism, with mice metabolizing 1,1,2-trichloroethane at a higher rate than rats ([Mazzullo et al., 1986](#); [Mitoma et al., 1985b](#)), were described using metabolic parameters K_M and V_{MAX} optimized against the kinetic data provided by ([Battelle, 2001](#)) with starting values from ([Gargas and Andersen, 1989](#)). Additionally, the optimized model incorporated suicide inhibition (*i.e.*, enzyme destruction via inactivation by a bound, reactive intermediate) to explain reductions in V_{MAX} observed in female mice and drawing from justification in ([White et al., 1985](#)). The model structure was modified to accommodate a suicide enzyme activation pathway for female mice, since female mice exposed to 1,1,2-trichloroethane by inhalation or corn oil gavage showed significantly higher blood concentrations of the parent compound 1,1,2-trichloroethane on days 3 and 5 compared to day 1. However, 1,1,2-trichloroethane metabolism produces multiple reactive metabolites which may explain more sensitive toxicology results in male mice.

The 1,1,2-Trichloroethane PBPK Model is applicable to systemic endpoints, which are described in the *Draft PBPK Model Review for 1,1,2-Trichloroethane* ([U.S. EPA, 2026e](#)). Because 1,1,2-trichloroethane toxicity can be caused by metabolic activation in the liver, as discussed in Section 2.3.1.1.4, the amount of 1,1,2-trichloroethane metabolized in the liver per L liver per day is the applicable internal dose metric for route-to-route extrapolation ([Sapphire Group, 2005](#)) for cancer endpoints for which toxicity is likely related to metabolic activation, such as liver tumors. To characterize immunotoxicity from the Sanders et al. ([1985](#)) study, described in 2.3.1.1.2, spleen concentrations can be used as a surrogate for richly-perfused bone marrow because it is rapidly perfused and non-metabolizing ([Sapphire Group, 2005](#)). However, as discussed above, suicide inhibition of metabolism occurs in female mice, but not male mice, resulting in higher blood and tissue concentrations of 1,1,2-trichloroethane in female mice than male mice—while overall amounts metabolized are similar in both male and female mice. This corresponds to toxic effects seen in both sexes and indicates that the amount metabolized in the liver is an appropriate metric. Route-to-route extrapolation for neurotoxic effects (characterized by gait impairment), described in 2.3.1.1.3, was conducted by predicting brain concentrations because gait impairment is related to nerve activity as impacted by the parent chemical ([Sapphire Group, 2004a](#)). The oral doses and exposure conditions were modeled to reflect those described in the studies summarized in Table S-1. Note that for the cancer study, time-averaged and non-time-averaged doses in mice were both modeled (a high dose of 390 mg/kg/day averaging to 278.6 mg/kg/day for 7 days). Extrapolation of non-cancer endpoints was conducted for both rats and mice. However, extrapolation of cancer endpoints was conducted for mice only because mice developed tumors at all dose levels, which provided more information to support the use of the dose metric (amount metabolized in the liver).

2.2.5.2 Summary of Model Development and Evaluation

EPA evaluated the ([Sapphire Group, 2002](#)) model against ADME (adsorption, distribution, metabolism, and excretion) data from ([Battelle, 2001](#)) and ([WIL Research, 2002](#)). Blood samples from inhalation studies in rodents were from WIL Research Laboratories. Oral gavage studies were performed separately by the HAP Task Force ([Battelle, 2001](#)). The PBPK model and model parameter optimizations generated by ([Sapphire Group, 2002](#)) provided simulations that fit the data. Thus, there is confidence in the accuracy of the model to predict internal concentrations of 1,1,2-trichloroethane in mice and rats after oral gavage (in water or oil) and inhalation exposures.

Inhalation Studies in Rodents

The inhalation PBPK model was validated using data from 36 female F-344 rats and 36 female B6C3F1 mice that were exposed by whole body inhalation to 1,1,2-trichloroethane in an inhalation chamber.

Groups of three female F344 rats or three female B6C3F1 mice per sample time (36 animals/species) were sacrificed, blood was collected by ([WIL Research, 2002](#)), and blood samples were analyzed at Battelle's Pacific Northwest Laboratory, where the ([Battelle, 2001](#)) oral studies were conducted. Rodents were exposed for six hours per day, 5 days per week, for four consecutive weeks, resulting in 20 exposures. The targeted exposure concentration was 100 ppm. On days 1, 3, and 5 of the 4th week, blood samples were collected at 4, 6, 6.25, and 8 hours after the start of the exposure for three animals, three species, and three timepoints. The delay that occurred between removal of animals from the chamber was noted so it could be accounted for in the exposure scenario of the model. Exposure errors are reported in ([WIL Research, 2002](#)) to explain variability in observations on day 1 of collection, in which collection times were delayed 1 hour (On day 1, target exposure time and blood sample collection were all delayed 1 hour such that target times were 5, 7, 7.25, and 9 hours). In mice and rats, maximum blood concentrations were similar at 2.1 and 2.2 µg/mL, respectively. A minimum detection limit of 0.1 ppb in air was used.

Oral Studies in Rodents

The oral route of exposure was validated with data conducted from 4 gavage studies ([Battelle, 2001](#)). Mice were given 1,1,2-trichloroethane for 1 to 5 days by gavage with target doses of 390 mg/kg/day (actual dose 356.6 mg/kg/day) in corn oil for group 1 and 10 mg/kg/day (actual dose 9.7 mg/kg/day) in water for group 2. Blood was collected on days 1, 3, and 5. No statistically significant differences in blood concentrations were found comparing days 1, 3, and 5 for group 2. Group 1 blood concentrations in day 1 were significantly lower than those on days 3 and 5, indicating a dose-dependent change in disposition. Rats were given 1,1,2-trichloroethane for 1 to 5 days by gavage with target doses of 92 mg/kg/day (actual dose of 94.2 mg/kg/day) in corn oil for group 1 and 1.7 mg/kg/day (actual dose of 1.6 mg/kg/day) in water for group 2. Blood was collected on days 1, 3, and 5. No statistically significant changes in maximum blood concentrations were observed between days 2 and 3 for group 1 and between days 1, 3, and 5 for group 2, indicating periodicity.

Determination of PBPK Parameters

([Battelle, 2001](#)) determined the metabolic rate constants for the PBPK model using the data from an experiment in which five female B6C3F1 mice were exposed by whole-body inhalation for 4 to 6 hours to 1,000, 500, and 250 ppm 1,1,2-trichloroethane in an 8.59-liter closed chamber. They were then placed within a 2.2-liter off-gassing chamber where chamber concentration was measured over time for 9 hours. Overt toxicity was observed during the 1,000 ppm exposure with one death and severe lethargy and ([Battelle, 2001](#)) noted that the time-course data for this dose was unusual and not expected and thus not included for parameter estimation. Measurements of the maximum chamber concentrations, which indicate the concentrations of 1,1,2-trichloroethane that exited the body through exhaled breath, showed that mice exposed to 250 and 500 ppm exhaled 6 and 17 ppm, respectively. Note that Michaelis-Menten constants were estimated using the exhaled breath technique from ([Gargas and Andersen, 1989](#)), which generally overestimate K_M . Compared to findings by ([Gargas and Andersen, 1989](#)) in F344 male rats, female rats exhibit an approximate 30% reduction in binding affinity and a 30% increase in metabolic capacity for saturable metabolic pathways. Partition coefficients are described in Section 2.2.2.

Evaluation

Figure 2-6 shows a plot predicting the log-transformed observations against the simulated values for both the oral and inhalation studies. Table 2-2 shows the RMSLE and R^2 goodness-of-fit values for each scenario. Generally, the model is predictive of internal blood concentrations from oral and inhaled doses of 1,1,2-trichloroethane in rats and mice.

The relationship between oral dose and internal concentration (or internal dose) is linear for most of the doses assessed for route-to-route extrapolation (non-cancer doses) but becomes nonlinear at higher oral doses (≈ 300 mg/kg/day). A linear concentration-internal dose relationship suggests that uptake and clearance remain linear (unsaturated). As discussed in Section 2.4.2, tumors in mice develop at doses within both the linear range and nonlinear ranges. However, because carcinogenicity is not fully captured by the PBPK model's dose metric, and the high cancer dose has not reached metabolic saturation, tumors can be assumed to be linear with dose. See also the *Draft PBPK Model Review for 1,1,2-trichloroethane* ([U.S. EPA, 2026e](#)).

Oral Predictions for Female F344 Rats and Female B6C3F1 Mice

The oral data plotted against simulations is from ([Battelle, 2001](#)). Figure 2-3 shows experimental data plotted against simulations of venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average body weight = 0.194 kg) were exposed to 9.7 mg/kg/day and rats (average body weight = 0.152 kg) were exposed to 1.6 mg/kg/day 1,1,2-trichloroethane as an oral gavage in water once daily for 5 days. Blood was collected for 1, 3, and 5 days. The lines are model simulations for the first hour of each day of data collection. Modeling of the water gavage study suggests that peak blood concentrations are achieved quickly (≈ 14 minutes post dose for rats and 5 minutes for mice). Figure 2-4 shows venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average BW 0.193 kg) were exposed to 365.5 mg/kg/day and rats (average BW 0.147 kg) were exposed to 94.2 mg/kg/day 1,1,2-trichloroethane as an oral gavage in corn oil once daily for 5 days. Data were collected for 1, 3, and 5 days. The lines are model simulations for the 8 hours of each day of data collection. For the corn oil gavage study, the model predicts that the maximum blood concentration is reached 46 minutes after dosing for rats, after which point it declines rapidly for about 3 hours post dose when elimination phase slows.

Inhalation Predictions for Female F344 Rats and Female B6C3F1 Mice

Figure 2-5 shows venous blood concentrations of mice and rats exposed to 100 ppm 1,1,2-trichloroethane for 6 hours a day, 5 days a week, for 4 weeks. Experimental data are from ([WIL Research, 2002](#)). Blood was collected on Days 1, 3, and 5 of week 4. The lines are model simulations from the 1st, 3rd, and 5th days of the 4th week, for the 8 hours of each day. The error bars are the standard deviation of the experimental data ($n = 3$ animals). Average body weight was 0.023 kg for mice and 0.16 kg for rats. The limit of detection was 0.013 $\mu\text{g/g}$. For mice, a single significant difference in blood concentration between days 3 and 5 at hour 8 was found, but it did not affect the overall kinetics significantly, indicating that steady-state (or periodicity) was achieved. In rats, blood levels at 4 hours post exposure showed no significant differences between days 3 and 5, indicating periodicity. While Day 1 levels were higher than days 3 and 5, the difference was less than 50%. For both rats and mice, concentration peaked at 6 hours.

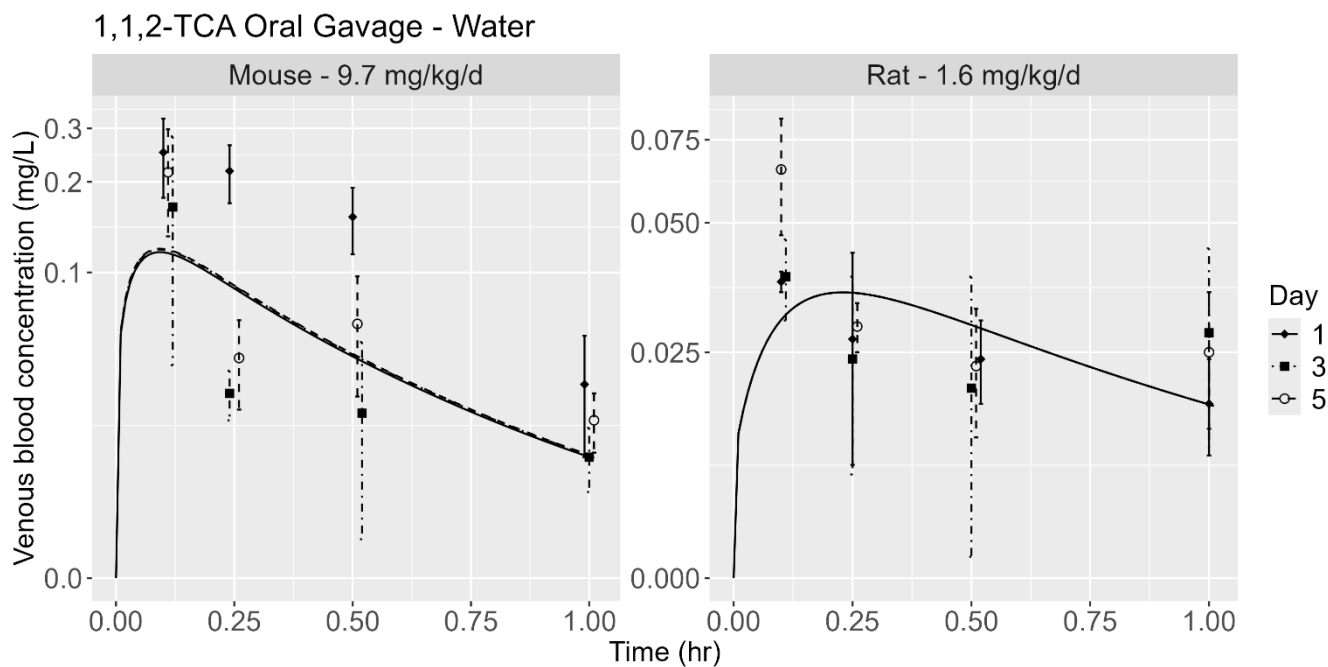


Figure 2-3. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats Following Oral Water Gavage

Venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice were exposed to 9.7 mg/kg/day and rats were exposed to 1.6 mg/kg/day 1,1,2-trichloroethane as an oral gavage in water once daily for 5 days.

Experimental data are from (Battelle, 2001). Data were collected for 1, 3, and 5 days. The lines are model simulations for the first hour of each day of data collection. The error bars are the standard deviation of the experimental data (n = 3 animals). Note that the overlaid simulated concentration curves are identical for rats and near identical for mice, indicating that the model predicted minor differences in mouse blood concentrations among the different days. Day 1 experimental data and simulations represented by the closed circle with solid line, Day 3 experimental data and simulations represented by closed triangle and dot-dashed line, and Day 5 experimental data and simulations represented by open circle and dotted line. Y-axis is log-transformed.

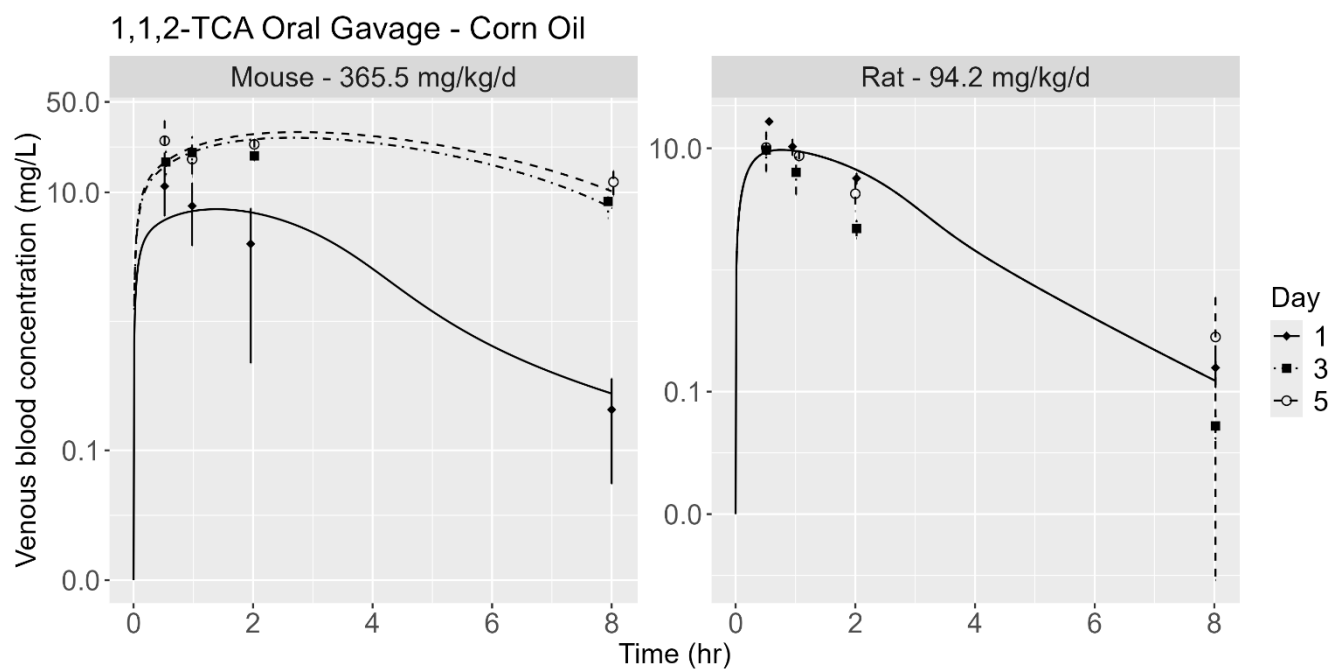


Figure 2-4. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats Following Corn Oil Oral Gavage (Single Day)

Venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice were exposed to 365.5 mg/kg/day and rats were exposed to 94.2 mg/kg/day 1,1,2-trichloroethane as an oral gavage in corn oil once daily for 5 days. Experimental data are from (Battelle, 2001). Data were collected for 1, 3, and 5 days (see legend on the right side of the diagram). The lines are model simulations for the 8 hours of each day of data collection. The error bars are the standard deviation of the experimental data (n = 3 animals). Day 1 experimental data and simulations represented by the closed circle with solid line, Day 3 experimental data and simulations represented by closed triangle and dot-dashed line, and Day 5 experimental data and simulations represented by open circle and dotted line. Y-axis is log-transformed.

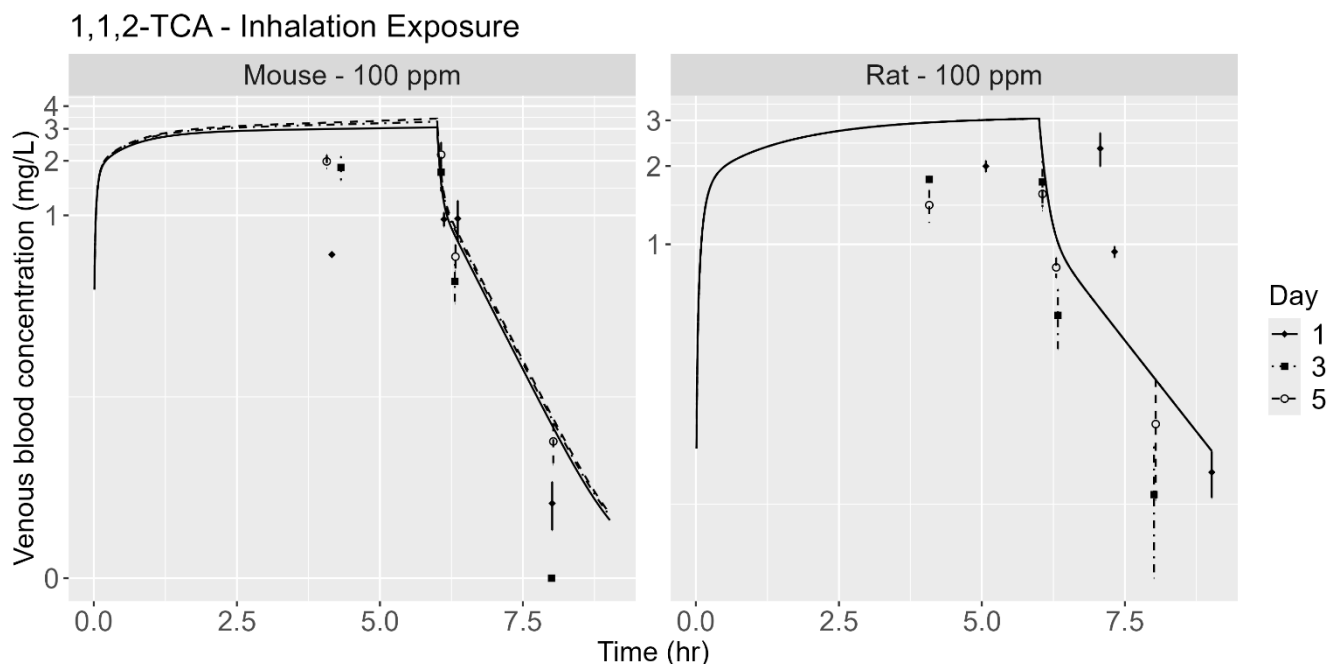


Figure 2-5. Simulated and Observed Blood Concentrations Of 1,1,2-Trichloroethane in Mice and Rats Following 100 ppm Inhalation Exposure

Venous blood concentrations of mice and rats exposed to 100 ppm 1,1,2-trichloroethane for 6 hours a day, 5 days a week, for 4 weeks. Experimental data are from ([Battelle, 2001](#)). Blood levels dropped rapidly after exposure ceased. Blood was collected on days 1, 3, and 5 of week 4. The lines are model simulations from the 1st, 3rd, and 5th days of the 4th week, for the 8 hours of each day. The error bars are the standard deviation of the experimental data (n = 3 animals). Day 1 experimental data and simulations represented by the closed circle with solid line, day 3 experimental data and simulations represented by closed triangle and dot-dashed line, and Day 5 experimental data and simulations represented by open circle and dotted line.

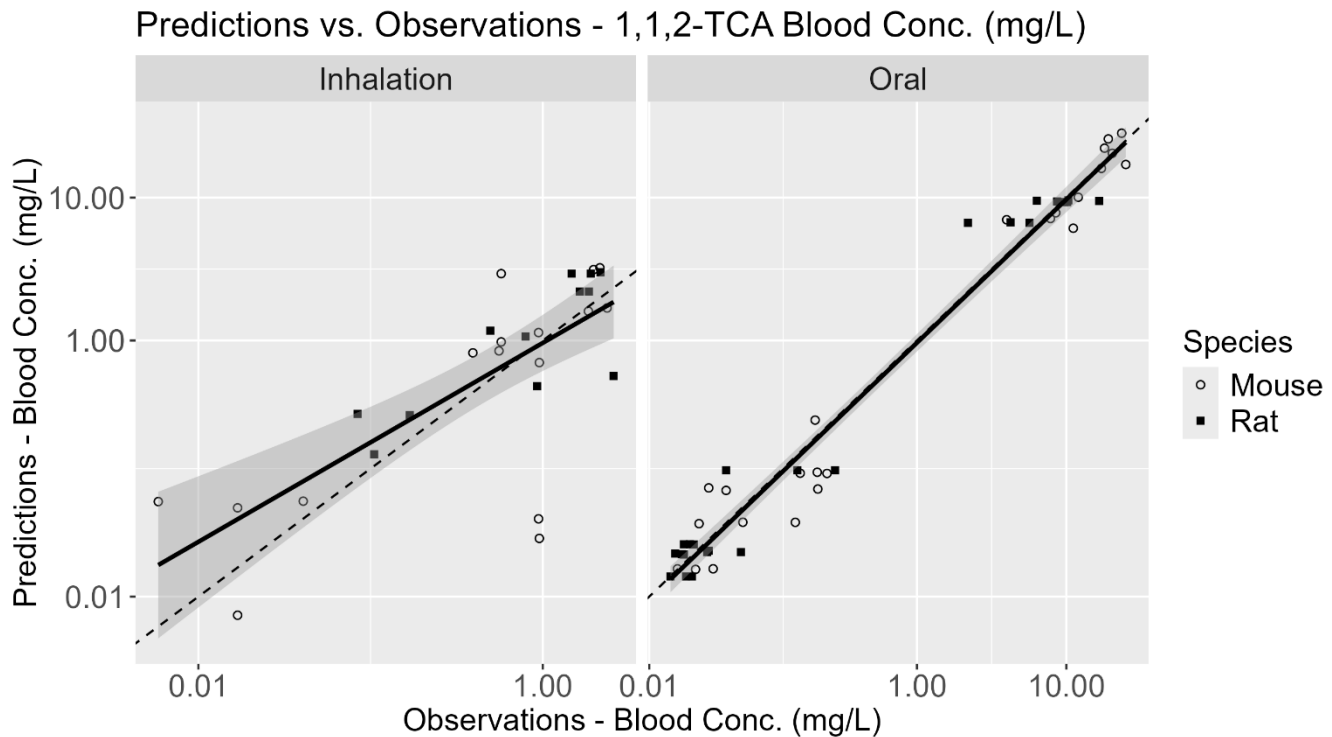


Figure 2-6. Predicted vs. Observed Blood Concentrations for Mice and Rats Following Inhalation and Oral Doses of 1,1,2-Trichloroethane

Observed vs. predicted 1,1,2-trichloroethane venous blood concentrations (mg/L) on log-transformed axes, grouped by route of exposure and species. Inhalation exposure in both rats and mice was 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks; blood was collected on days 1, 3, and 5 of week 4. Oral exposure occurred via gavage for 5 days: rats were exposed to 1,1,2-trichloroethane doses of 365.5 mg/kg/day in corn oil or 1.6 mg/kg/day water and mice were exposed to 1,1,2-trichloroethane doses of 94.2 mg/kg/day in corn oil and 9.7 mg/kg/day water. All experimental data are from (Battelle, 2001). The predictions are simulations from the PBPK model used for each exposure scenario. The dashed line is the identity line with slope = 1; points that fall on this line have been predicted accurately while points that fall above the line have been over-predicted and points below the line have been under-predicted. The gray shaded region is a 95% confidence band.

Table 2-2. RMSLE and R^2 Values Evaluating PBPK Model Goodness of Fit Against Data

Route	Vehicle (if Oral)	Observation	Species	RMSLE		RMSLE – Total Route	R ² - Total Route
Inhalation		Concentration in blood (mg/L)	Mouse	0.32		0.33	0.54
			Rat	0.33			0.44
Oral	Water	Concentration in blood (mg/L)	Mouse	0.06	0.19	0.22	0.91
	Corn oil			0.27			
	Water		Rat	0.01	0.24		0.83
	Corn oil			0.33			
PBPK = physiologically-based pharmacokinetic; RMSLE = root mean squared logarithmic error							

Sensitivity and Uncertainty Analysis

Confidence in a model for route-to-route extrapolation depends on several factors. Model-specific confidence relies on (1) the characterization of influential parameters, and (2) general PBPK model uncertainty. Local sensitivity analysis was conducted to characterize PBPK model and parameter uncertainty and to determine the level to which parameters influence model outcomes. Across both routes of exposure and for the endpoints corresponding to amount metabolized in the liver, the liver volume, enzyme affinity, maximum metabolic capacity, and blood-to-air partition coefficient were the most influential. The tissue and blood concentrations are sensitive to the metabolic rate constants and oral absorption rate constants, indicating that estimation conducted by ([Sapphire Group, 2002](#)) is appropriate for determining the values of these particular parameters.

Note that despite the amount metabolized in the liver being sensitive to liver volume, route-to-route extrapolation outcomes are not affected by liver volume because changes would similarly affect each route by decreasing or increasing the chemical concentration in the liver. For higher doses, ventilation rate and stomach absorption rate highly impacted liver metabolism output. For the endpoint corresponding to maximum brain concentration, ventilation rate, maximum metabolic capacity, blood-to-air partitioning, and blood-to-brain partitioning were the most influential. See the *Draft PBPK Model Review for 1,1,2-Trichloroethane* ([U.S. EPA, 2026e](#)) for details of the sensitivity analysis. Generally, the inhalation model contains a larger subset of influential parameters than that of the oral model; that is, small perturbations to many inhalation parameters created measurable changes in the output, while only a few parameters caused a change in the oral model output. This aspect is consistent with the kinetics of inhalation exposure compared with the limiting absorption and first-pass metabolism kinetics of oral dosing. As doses increase and reach metabolic saturation, the level to which parameters affect the output change. Most of the influential parameters are physiological or anatomical and their values are supported by data, providing high confidence. Thus, the route-to-route extrapolation results that rely on these influential parameters have correspondingly high levels of confidence.

Reasonable confidence in factors such as the estimated PODs for systemic effects from toxicity studies and the assumptions used for extrapolation and the pharmacokinetics describing ADME from both exposures, provides a relative advantage for the PBPK model compared to the default approach, which compares calculated bioavailable doses between the two routes without being able to account accurately for realistic exposure scenarios in toxicity studies and effects of ADME factors on target tissue exposure (e.g., suicide inhibition of metabolism). Because the PBPK model accounts for these elements, it can reduce uncertainty from the default approach for route-to-route extrapolation.

The model applies to both inhaled and oral routes of exposure in rats, confirmed by experimental rodent data. Pharmacokinetic data for female F344 rats exposed to repeated doses of 1,1,2-trichloroethane (≈ 100 ppm inhalation doses, 94.2 mg/kg/d corn oil gavage or 1.6 mg/kg/d water gavage) were comparable across days 1, 3, and 5 of exposure. Compared to findings by ([Gargas and Andersen, 1989](#)) in F344 male rats, female rats exhibit an approximate 30% reduction in binding affinity and a 30% increase in metabolic capacity for saturable metabolic pathways. Note that Michaelis-Menten constants estimated using the exhaled breath technique from ([Gargas and Andersen, 1989](#)) generally overestimate K_M . The model effectively simulates the 8-hour data point from the corn oil gavage studies. However, the elimination phase is difficult to define on days 3 and 5 due to minimal concentration changes over the first 2 hours post-dosing. There is a high level of confidence that the PBPK model adequately characterizes systemic dosimetry across exposure routes, supporting a basis for route-to-route extrapolation.

Model Applicability

EPA used the ([Sapphire Group, 2002](#)) PBPK model for rodent route-to-route extrapolation and to describe ADME of 1,1,2-trichloroethane for inhalation and oral exposures and route-to-route extrapolation. There is a high level of confidence that the PBPK model adequately characterizes systemic dosimetry across exposure routes, supporting a basis for route-to-route extrapolation. This model supports that sex and species-specific differences among mice and rats can predict dose metrics that support internal concentrations of the parent chemical as well as the amount of chemical metabolized in the liver, which is an endpoint of interest for metabolically active compounds. Sensitivity analysis indicated that the dose metric of interest, amount metabolized in the liver, is most sensitive to maximum metabolic rate via CYP pathway and other metabolism parameters, meaning that model confidence is highly dependent on how well metabolism is characterized. Because these parameters were able to be captured by the model to predict species differences in metabolism, and because many other influential parameters are physiological and anatomical, the values of which are well known and certain, model confidence is further supported.

The current PBPK model was developed and evaluated using rat and mouse data for oral-to-inhalation route-to-route extrapolation. Extrapolation of non-cancer endpoints was conducted for both rats and mice, depending on the study details. Extrapolation of cancer endpoints was conducted for mice only because mice developed tumors at all dose levels tested, which provided more information to support the use of the dose metric (amount metabolized in the liver). Extension of the model to support quantitative animal-to-human extrapolation was considered but not performed due to limitations in the available dataset and uncertainties associated with species-specific metabolic differences. Specifically, due to the lack of data for critical human kinetic parameters, including metabolic parameters to describe saturable metabolism, tissue-to-blood partition coefficients, and validated descriptions of metabolic pathways (*i.e.*, the presence of suicide inhibition in mice but not humans, which may preclude the assumption of conserved metabolic pathways needed to reliably scale across species). As a result, and because 1,1,2-trichloroethane is metabolically active and internal dose characterization relies on accurate metabolism parameters, development of a human PBPK model would introduce unverified assumptions that could increase model uncertainty and reduce confidence in internal dose metrics. In lieu of chemical-specific human PK data, human equivalent concentrations (HECs) were derived using a default interspecies scaling factor, described more in Section 2.2.5.2.

The dose metric in the PBPK model quantifies total amount of 1,1,2-trichloroethane metabolized in the liver via cytochrome P450. The PBPK model simulations that mirrored the mouse cancer study ([NCL, 1978](#)) indicate that liver metabolism in mice exposed to oral daily gavage doses is expected to be linear for doses up to approximately 300 mg/kg (5 days a week for 78 weeks), at which point metabolism starts to become non-linear (see Figure 2-7). See Section 2.4.1 for a detailed discussion about this, which is summarized as follows. While PBPK simulations based on cytochrome P450 metabolism suggested deviations from linearity at the highest dose in the cancer study (≈ 390 mg/kg/day for 5 days, over 78 weeks), the body weights of male and female mice were not markedly affected by treatment, supporting that the high dose did not exceed the maximum tolerated dose as the study authors concluded ([NCL, 1978](#)). The PBPK-predicted amount of 1,1,2-trichloroethane metabolized in the liver is also a partial metric. The non-linearity of cytochrome P450 metabolism indicated by the PBPK model at higher doses may indicate dose metric does not capture the complexity of the mode of action (MOA)—including the formation of reactive intermediates, DNA-adduct formation, or the impact of glutathione, or the relevance of the unknown biologically effective dose metric. Additionally, inhalation exposures that were extrapolated from the oral doses via the PBPK model occur in dose ranges for which metabolism is linear. As a result, internal dose metrics relevant to tumor formation are expected to scale proportionately with exposure under inhalation conditions.

Internal Dose as a Function of External Dose
(1,1,2-TCA Metabolized in Liver per Liter Liver mg/L-d)

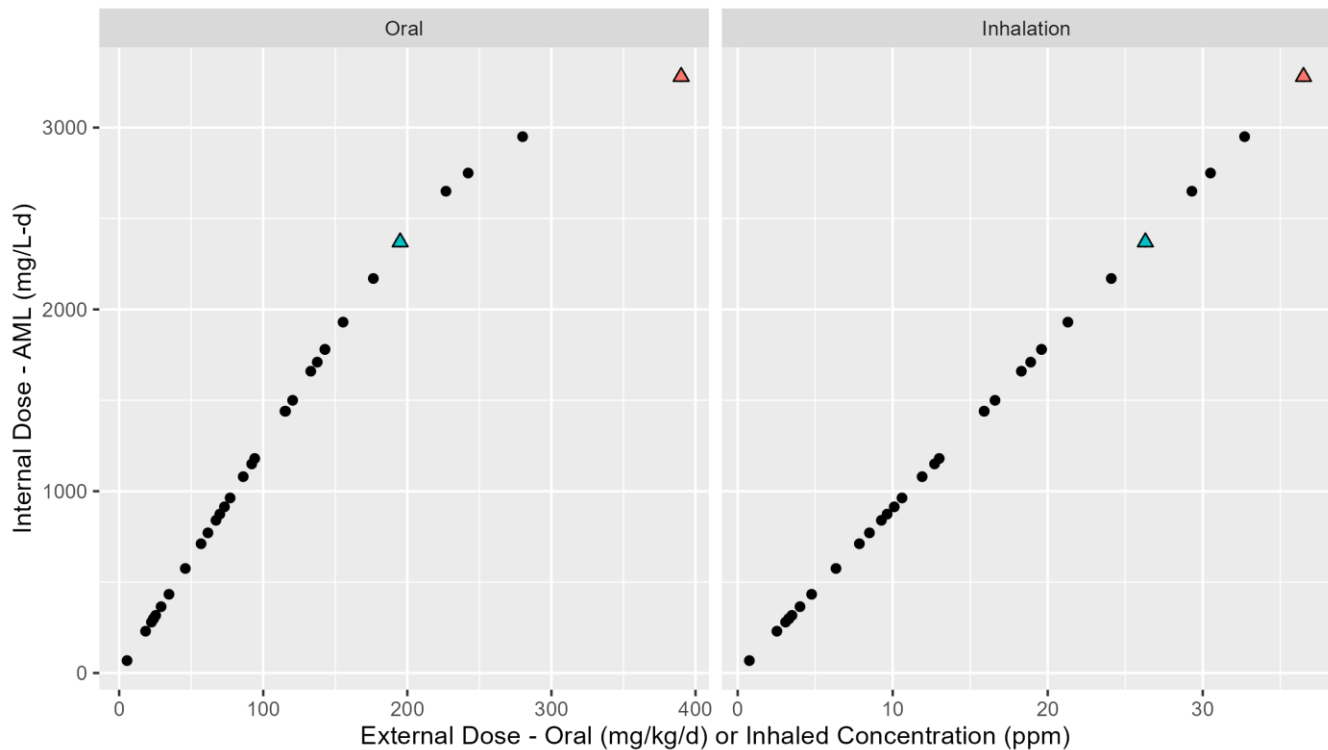


Figure 2-7. Kinetic Profile of the Internal Dose (Amount Metabolized in the Liver) as Function of External Dose for 1,1,2-Trichloroethane via PBPK Model

External doses of 1,1,2-trichloroethane plotted as a function of corresponding internal dose (AML or amount of 1,1,2-trichloroethane metabolized in the liver by cytochrome P450 enzymes, mg/L-d), for mice exposed to oral doses via corn-oil oral gavage for 5 days a week over 53 weeks. Continuously inhaled concentrations (right panel) are the corresponding concentrations for each oral dose (left panel) that generated the same internal dose. Notice that the internal dose is linear with extrapolated inhaled PODs, whereas AML metabolism starts to deviate from linearity around 300 mg/kg/day of the oral doses. Because inhalation exposure enters systemic circulation directly and bypasses liver first pass metabolism, a linear concentration-internal relationship indicates that uptake and clearance are linear. The red triangle represents the highest oral dose given in the cancer study (390 mg/kg/d) and its corresponding inhaled POD; the teal triangle represents the lower dose in the cancer study (195 mg/kg/d).

The Mouse PBPK Model was used to calculate the HEC for cancer study to obtain the corresponding IUR value, as described in Section 2.4.4. The PBPK model route-to-route extrapolation results were not used to generate HECs for non-cancer cases because good quality inhalation studies indicated portal of entry hazards (see Section 2.3.1.4) that cannot be addressed by extrapolating from an oral study via PBPK modeling, which requires systemic effects; this results in a HEC that covers both system and local effects.

PBPK models are preferred for extrapolation across exposure routes and species based on internal exposure equivalency rather than simple external-dose conversions. To be able to estimate dermal human equivalent doses (HEDs) from non-dermal animal PODs by PBPK modeling, systemic PBPK

models for both species, animal and human, are needed and they should be capable of simulating both dermal and non-dermal routes of exposure. EPA did not use PBPK modeling for estimation of dermal HEDs from oral PODs for 1,1,2-trichloroethane. 1,1,2-Trichloroethane is metabolically active, but the lack of MOA-relevant and human-specific metabolic clearance information needed to parameterize metabolic pathway-specific clearance cautioned EPA from applying PBPK modeling to dermal risk evaluation. Given the physicochemical properties of 1,1,2-trichloroethane and the ADME data suggesting rapid dermal absorption of this chemical, developing a rodent dermal route of exposure sub-model would have been possible by leveraging *in silico* models, however, limited information to support species-specific total clearance and pathway specific-metabolic clearance data precluded expanding the current rodent PBPK model to humans with an additional route of dermal exposure as doing so would introduce additional uncertainty.

It should be noted that since 1,1,2-trichloroethane is volatile and rapidly cleared from the body, not accounting for systemic clearance contribution to the overall systemic exposure through the dermal route could potentially mischaracterize dermal risk. This concern is partly addressed by accounting for 1,1,2-trichloroethane evaporation based on the fractional absorption data from an *in vitro* skin absorption study used in human exposure estimates. While oral-to-dermal rodent-only PBPK modelling was considered by adding a dermal sub-compartment to the existing Sapphire Group model structure, it was ultimately not pursued because *in vitro* human skin absorption data indicated that only approximately 1% of the applied dose is absorbed, and assumptions would have to be made regarding a rodent absorption *in silico* model, which would compound uncertainties. Furthermore, the available empirical human absorption data provides a direct and reliable basis to reduce uncertainty in overall risk since it comes from a human-relevant study and can be applied directly to the exposure doses via the DEVL model.

2.3 Non-Cancer Hazard Assessment

The sections below describe adverse outcome and mechanistic data available and evidence integration conclusions for relevant human health hazard outcomes for 1,1,2-trichloroethane. For complete details on evidence integration judgements within and across evidence streams, see the evidence profile tables for each organ system in Table_Apx A-1.

EPA independently conducted a systematic review of the literature up to April 2025 and also evaluated available guideline studies and conducted an independent dose-response evaluation and benchmark dose (BMD) analysis. The Agency evaluated all reasonably available data sources for hazards and regulatory doses, both qualitatively and quantitatively. The endpoints and PODs selected across the various routes and durations for 1,1,2-trichloroethane were derived from literature studies with medium or high data quality or standard guideline studies based on the same criteria. The endpoints and PODs were based on the best available science that provided an endpoint that was protective for others identified for the scenario duration and exposure route. For the inhalation route, the POD for the adverse effect on olfactory tissue decreased from 316 mg/m³ for the acute duration to 31 mg/m³ for the subchronic duration, without a chronic inhalation study for comparison. For the oral route, the HED POD for the acute duration decreased from 12.6 mg/kg based on neurotoxicity to an HED POD of 0.52 mg/kg/day based on immunotoxicity for the subchronic duration, without a chronic study for comparison. This assessment in most cases has the same endpoints utilized in previous assessments published by ATSDR (2021), IRIS (U.S. EPA, 1987), and U.S. EPA PPRTV (U.S. EPA, 2011a)—all with very similar POD values as provided/contrasted in Table 2-3. In cases where NOAEL or LOAEC values were utilized for PODs, benchmark dose modeling could not be performed, as supported by the harmonization of this

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approach with the ATSDR and PPRTV analysis of the data. Thus, there is confidence in these results that represent the best available science under TSCA.

Table 2-3. Comparison of EPA 2026, ATSDR 2021 ([ATSDR, 2021](#)), IRIS 1987 ([U.S. EPA, 1987](#)) and PPRTV 2011 ([U.S. EPA, 2011a](#)) PODs^a

Scenario	EPA 2026 POD, Study, Rating	ATSDR 2021 POD, Study, Rating	PPRTV 2011 Screening POD, Study, Rating	IRIS 1987 POD, Study, Rating
Acute oral/dermal	NOAEL HED = 12.6 mg/kg, Neurotoxicity (WIL Research, 2004), High; Study with similar POD: (Tyson et al., 1983) used by ATSDR Total UF = 30	NOAEL HED = 11.0 mg/kg, Liver toxicity (Tyson et al., 1983), Medium, Total UF = 100	N/A	N/A
Intermediate oral/dermal	NOAEL HED = 0.52 mg/kg/day, Immunotoxicity LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg (Sanders et al., 1985), High Total UF = 30	NOAEL HED = 0.51 mg/kg/day, Immunotoxicity LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg (Sanders et al., 1985), High, Total UF = 100	Immunotoxicity LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg (Sanders et al., 1985), High, Total UF = 1,000	N/A
Chronic oral/dermal	NOAEL HED = 0.52 mg/kg/day, Immunotoxicity LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg (Sanders et al., 1985), High Total UF = 300	NA	Immunotoxicity LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg (Sanders et al., 1985), High, Total UF = 1,000	Immunotoxicity LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg (Sanders et al., 1985), High, Total UF = 1,000
Acute inhalation	LOAEC = 316 mg/m ³ (58 ppm), Olfactory necrosis (WIL Research, 2001) High, Total UF = 100	LOAEC = 316 mg/m ³ (58 ppm), Olfactory necrosis (WIL Research, 2001) High, Total UF = 270	N/A	N/A WIL inhalation studies performed after IRIS 1987
Intermediate inhalation	BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm) Olfactory tissue lesions (WIL Research, 2002), High, Total UF = 30	BMCL ₁₀ HEC = 0.38 mg/m ³ (0.07 ppm) Olfactory tissue lesions (WIL Research, 2002), High, Total UF = 30	BMCL ₁₀ HEC = 0.51 mg/m ³ (0.09 ppm) Olfactory tissue lesions (WIL Research, 2002), High Total UF = 300	N/A WIL inhalation studies performed after IRIS 1987
Chronic inhalation	BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm) Olfactory tissue lesions (WIL Research, 2002), High, Total UF = 300	N/A	BMCL ₁₀ HEC = 0.51 mg/m ³ (0.09 ppm) Olfactory tissue lesions (WIL Research, 2002), High, Total UF = 3,000	N/A WIL inhalation studies performed after IRIS 1987
Oral/Dermal cancer slope factor	Liver tumors 0.0348 per mg/kg/day (NCI, 1978), Medium	N/A	Liver tumors 0.057 per mg/kg/day (NCI, 1978)	Liver tumors 0.057 per mg/kg/day (NCI, 1978)
Inhalation unit risk	Liver tumors 2.98E-06 per µg/m ³ Oral data PBPK model refinement (NCI, 1978), Medium	N/A	Liver tumors 1.6E-05 per µg/m ³ Extrapolation from oral data (NCI, 1978)	Liver tumors 1.6E-05 per µg/m ³ Extrapolation from oral data (NCI, 1978)

Scenario	EPA 2026 POD, Study, Rating	ATSDR 2021 POD, Study, Rating	PPRTV 2011 Screening POD, Study, Rating	IRIS 1987 POD, Study, Rating
BMCL = benchmark concentration lower bound; HEC = human equivalent concentration; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PBPK = physiologically-based pharmacokinetic; POD = point of departure; ppm = parts per million; N/A = not applicable, EPA 2026 utilized empirical body weights from the studies to calculate the HEC, HED, oral cancer slope factor and inhalation unit risk values rather than default values utilized in other assessments, thus the EPA 2026 values have been refined with the best available science. ^a The study ratings are evaluations by the EPA systematic review, in several cases ATSDR, IRIS, and PPRTV utilized the same studies for POD selection. PPRTV and ATSDR did not have study evaluations by the same process.				

2.3.1 Hazard Identification

The sections below describe adverse outcome and mechanistic data available, evidence integration, and weight of scientific evidence conclusions for relevant human health hazard outcomes for 1,1,2-trichloroethane. Full details on all evaluated health outcomes from all key studies are in the *Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for 1,1,2-Trichloroethane* ([U.S. EPA, 2026d](#)) and *Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for 1,1,2-Trichloroethane* ([U.S. EPA, 2026c](#)).

2.3.1.1 Critical Human Health Hazard Outcomes

The sections below focus on hazard identification and evidence integration critical human health hazard outcomes associated with 1,1,2-trichloroethane following evaluation of all available data by the EPA systematic review process. The 1,1,2-trichloroethane human health toxicology database included literature studies with medium or high data quality and standard guideline studies with the same criteria covering through April 2025, which provided confidence in the endpoint and POD selection. The non-cancer hazard endpoints for the oral and inhalation routes identified for 1,1,2-trichloroethane were neurotoxicity, respiratory tract pathology, immunotoxicity as measured by hemagglutination titers, altered thymus weights, decreased white blood cells, liver pathology, irritation, male reproductive toxicity, body weight changes, and mortality—all with the endpoints selected for POD derivation listed previously. The tables with the various studies, separated by oral and inhalation routes, are listed in Tables Table 2-6, Table 2-8, Table 2-10, Table 2-12, and Table 2-14. Section 2.3.1.3 provides details on the endpoint and POD selection rationales.

2.3.1.1.1 Respiratory Tract Toxicity

Human Evidence

No studies of sufficient quality were identified through systematic review or previous assessments that evaluated respiratory effects of 1,1,2-trichloroethane in exposed humans ([ATSDR, 2021](#); [U.S. EPA, 2011a](#)). A single study of a community living next to two Superfund sites containing 1,1,2-trichloroethane and other chemicals found no significant differences in the prevalence of respiratory symptoms of “highly exposed” community members as compared with community members with “limited exposure,” though this study was considered uninformative for dose-response due to the crude measurement of exposure and the multitude of chemicals present at the dumpsite ([Dayal et al., 1995](#)).

Laboratory Animal Evidence

Effects of 1,1,2-trichloroethane on respiratory tract organ weights and/or histopathology were evaluated in two high-quality inhalation studies: a 4-hour guideline inhalation exposure study in rats ([WIL Research, 2001](#)) and a 90-day guideline repeated inhalation exposure study in rats ([WIL Research, 2002](#)).

Respiratory tract effects were also assessed following oral exposure in a 90-day drinking water study in mice ([White et al., 1985](#)). While the overall rating for the 90-day drinking water study was high, the results for the high-dose males are considered uninformative and were not considered for dose-response analyses due to reduced drinking water consumption, which affects the received dose and may also have resulted in dehydration. There were no significant effects or concerns for water consumption in males at other doses or in females at any dose. Medium-quality studies include a 14-day gavage study in male mice ([White et al., 1985](#)) and a 78-week gavage study in rats and mice ([NCI, 1978](#)). A 6-month repeated inhalation exposure study in a single dog ([Mellon Institute, 1947](#)) was found to be uninformative. Note that uninformative or unacceptable studies can still be used qualitatively for the weight of scientific evidence.

Results of acute and subchronic high-quality guideline studies indicated that inhalation exposure to 1,1,2-trichloroethane altered the nasal cavity tissue of rats. Following a 4-hour exposure to greater than or equal to 58 ppm, minimal to severe olfactory epithelial necrosis was observed in male and female rats, with dose-responsive increases in severity and incidence as shown below in Table 2-4 ([WIL Research, 2001](#)). For females, the total incidences across all nasal levels were 0/15, 8/15, 13/15, and 15/15, with male incidences at 0/15, 3/15, 14/15, and 15/15 for concentrations at 0, 58, 181, and 1,527 ppm, respectively. The total incidences of necrosis at various levels of the olfactory epithelium tissue (levels III, IV, and V) were dose responsive for each sex separately (maximum total necrosis incidence score is 15). However, the dose-response had improved statistical power when male and female necrosis incidence data were combined (maximum total necrosis incidence score is 30 for combined sex data). The table of incidences at each severity category for each olfactory epithelium level for each sex is available from the original study report is listed below ([WIL Research, 2001](#)). The data support a LOAEC value of 58 ppm at the lowest concentration tested and that a UF_L of 3 is chosen because 10% of the response range for the male + female incidence data occurs at approximately one-third of the 58 ppm concentration value (*i.e.*, a score of 3 of a possible total score of 30 for the combined scores at a concentration of ≈ 19 ppm). Animals exposed to 1,527 ppm, the highest concentration tested, also exhibited single cell necrosis in the turbinates and lateral wall of the nasal transitional epithelium. At this exposure level, three of the five exposed female rats (but no males) died the day after exposure ([WIL Research, 2001](#)).

Table 2-4. Incidences of Necrosis in the Nasal Olfactory Epithelium in Rats Exposed to 1,1,2-Trichloroethane by Inhalation for 4 Hours ([WIL Research, 2001](#))

Sex	Necrosis, Olfactory Epithelium Severity Grade	0 ppm	58 ppm	181 ppm	1,527 ppm
Nasal level III necrosis incidence					
Male	Total	0	0	4	5
	Minimal	N/A	N/A	1	1
	Mild	N/A	N/A	2	1
	Moderate	N/A	N/A	1	1
	Severe	N/A	N/A	0	2
Female	Total	0	1	3	5
	Minimal	N/A	1	0	0
	Mild	N/A	0	3	0
	Moderate	N/A	0	0	2

Sex	Necrosis, Olfactory Epithelium Severity Grade	0 ppm	58 ppm	181 ppm	1,527 ppm
Female	Severe	N/A	0	0	3
Male + Female	Total	0	1	7	10
Nasal level IV necrosis incidence					
Male	Total	0	2	5	5
	Minimal	N/A	2	0	1
	Mild	N/A	0	5	3
	Moderate	N/A	0	0	1
Female	Total	0	5	5	5
	Minimal	N/A	3	0	0
	Mild	N/A	2	5	1
	Moderate	N/A	0	0	3
	Severe	N/A	0	0	1
Male + Female	Total	0	7	10	10
Nasal level V necrosis incidence					
Males	Total	0	1	5	5
	Minimal	N/A	1	4	4
	Mild	N/A	0	1	1
Females	Total	0	2	5	5
	Minimal	N/A	1	1	1
	Mild	N/A	1	4	4
Males + Females	Total	0	3	10	10
ppm = parts per million; NA = not applicable 5 males, 5 females, so sexes were combined for 10 rats in total; deaths occurred at 1,527 ppm; the various regions of the olfactory tissue organization were evaluated from levels III, IV, and V, which indicate different olfactory regions of tissue. Note that the level does not refer to the magnitude of necrosis.					

In a 90-day guideline inhalation exposure study in rats exposed to 1,1,2-trichloroethane, treatment-related lesions were also observed in the olfactory epithelium of the nasal turbinates ([WIL Research, 2002](#)). The specific histopathological changes and their incidences are replicated in Table 2-5 with the pairwise statistics separately listed by sex. Vacuolization and cysts are adverse histopathology responses and were observed at all 1,1,2-trichloroethane exposure levels in both males and females, with statistically significant increased incidences in both sexes at the highest concentration (100 ppm). The incidence of nasal olfactory epithelium atrophy was significantly increased on a pairwise basis at and exceeding 40 ppm and was not statistically significant in any animals at 15 ppm. Metaplasia was observed at increased incidence at the highest concentration (100 ppm) in both males and females; the increase was statistically significant only in females ([WIL Research, 2002](#)). However, BMD analysis of the male and female combined vacuolization/cyst data with higher statistical power (due to the increased number of animals in the same analysis) was dose responsive as shown in Appendix B.2.2 and Figure

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2-8, and produced BMC₁₀, BMCL₁₀, and BMCL₁₀ HEC values of 5.7 ppm, 4.0 ppm, and 0.11 ppm (31.1, 22.1, and 0.62 mg/m³), respectively. The BMD fitting routine for POD derivation was the Multistage 1 Model. It was selected on a weight of scientific evidence based on it had the highest p-value for data fitting, the smallest residuals near the BMC value, good visual fit near the BMC value, a BMC to BMCL ratio of only 1.4-fold and a small confidence interval—all of which provides confidence that the model well represents the empirical data.

Table 2-5. Incidences of Histopathological Lesions in the Nasal Olfactory Epithelium in Rats Exposed to 1,1,2-Trichloroethane by Inhalation for 90 days ([WIL Research, 2002](#))

Nasal Turbinate Lesion	Concentration (ppm)			
	0	15	40	100
Male rats				
Metaplasia	0/10 ^a	1/10	1/10	3/10
Atrophy	0/10	0/10	6/10 ^b	7/10 ^b
Vacuolization/cyst	1/10	2/10	6/10	10/10 ^b
Female rats				
Metaplasia	0/10	0/10	1/10	5/10 ^b
Atrophy	0/10	0/10	7/10 ^b	10/10 ^b
Vacuolization/cyst	1/10	4/10	4/10	8/10 ^b

^a Number of animals affected/number examined. Six sections were evaluated for each animal.
^b Statistically significantly different from control (p < 0.05) by Fisher's Exact test performed by ([U.S. EPA, 2011a](#)).

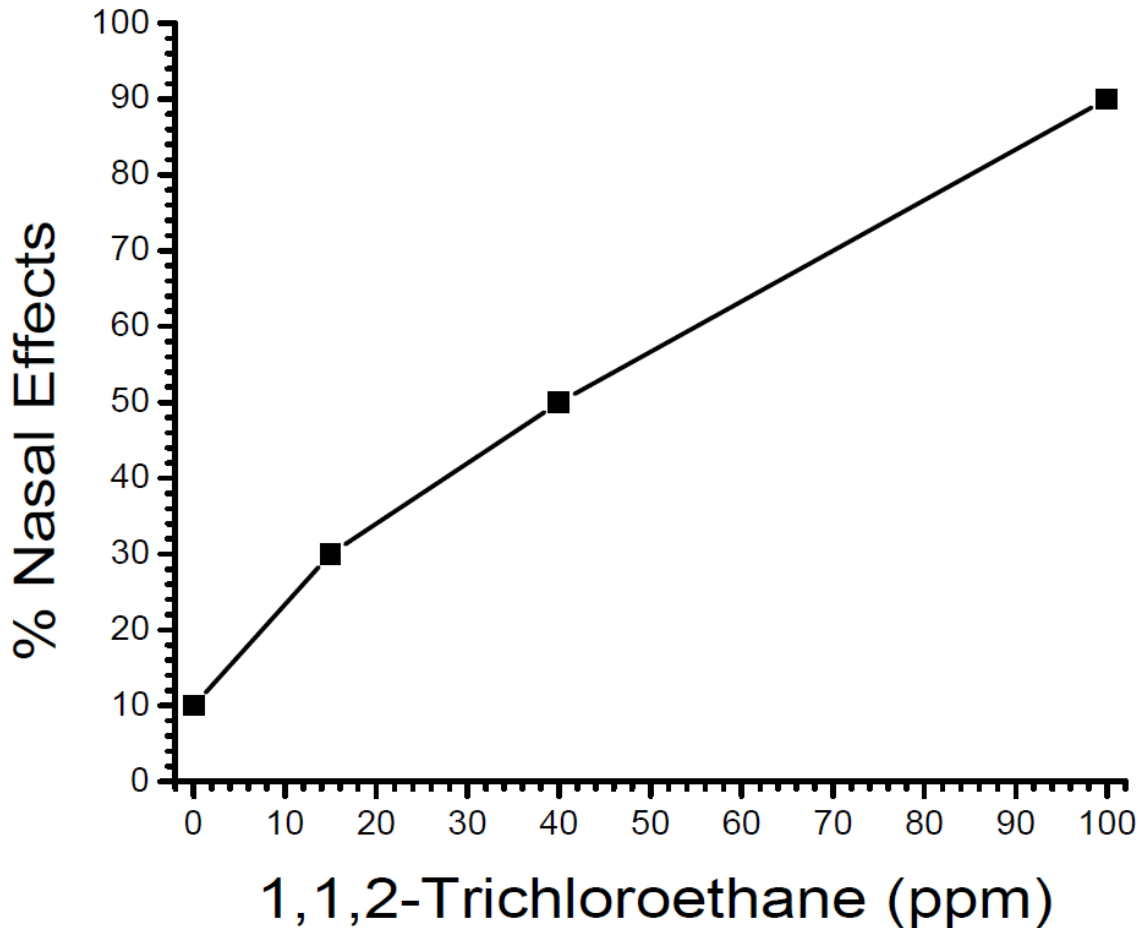


Figure 2-8. Subchronic Inhalation Study Combined Dose-Response for Nasal Vacuolization/Cysts (WIL Research, 2002)

Limited evidence for effects on the lower respiratory tract of rats was observed in the acute-duration inhalation study. Minimal to mild acute inflammation of the larynx was observed in male and female rats exposed at or exceeding 58 and 1,527 ppm, respectively, for 4 hours (WIL Research, 2001). In separate studies exposing male and female rats up to 1,474 and 840 ppm, respectively, for 4 hours, analysis of bronchoalveolar lavage fluid to assess the alveolar tissue showed an increase in total protein in the highest exposure groups for each sex and the phagocytic activity of alveolar macrophages was decreased at all concentrations relative to controls (WIL Research, 2001). It should be noted that three of five female rats died in the 840 ppm group.

No changes to respiratory tract gross pathology or histopathology were observed in a single male dog that was exposed to an analytical concentration of 84 ppm for 7 hours/day on alternating days for 6 months (Mellon Institute, 1947). Because only one exposed and one control dog were tested, limited conclusions can be drawn from this study (Mellon Institute, 1947).

Results of oral exposure studies with 1,1,2-trichloroethane are limited for assessing effects on the respiratory tracts of rodents because the nasal cavity was not examined microscopically in the available studies. No effects on absolute or relative lung weight were identified in male mice administered gavage doses up to and at 38 mg/kg-day for 14 days (White et al., 1985). In a 78-week repeated oral dose toxicity test, there were no changes to the histopathology of the lungs, bronchi, or trachea of rats or mice

administered time-weighted average gavage doses up to 92 and 390 mg/kg-day, respectively ([NCI, 1978](#)). In a drinking water study, absolute and relative lung weights were not affected in male and female mice exposed for 90 days ([White et al., 1985](#)). The lung weight results in males (but not females) may be confounded by the significantly decreased water consumption and reduced body weights observed only in high-dose male mice.

Mechanistic and Supporting Evidence

No studies related to mechanisms of 1,1,2-trichloroethane effects on the respiratory tract were located.

Evidence Integration Summary

No human data are available to evaluate the respiratory effects of 1,1,2-trichloroethane. There is moderate and consistent evidence from high-quality acute and subchronic studies for 1,1,2-trichloroethane effects on the nasal cavity of rats after inhalation exposure. There is some evidence from a high-quality acute study in rats for 1,1,2-trichloroethane effects on the larynx following inhalation exposure. Mechanistic data pertaining to respiratory effects of 1,1,2-trichloroethane were not located.

2.3.1.1.2 Immunological/Hematological Toxicity

Human Evidence

No studies were identified through systematic review or previous assessments that evaluated immunological effects of 1,1,2-trichloroethane in exposed humans ([ATSDR, 2021](#); [U.S. EPA, 2011a](#)).

Laboratory Animal Evidence

Effects of 1,1,2-trichloroethane on immunological or hematological endpoints were evaluated in two high-quality studies: a 13-week inhalation study in rats ([WIL Research, 2002](#)) and a 90-day drinking water study in mice ([Sanders et al., 1985](#); [White et al., 1985](#)). Although the overall rating for the 90-day drinking water study was high, the results for the high-dose males are considered uninformative and were not considered for dose-response analyses due to markedly reduced drinking water consumption, which affects the received dose and may also result in dehydration. There were no significant effects or concerns for water consumption in males at other doses or in females at any dose. A 14-day gavage dose study in male mice was rated medium to high quality ([Sanders et al., 1985](#); [White et al., 1985](#)). A 6-month inhalation exposure study in a male dog ([Mellon Institute, 1947](#)) and a 78-week gavage cancer study in rats and mice ([NCI, 1978](#)) were rated medium quality. A two-generation reproduction study in rats with drinking water dosing was rated uninformative for dose-response analysis due to markedly decreased water consumption in high-dose females during gestation and lactation ([DuPont, 2006](#)). In addition, the reproduction study ([DuPont, 2006](#)) dosed up to 82.2 mg/kg/day via drinking water in male rats failed to report testes, brain, and thymus pathology detected at a much lower dose of 38 mg/kg/day in the ([White et al., 1985](#)) gavage study indicating uncertainty in the dosing to rats via drinking water for a volatile solvent.

Effects on Immune Function: No inhalation exposure studies evaluating immune function were located. In a high-quality subchronic oral study, markers of humoral immune response were depressed in male and female mice exposed to 1,1,2-trichloroethane via drinking water for 90 days ([Sanders et al., 1985](#)). The humoral immunosuppression response to 1,1,2-trichloroethane was measured both by the T-cell dependent antigen response (TDAR) from blood serum samples based on the hemagglutination titer method and TDAR antibody forming cells (AFC) method based on spleen tissue utilizing sheep red blood cells as the antigen in both assays ([Sanders et al., 1985](#)). The subchronic Sanders (90-day oral drinking water dosing) study ([Sanders et al., 1985](#)) showed that there was a large decrease of the immune response (by over 40% consistently in both sexes) as measured by the specific serum hemagglutination titer assay which is one method for measuring humoral immunity via the T-cell

dependent antigen response (TDAR) utilizing sheep red blood cells as the antigen. The TDAR was also shown to be decreased by the secondary TDAR method by 31% in male mice with a shorter 14-day dosing via gavage at the lower dose of 38 mg/kg/day and decreased by 23% at 3.8 mg/kg/day, utilizing the spleen antibody forming cell (AFC) assay which is widely utilized. The T-cell dependent antigen response is considered a reliable immunotoxicity metric ([Luster et al., 1988](#)) and for 1,1,2-trichloroethane immunosuppression was indicated by both the antibody forming cells assay and the hemagglutination titer assay for measuring TDAR ([Sanders et al., 1985](#)).

In context, the serum hemagglutination TDAR assay measures the antibody response from all immune tissues based on blood serum (also sampled for human immune testing) and the spleen AFC TDAR assay only measures antibodies from one tissue, spleen cells. In mice, these alterations included statistically significant, dose-responsive decreases in hemagglutination titers of 40% or greater in females (square symbols) and 47% or greater in males (circle symbols), compared to controls, at greater than or equal to 44 mg/kg-day Figure 2-9 and a significant decrease in spleen lymphocyte responsiveness to lipopolysaccharide (LPS, a B-cell mitogen) of greater than or equal to 27% at 384 mg/kg-day. At 384 mg/kg-day, a significant (40%) increase in antibody-forming cells per million cells (AFC/10⁶ cells) was observed in females 4 days after challenge with sheep red blood cells (sRBCs); however, there was no significant difference when expressed on a per spleen basis (AFCs/spleen). [Sanders et al. \(1985\)](#) also evaluated functional activity of the fixed macrophages of the reticuloendothelial system (RES) by measuring vascular clearance and organ distribution of ⁵¹Cr-labeled sRBCs. The phagocytic index of the RES was significantly altered in females, but without a monotonic dose-response: the index was significantly decreased by 33% at 44 mg/kg-day and significantly increased by 33% at 384 mg/kg-day. Significant changes to radiolabel uptake were seen in females at the high dose, relative to controls (cpm/mg organ was decreased by 54% in the spleen and increased by 17% in the liver). Measures of macrophage function (phagocytic ability) of thioglycolate-recruited peritoneal exudate cells (PECs) showed no effects in females ([Sanders et al., 1985](#)). Other supporting indicators of immune system adverse effects are the changes in thymus weights in mice at a similar oral gavage dose of 38 mg/kg/day in the [White et al. \(1985\)](#) study and decreased white blood cells in dogs in the [Hobara et al. \(1984\)](#) inhalation study.

Similar to females, male mice in the 90-day drinking water study exhibited significant and large decreases in hemagglutination titers (47–59%, compared to controls, circles in Figure 2-9) at greater than or equal to 46 mg/kg-day ([Sanders et al., 1985](#)). No changes in spleen lymphocyte responsiveness to LPS or AFC response to sRBC challenge were seen in males. At the highest dose tested, 305 mg/kg-day, a significant decrease in spleen weight of 21% was observed in male mice on day 5 after challenge with sRBCs, but this may have been due in part to the 12% decrease in body weight in these mice ([Sanders et al., 1985](#)). Male mice at this dose also showed impairment of macrophage function, as shown by a 55% decrease in the phagocytic ability of PECs ([Sanders et al., 1985](#)). Effects observed in males at the highest dose should be interpreted with caution due to markedly reduced drinking water consumption. No changes in activity of fixed macrophages in the RES were noted in males at any dose tested.

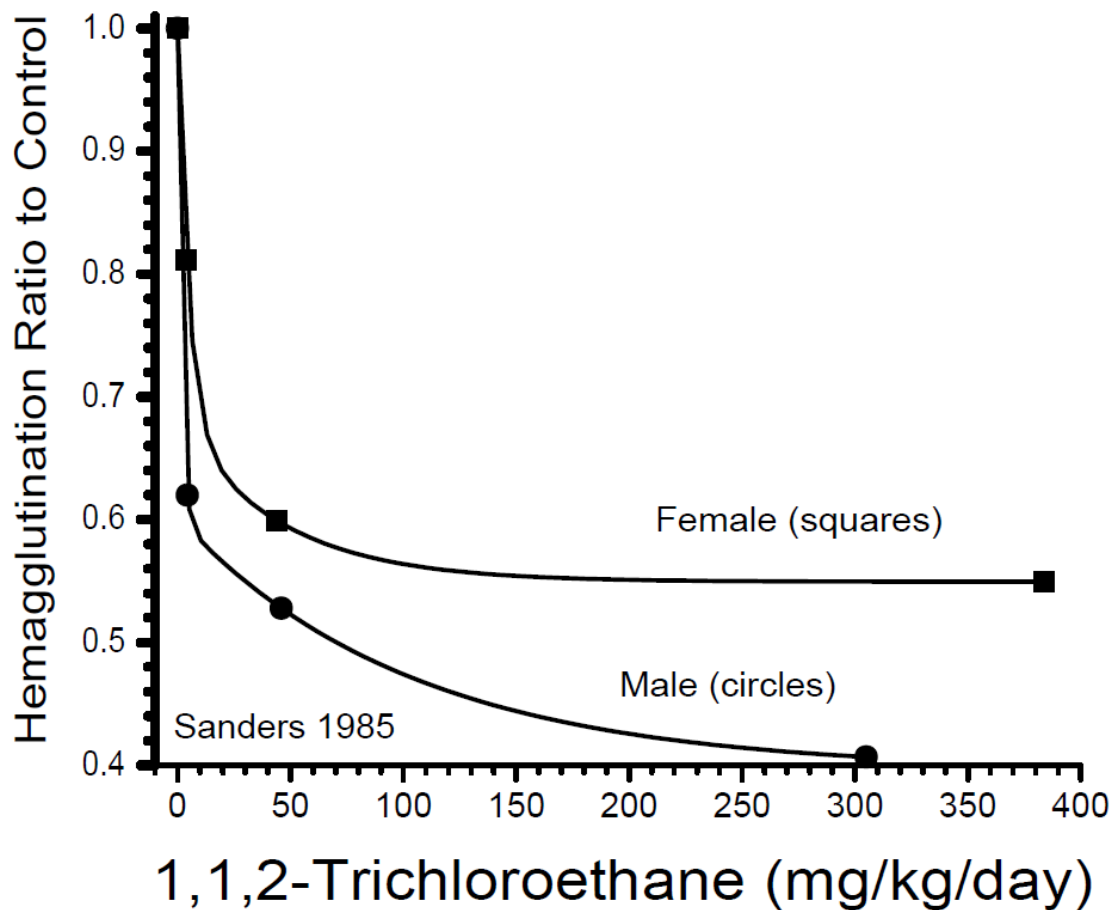


Figure 2-9. Hemagglutination Titers Ratio to Control Values in Mice Exposed to 1,1,2-Trichloroethane

Neither male nor female mice exhibited effects on cell-mediated immune responses (measured via delayed-type hypersensitivity, popliteal lymph node proliferation response to sRBC, and splenic lymphocyte responsiveness to the T-cell mitogen, Concanavalin A) or bone marrow DNA synthesis after 90 days of exposure to less than or equal to 305 or 384 mg/kg-day, respectively (Sanders et al., 1985). No effects on humoral or cell-mediated immune responses were observed in male mice exposed up to 38 mg/kg-day via gavage for 14 days (Sanders et al., 1985).

Effects on Hematology: Available studies examining hematology parameters after 1,1,2-trichloroethane exposure do not show clear evidence of adverse hematological effects. No treatment-related changes to hematological parameters were observed in rats exposed by inhalation up to 100 ppm for 13 weeks (WIL Research, 2002), in a single mongrel dog exposed to 84 ppm for 6 months (Mellon Institute, 1947), or in male mice given gavage doses up to 38 mg/kg-day for 14 days (White et al., 1985). In a 90-day drinking water study, there were small, but statistically significant, reductions (5–6%) in hemoglobin and hematocrit in females exposed to 384 mg/kg-day, the highest dose tested, relative to controls (White et al., 1985). Also in females, significant increases in leukocyte count (48%) and platelet count (11%) were observed at 384 mg/kg-day, relative to controls. Prothrombin time was significantly decreased (7–18% lower than controls) in females at or exceeding 44 mg/kg-day; there were no changes to activated partial thromboplastin time (White et al., 1985). Finally, fibrinogen was significantly increased in all exposed females, but the changes showed no clear relationship to dose (White et al., 1985). No hematological changes were observed in males in the 90-day drinking water study (White et al., 1985), though the results in high-dose males were considered uninformative due to greatly decreased

water consumption. However, decreased white blood cells were reported in the inhalation study in dogs (Hobara et al., 1984).

Organ Weights and Histology: Studies examining weights and histology of immune and hematopoietic system organs have not shown consistent effects of 1,1,2-trichloroethane exposure. No treatment-related effects were observed on spleen or thymus weights or on histopathology of bone marrow, lymph node, spleen, or thymus in rats exposed up to 100 ppm by inhalation for 13 weeks (WIL Research, 2002). No effects on spleen weights were observed in male mice administered gavage doses up to or at 38 mg/kg-day for 14 days; however, absolute (but not relative) thymus weights were increased by 25% compared to controls in the oral study (White et al., 1985). In female mice exposed by drinking water for 90 days, a significant increase in absolute (but not relative) spleen weight was noted at the highest dose (384 mg/kg-day) (White et al., 1985). Male mice in the 90-day drinking water study showed no statistically significant changes to spleen or thymus weights (White et al., 1985). In an uninformative for dose-response drinking water 2-generation reproductive toxicity study, no exposure-related changes in spleen weight were observed in F0 or F1 adult rats; estimated doses in the high-dose group ranged from 82.2 to 173 mg/kg-day with higher exposures (201–230 mg/kg-day) during the first 2 weeks of lactation (DuPont, 2006). Histological examination of a single dog exposed to 84 ppm for 6 months showed no splenic lesions (Mellon Institute, 1947). No gross or histopathological changes to the lymph nodes, spleen, or thymus were identified in rats and mice exposed up to or at 92 and 390 mg/kg-day, respectively, via gavage for 78 weeks in the NCI cancer study (1978).

Mechanistic and Supporting Evidence

No data related to mechanisms of 1,1,2-trichloroethane effects on the immunological or hematological systems were located.

Evidence Integration Summary

No human studies evaluating the immunological or hematological effects of 1,1,2-trichloroethane were located. There is overall moderate evidence of adverse effects to the immune system function by 1,1,2-trichloroethane in mice and dogs. A high-quality 90-day study in male and female mice for 1,1,2-trichloroethane-induced suppression of humoral immune function. In support of immunosuppression, altered thymus weight and a 31% decrease in the antibody forming cells were reported in a 14-day gavage study in mice (White et al., 1985), and decreased white blood cell counts were observed in an inhalation study in a dog (Hobara et al., 1984). Available data provide evidence for effects on hematological parameters and organ weight with limited evidence for 1,1,2-trichloroethane effects on histopathology of immune and hematological organs. No mechanistic data pertaining to these endpoints were located.

2.3.1.1.3 Neurological/Behavioral Toxicity

Human Evidence

A single study of a community living next to two Superfund sites containing 1,1,2-trichloroethane and other chemicals found significant neurological differences in the prevalence of dizziness/blackouts, learning difficulties, nervousness, numbness in fingers/toes, sleeping difficulties, unusual fatigue, and decreased sense of smell in “highly exposed” community members as compared with community members with “limited exposure”; however, this study was considered uninformative for dose-response due to the crude measurement of exposure and the multitude of chemicals present at the dumpsite (Dayal et al., 1995).

Laboratory Animal Evidence

Effects of 1,1,2-trichloroethane on neurobehavior, neurological clinical signs, and/or nervous system organ weights and histopathology were evaluated by EPA for all of the reasonably available information with varying degrees of study quality. The following high quality studies include a less than or equal to 4-hour inhalation exposure studies in male and female rats ([WIL Research, 2001](#); [Niklasson et al., 1993](#)), a 13-week inhalation study in male and female rats ([WIL Research, 2002](#)), an acute neurotoxicity test in male and female rats administered single gavage doses ([WIL Research, 2004](#)); and a 90-day drinking water study in mice ([White et al., 1985](#)). While the overall rating for the 90-day drinking water study was high, the results for the high-dose males are considered uninformative due to markedly reduced drinking water consumption, which affects the received dose and may also result in secondary effects due to dehydration; there were no significant effects or concerns for water consumption in males at other doses or in females at any dose. A 14-day gavage study in male mice ([White et al., 1985](#)) and a 78-week gavage study in male and female rats and mice ([NCI, 1978](#)) was rated medium quality. An acute inhalation exposure study in female mice ([Gehring, 1968](#)) and an acute gavage study in male and female mice ([White et al., 1985](#)) were both rated low quality.

Two drinking water studies were assigned as uninformative for dose-response rating based on potential confounding effects due to decreased water intake. In a 90-day rat neurotoxicity study, markedly decreased water intake was reported in high-dose males and females ([Dow Chemical, 2005](#)). In a two-generation reproduction rat study, markedly decreased water intake in high-dose females was reported during gestation and lactation ([DuPont, 2006](#)). In addition, the two-generation reproduction rat study dosed up to 82.2 mg/kg/day in males failed to indicate testes pathology reported in other studies at lower doses and the 90-day neurotoxicity rat study dosed up to 86 mg/kg/day failed to result in brain pathology, with both endpoints detected at a much lower dose of 38 mg/kg/day in a gavage study in mice ([White et al., 1985](#)). Similarly, the developmental rat study ([WIL Research, 2005](#)) was also rated low due to uncertainties in water consumption due to palatability as animals dosed via drinking water up to 111 mg/kg/day failed to identify any effects reported at much lower doses in other studies (*i.e.*, [White \(1985\)](#)). These data support the conclusion that the rodents in the rat reproduction study, the rat developmental study and the rat neurotoxicity study likely achieved indeterminate internal doses via drinking water which were less than the predicted dosing regimen. The maximum tolerated dose in rats by oral gavage was reported at 100 mg/kg/day ([Milman et al., 1988](#)).

With oral gavage exposure in a guideline OECD 424 acute neurotoxicity study, neurobehavioral effects consistent with CNS depression were observed in rats evaluated in a functional observational battery (FOB) with locomotor activity assessment following single gavage doses of 1,1,2-trichloroethane ([WIL Research, 2004](#)). No deaths were observed at dose less than or equal to 200 mg/kg. Findings included decreased mean body temperatures and increased incidences of hypoactivity and disruption of habituation in males and females at doses at or exceeding 95 mg/kg ([WIL Research, 2004](#)). There was decreased motor activity by 23.9 to 43.6% at doses at or exceeding 95 mg/kg in the 0 to 15-minute interval and 72.5 to 76.2% decreases at doses at or exceeding 95 mg/kg in the 16 to 30-minute interval; therefore, a consistent study LOAEL at 95 mg/kg can be supported as shown in Figure 2-10. The acute neurotoxicity data supports the rapid absorption and rapid clearance of 1,1,2-trichloroethane in rats, where peak concentrations in the blood are reached within an hour and decline within three hours, coinciding with rapid effects on motor activity. Higher incidences of slight gait impairment, abnormal gait and decreased urination were observed in males and females at 200 mg/kg; greatly decreased motor activity was observed at doses of 95 mg/kg and higher; these effects had resolved when animals were evaluated at 7 days post-exposure ([WIL Research, 2004](#)). In male and female mice administered single lethal gavage doses at or exceeding 450 mg/kg, sedation was observed in all animals within 1 hour, and

loss of righting reflex was observed in 10% of animals; the numbers of animals affected in each dose group were not specified and no control group was available for comparison ([White et al., 1985](#)).

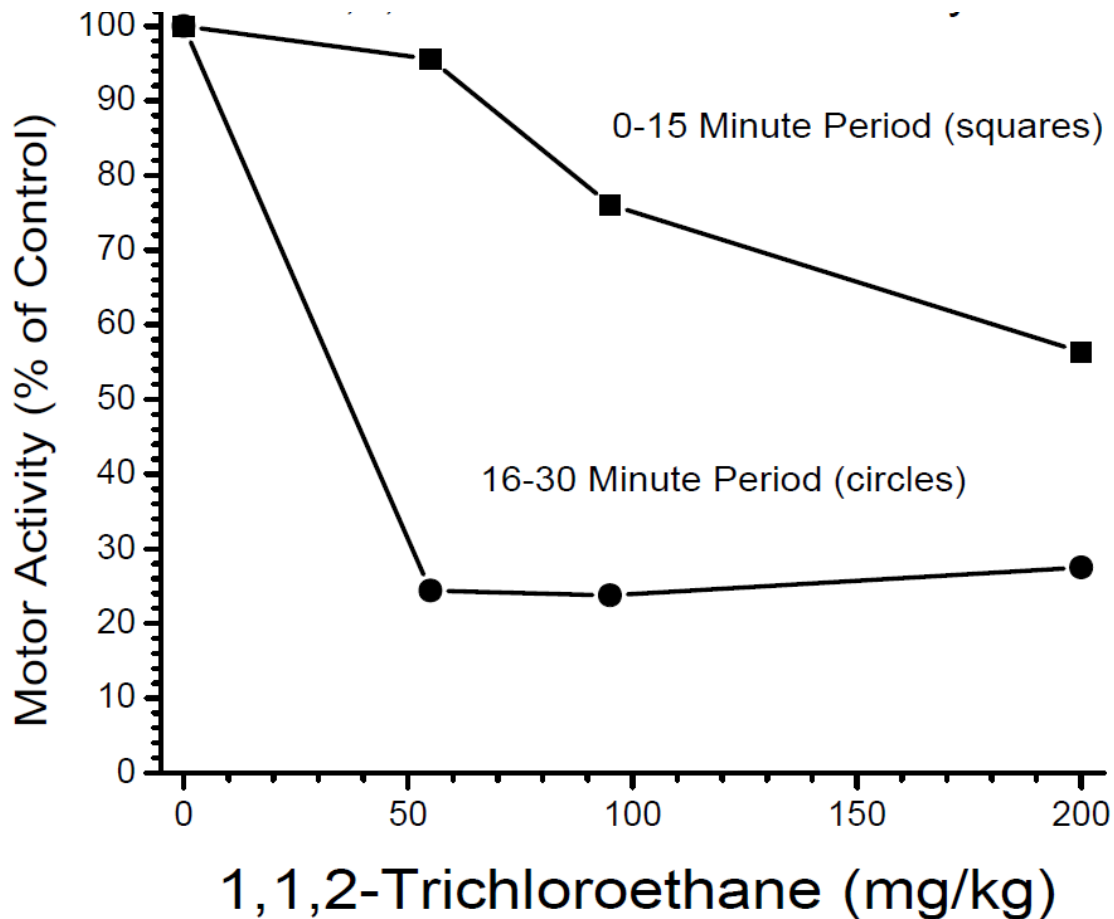


Figure 2-10. Motor Activity in Male Rats, Acute Neurotoxicity Study for 1,1,2-Trichloroethane ([WIL Research, 2004](#))

In a 90-day drinking water neurotoxicity study, no exposure-related changes were observed in survival, FOB parameters, grip strength, foot splay, motor activity, or rectal temperature at estimated doses of up to or at 86.0 and 98.2 mg/kg-day in male and female rats, respectively ([Dow Chemical, 2005](#)). However, this study was rated uninformative due to potential confounding factors by decreased water consumption in high-dose males and females ($\leq 25.3\%$ and 26.1% compared to controls) and it failed to detect adverse brain effects reported in the White study at much lower dose of 38 mg/kg/day. No clinical signs of CNS depression were noted in rats or mice exposed up to or at 92 or 390 mg/kg-day, respectively, via gavage for 78 weeks; however, detailed behavioral testing (*e.g.*, FOB) was not conducted in this cancer study ([NCI, 1978](#)).

Similarly, no clinical signs of neurotoxicity were observed in F0 or F1 rats in an uninformative two-generation drinking water study; estimated doses in the high-dose group ranged from 82.2 to 173 mg/kg-day, with higher exposures (201–230 mg/kg-day) during the first 2 weeks of lactation ([DuPont, 2006](#)). Thus, the lack of neurotoxicity findings in the two-generation study at much higher-administered doses raises uncertainty about dosing accuracy and suggests this study has limited utility for dose-response POD selection. Similarly, the drinking water developmental study with a low-quality rating ([WIL](#)

[Research, 2005](#)) dosed up to 111 mg/kg/day also failed to detect neurotoxicity reported at much lower doses than in the White study ([White et al., 1985](#)). The two-generation reproduction study, the developmental study, and the subchronic neurotoxicity study with much higher PODs only have qualitative value to support that the immunotoxicity NOAEL of 3.9 mg/kg/day in the Sanders study ([Sanders et al., 1985](#)) is human health-protective for reproductive, developmental, and neurotoxicity endpoints.

Acute inhalation exposures to 1,1,2-trichloroethane produced neurological clinical signs of toxicity consistent with central nervous system (CNS) depression in laboratory animals at high, lethal exposure levels. No reaction to a novel stimulus (sudden noise) was observed in male or female rats during a 4-hour exposure to 1,527 ppm, a concentration that was lethal for 3/5 females ([WIL Research, 2001](#)). At the end of the exposure period, all animals “appeared to be sleeping,” and during the 24-hour post-exposure observation period, males and surviving females were lethargic and surviving females were cool to the touch (hypothermic) ([WIL Research, 2001](#)). Anesthesia (immobilization) was observed in female mice exposed to 3,750 ppm for up to 1,000 minutes; the estimated time for anesthesia to occur in 50% of exposed mice was 18 minutes ([Gehring, 1968](#)). This concentration was lethal, with 50% mortality occurring within 600 minutes ([Gehring, 1968](#)). In a 13-week inhalation study, no clinical signs of CNS depression were observed in rats exposed up to and at 100 ppm ([WIL Research, 2002](#)).

A specialized study of the function of the central vestibular system was performed in rats exposed to 1,1,2-trichloroethane via inhalation for approximately 1 hour ([Niklasson et al., 1993](#)). When rats were presented with conflicting vestibular stimulation and visual input, dose-related decreases in optokinetic capacity and slow-phase eye velocity were observed in rats exposed to 1,900 to 9,400 mg/m³ (350–1,700 ppm). This dose-related decrease in optokinetic gain impaired normal compensatory eye movements via the vestibulo-oculomotor reflex, which would typically steady vision by moving the eyes in the opposite direction of head movement in a coordinated manner, indicating alterations in the central vestibular system with exposure.

A slight (5%) increase in relative brain weight was observed in male rats exposed via inhalation to 1,527 ppm for 4 hours, but given the absence of changes to absolute weight this effect may be a result of the decreased body weight observed for this group ([WIL Research, 2001](#)). No changes in absolute or relative brain weights were observed in rats exposed up to 100 ppm via inhalation for 13 weeks ([WIL Research, 2002](#)). A significant (11%) increase in absolute brain weight was observed in male mice exposed to 38 mg/kg-day in a medium-quality study dosed via gavage for 14 days; no effects were observed on relative brain weights or body weights ([White et al., 1985](#)). No effects on brain weights or dimensions were observed in rats administered single gavage doses up to 200 mg/kg ([WIL Research, 2004](#)) or in male or female mice exposed up to or at 305 or 384 mg/kg-day, respectively, via drinking water for 90 days ([White et al., 1985](#)). In a two-generation drinking water study, no exposure-related changes in brain weights were observed in F0 or F1 rats; however, this study was rated uninformative for dose-response due to uncertainties in the administered doses as described previously, which confounded its interpretation ([DuPont, 2006](#)). No consistent pattern of 1,1,2-trichloroethane effects on brain weight can be established based on the available data; however, in context several studies had uninformative or low ratings that should not negate the positive findings in the higher-quality studies. In context, the maximum tolerated dose for rats is reported to be 100 mg/kg/day ([Milman et al., 1988](#)).

1,1,2-trichloroethane did not alter histopathology findings in nervous systems of animals exposed via inhalation or ingestion. No gross pathological or histopathological changes were observed in the brain, spinal cord, or peripheral nerves in rats exposed up to 1,527 ppm via inhalation for 4 hours ([WIL Research, 2001](#)), in rats exposed up to or at 100 ppm via inhalation for 13 weeks ([WIL Research, 2002](#)),

in rats administered single gavage doses up to 200 mg/kg ([WIL Research, 2004](#)), or in rats and mice exposed up to or at 92 and 390 mg/kg-day, respectively, via gavage for 78 weeks in a targeted cancer study ([NCI, 1978](#)). Similarly, no exposure-related gross pathological or histopathological changes were observed in neurological tissues of rats in drinking water exposures for 90 days dosed up to 86 mg/kg/day ([Dow Chemical, 2005](#)) or over two generations in a reproduction study dosed via drinking water dosed up to 82 mg/kg/day ([DuPont, 2006](#)); however, both of these studies had uninformative for dose-response ratings and failed to detect brain weight changes reported in a higher quality mouse study ([White et al., 1985](#)) or decreased motor activity ([WIL Research, 2004](#)). Note that neurotoxicity may not necessarily also cause histopathology findings to be adverse such as the decreased motor activity at 95 mg/kg in the guideline acute gavage neurotoxicity study in rats ([WIL Research, 2004](#)).

Mechanistic and Supporting Evidence

No studies related to mechanisms of neurological or behavioral effects of 1,1,2-trichloroethane were located.

Evidence Integration Summary

The evidence for neurological effects of 1,1,2-trichloroethane from human studies is indeterminate based on a single human study evaluating the prevalence of neurological symptoms in community members living next to two Superfund sites containing 1,1,2-trichloroethane and other chemicals ([Dayal et al., 1995](#)). There is moderate evidence for neurological effects of 1,1,2-trichloroethane from high-quality acute studies in rats after inhalation or ingestion exposure, with support from low-quality acute studies in mice. CNS depression as measured by decreased motor activity was observed at only 95 mg/kg and higher doses in the gavage acute neurotoxicity study in rats, with limited data indicating impaired vestibulo-oculomotor reflex and alterations in FOB observations at lower non-lethal levels. There were several subchronic studies that measured neurotoxicity endpoints; however, they were uninformative for dose-response. The ([Dow Chemical, 2005](#)) subchronic neurotoxicity study did not report any effects at the highest dose tested of 86 mg/kg/day in this drinking water study rated as uninformative for dose-response. Supporting evidence to the acute study findings is an increased brain weight was measured in a 14-day study in mice ([White et al., 1985](#)). There is limited evidence for effects of 1,1,2-trichloroethane on brain weight, and no treatment-related histopathology has been reported in nervous system tissues. No mechanistic studies related to neurological/behavioral effects of 1,1,2-trichloroethane were located.

2.3.1.1.4 Liver/Hepatic Toxicity

Human Evidence

No studies were identified through systematic review or previous assessments that evaluated hepatic effects of 1,1,2-trichloroethane in exposed humans ([ATSDR, 2021](#); [U.S. EPA, 2011a](#)).

Laboratory Animal Evidence

Effects of 1,1,2-trichloroethane on the liver were evaluated in the following high-quality studies: a 4-hour acute inhalation test in rats ([WIL Research, 2001](#)), a 13-week inhalation study in rats ([WIL Research, 2002](#)), and a 90-day drinking water study in mice ([White et al., 1985](#)). While the overall rating for the 90-day drinking water study was high, the results for the high-dose males are considered uninformative due to markedly reduced drinking water consumption, which affects the received dose and may also result in dehydration. There were no significant effects or concerns for water consumption in males at other doses or in females at any dose. Studies rated medium quality included acute inhalation exposure studies in rats and mice ([Carlson, 1973](#); [Gehring, 1968](#)), an acute gavage study in rats ([Xia and Yu, 1992](#)), a 14-day gavage study in mice ([White et al., 1985](#)), 78-week gavage studies in rats and mice ([NCI, 1978](#)), an acute subcutaneous (s.c.) injection study in mice ([Plaa et al., 1958](#)), and acute

intraperitoneal (i.p.) injection studies in rats ([Charbonneau et al., 1991](#); [Lundberg et al., 1986](#); [Harms et al., 1976](#); [Klaassen and Plaa, 1969](#)). A two-generation reproduction study in rats was assigned an uninformative rating due to markedly decreased water intake in high-dose females during gestation and lactation, and it failed to detect testes pathology reported in other studies at lower doses ([DuPont, 2006](#)).

Results of animal inhalation exposure studies indicate that 1,1,2-trichloroethane can alter liver histology and induce serum biomarkers of hepatic damage in rodents. Centrilobular necrosis was observed in the livers of 4/5 female rats exposed to 181 ppm (minimal-to-mild) and in all (5/5) males and females at 1,527 ppm (moderate-to-severe) for 4 hours ([WIL Research, 2001](#)). Necrosis was not observed in the livers of control animals. In a 13-week inhalation study, hepatocellular vacuolization (minimal severity) was observed in rats exposed to at least 15 ppm of 1,1,2-trichloroethane (respective incidences of 0/10, 0/10, 0/10, and 5/10 in males and 0/10, 3/10, 3/10, and 10/10 in females at concentrations of 0, 15, 40, and 100 ppm) ([WIL Research, 2002](#)). Studies evaluating liver histology in rats did not evaluate serum markers of hepatic function; however, two acute inhalation studies reported significantly elevated levels of serum alanine aminotransferase (ALT) in male rats exposed to 2,080 ppm for 2 hours (increase of 2.4-fold) ([Carlson, 1973](#)) and female mice exposed to 3,750 ppm for up to 1,000 minutes (increase of ≥ 2 -fold) ([Gehring, 1968](#)). No changes in serum aspartate aminotransferase (AST) or hepatic glucose-6-phosphatase levels were observed in male rats exposed up to 2,080 ppm for 2 hours ([Carlson, 1973](#)). No effects on liver weight were observed in rats exposed to 2,080 ppm for 2 hours ([Carlson, 1973](#)), up to 1,527 ppm for 4 hours ([WIL Research, 2001](#)), or up to 100 ppm for 13 weeks ([WIL Research, 2002](#)).

Evidence of hepatic effects of 1,1,2-trichloroethane is available from studies of oral exposures of rats and mice. The most sensitive indicator of acute liver pathology occurred in an acute oral study via gavage dosing in male rats in which elevated serum ALT and AST were observed at 92 mg/kg (NOAEL = 46 mg/kg) in a literature study by Tyson et al. ([Tyson et al., 1983](#)), which is a LOAEL causing acute decreases in motor activity. In a gavage study in female rats, histopathological changes in the liver were observed after a single dose of 667 mg/kg ([Xia and Yu, 1992](#)). Lesions included vacuolar degeneration of hepatocytes and scattered necrosis observed at 12 hours post-exposure, followed by immune cell infiltrates and Kupffer cell proliferation at 24 to 36 hours after dosing (incidence of lesions not reported) ([Xia and Yu, 1992](#)). By 72 hours after dosing, the livers had fully recovered. These changes were associated with elevated serum ALT, sorbitol dehydrogenase (SDH), and glutamate dehydrogenase (GDH) levels, which peaked at levels at least 4-fold higher than control values at 24 to 36 hours post-exposure ([Xia and Yu, 1992](#)). No changes in liver weights or serum ALT levels were observed in male mice following exposure to gavage doses up to and at 38 mg/kg-day for 14 days ([White et al., 1985](#)). Similarly, no non-neoplastic histopathological effects were identified in the livers of rats or mice administered repeated gavage doses up to or at 92 mg/kg-day (rats) or 390 mg/kg-day (mice) in 78-week cancer studies ([NCI, 1978](#)). Both male and female mice in this study exhibited greatly increased incidences of hepatocellular carcinomas up to 89% in female mice at the highest dose ([NCI, 1978](#)); further details on this finding are provided in the cancer section (2.4).

In a 90-day drinking water study in mice, absolute and relative liver weights of females were significantly elevated by 32 and 26%, respectively, at 384 mg/kg-day ([White et al., 1985](#)). Statistically significant clinical chemistry changes in female mice, including increased serum ALT at 384 mg/kg-day and increased AST and alkaline phosphatase (ALP) at or exceeding 3.9 mg/kg-day, were not considered to be adverse (< 2 -fold increase relative to controls) ([White et al., 1985](#)). In male mice in the same 90-day study, absolute liver weights were significantly decreased by 11 to 12% at or exceeding 46 mg/kg-day; however, no changes in relative liver weights were observed and absolute liver weights mirrored decreases observed in body weights and water intake ([White et al., 1985](#)). There were no increases in serum ALT or AST in male mice; although a small (< 2 -fold compared to controls) increase in serum

ALP was observed in males at the highest dose (305 mg/kg-day), the data for this group were considered uninformative due to greatly decreased water consumption ([White et al., 1985](#)). Microscopic examination of the liver was not performed in this study. In a two-generation reproductive toxicity drinking water study no exposure-related increases in liver weight were observed in F0 or F1 adult rats, however in context the study was rated uninformative for dose-response. Estimated doses in the high-dose group ranged from 82.2 to 173 mg/kg-day, with higher exposures (201–230 mg/kg-day) during the first 2 weeks of lactation ([DuPont, 2006](#)). Important metrics of hepatic injury liver histology and serum chemistry were not evaluated in the two-generation study and increased serum AST and ALT were elevated at a lower dose of 92 mg/kg/day in the acute Tyson study in male rats ([1983](#)).

Injection (subcutaneous or intraperitoneal) studies in rats and mice support the finding that the liver is a target of toxicity at some exposure levels. In male mice administered a single s.c. injection of 1,1,2-trichloroethane at 1.2 to 2.9 millimol/kg, observed effects included cytoplasmic vacuolation in the lower-dose groups and central necrosis accompanied by congestion and fibroid necrosis in the higher-dose groups (no further details were provided) ([Plaa et al., 1958](#)). Liver triglycerides were increased in male rats administered single i.p. injections of approximately 700 mg/kg ([Klaassen and Plaa, 1969](#)). Significantly increased serum SDH levels were identified in female rats following single i.p. injections of 50.6 mg/kg ([Lundberg et al., 1986](#)). Hepatic bile flow was not affected in male rats administered single i.p. injections of approximately 400 mg/kg ([Harms et al., 1976](#)). No alterations in liver histology or serum ALT were observed in male rats following a single i.p. injection of 147 mg/kg 1,1,2-trichloroethane ([Charbonneau et al., 1991](#)). 1,1,2-Trichloroethane causes liver tumors in mice in the NCI study and has been reported to be a complete carcinogen having both tumor initiator and tumor promoting activities in the liver after 7 weeks of gavage dosing ([Milman et al., 1988](#)).

Mechanistic and Supporting Evidence

Studies of the mechanisms for 1,1,2-trichloroethane hepatotoxicity are limited, but suggest possible roles for formation of reactive metabolites and induction of oxidative stress. 1,1,2-Trichloroethane-mediated hepatotoxicity (increased serum AST and/or ALT) has been potentiated by pretreatment with acetone, ethanol, or phenobarbital ([MacDonald et al., 1982](#); [Traiger and Plaa, 1974](#); [Carlson, 1973](#); [Klaassen and Plaa, 1966](#)) as cited in ([ATSDR, 2021](#)), compounds that induce liver enzyme production. These findings suggest that the induced enzymes catalyze the formation of reactive metabolites of 1,1,2-trichloroethane that are involved in its hepatotoxicity.

A single study suggested that 1,1,2-trichloroethane increases oxidative stress in the liver. Following a single gavage dose of 1,1,2-trichloroethane at 667 mg/kg in rats, the concentration of free radicals in the liver increased significantly over controls ([Xia and Yu, 1992](#)). 1,1,2-Trichloroethane metabolism has been reported to produce a dichloroethane free radical.

A study of liver microsomes exposed to 1,1,2-trichloroethane suggested the potential for age-related differences in susceptibility to 1,1,2-trichloroethane hepatotoxicity. Hepatic microsomes isolated from aged rats (27 months old) had lower amounts of 1,1,2-trichloroethane covalently bound to proteins and lipids relative to those isolated from younger animals (≤ 11 months old) ([DiRenzo et al., 1982b](#)). These aged animals also had decreased hepatic microsomal CYP450 content and NADPH cytochrome c reductase activity, indicating that covalent binding may have been due to microsomal bioactivation of 1,1,2-trichloroethane to reactive metabolites.

Evidence Integration Summary

No human data are available to evaluate the hepatic effects of 1,1,2-trichloroethane. There is moderate evidence for hepatic effects for 1,1,2-trichloroethane based on histopathological lesions and serum

chemistry changes reported in high-quality acute and subchronic inhalation studies in rodents, with support from medium-quality acute gavage and injection studies in rodents. There is limited evidence for treatment-related effects of 1,1,2-trichloroethane on liver weight in a 90-day oral study ([White et al., 1985](#)) and induce abnormal liver foci after 7 weeks of dosing ([Milman et al., 1988](#)). Some mechanistic data suggest that hepatic effects may be mediated by reactive metabolites and/or involve oxidative stress. One study suggests the potential for age-related differences in susceptibility to 1,1,2-trichloroethane hepatotoxicity, but the data are limited.

2.3.1.1.5 Reproductive/Developmental Toxicity

Human Evidence

A single study of sufficient quality was identified through systematic review and previous assessments that evaluated reproductive or developmental effects of 1,1,2-trichloroethane in exposed humans ([ATSDR, 2021](#); [U.S. EPA, 2011a](#)). A study of maternal proximity to chemical emissions sources for 14 chlorinated solvents and birth outcomes showed increased odds of spina bifida in offspring in the “low” intensity of exposure to 1,1,2-trichloroethane risk group compared with no intensity of exposure to 1,1,2-trichloroethane risk, but this result was not consistent in the “medium” or “high” intensity of exposure risk groups ([Brender et al., 2014](#)). When comparing mothers with exposure risk to 1,1,2-trichloroethane greater than zero to those mothers with no exposure risk, the Brender et al. (2014) study found increased odds of neural tube defects, spina bifida, and septal heart defects. The Brender et al. (2014) study also found increased odds of isolated cleft palate in the “high” intensity of exposure risk group compared with the no exposure group, and increased odds of septal heart defects in offspring in the “medium” intensity of exposure group compared with no exposure, but not in the “low” or “high” groups.

Laboratory Animal Evidence

No animal studies were identified that caused functional reproductive or developmental hazards.

Mechanistic and Supporting Evidence

No studies related to mechanisms of reproductive or developmental effects of 1,1,2-trichloroethane were located.

Evidence Integration Summary

No animal data are available to evaluate the reproductive or developmental effects of 1,1,2-trichloroethane. The evidence for reproductive or developmental effects of 1,1,2-trichloroethane from human studies is indeterminate based on a single human study evaluating odds of adverse birth outcomes and risk of exposure estimated from maternal proximity to chemical emissions sources ([Brender et al., 2014](#)).

2.3.1.2 Non-Cancer Dose-Response Assessment

The endpoints and hazards utilized for POD selection for 1,1,2-trichloroethane are described in Section 2.3.1.1. The 1,1,2-trichloroethane human health toxicology database included high-quality literature studies and reliable guideline studies that provide confidence in the endpoint and POD selection. Studies were analyzed by BMD analyze as feasible and dosimetric modeling was performed to calculate (HED and HEC for refinement to reduce the UF_A value from the default of 10 to 3 (*i.e.*, inter-species modeling by body weight ³/₄-scaling for oral data and regional gas dosimetric ratio or RGDR analysis for inhalation data).

2.3.1.3 Selection of Studies and Endpoints for Non-Cancer Dose-Response Analysis

For non-cancer PODs for estimating risks for acute, intermediate, and chronic exposure scenarios, EPA reviewed the suite of human and animal studies and individual adverse health effects for which 1,1,2-trichloroethane is likely to cause effects. EPA selected studies and relevant health effects for POD selection based on study quality, exposure duration, dose selection, metabolism, relevance to the chemical, endpoint sensitivity and uncertainties.

The following sections provide comparisons of the above attributes for studies and hazard outcomes with associated health effects for each exposure duration (acute, intermediate, and chronic) with study details listed in Table 2-6 through Table 2-16.

2.3.1.3.1 Non-Cancer PODs for Acute Exposures

The toxicology database for acute oral, dermal and inhalation exposures for 1,1,2-trichloroethane contains high quality literature studies and guideline studies with endpoints including neurotoxicity, upper respiratory tract tissue damage, liver pathology and dermal irritation (GHS category 2, H315 dermal irritant). These endpoints are described in Table 2-7 and Table 2-8 for acute oral studies and Table 2-9 for acute inhalation studies.

Acute Oral and Dermal PODs for 1,1,2-Trichloroethane

Table 2-6 below lists the complete acute oral and dermal toxicology database for 1,1,2-trichloroethane for POD and endpoint selection, sorted by ascending LOAEL values with critical studies in bold font and shaded gray.

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Table 2-6. Acute Oral and Dermal Toxicology Study Profiles for 1,1,2-Trichloroethane^a

Study	Species Sex	Doses	Acute Exposure Duration	Endpoint Target Organ	NOAEL mg/kg	LOAEL mg/kg	Comment	Study Data Quality Score from Systematic Review
Dow Chemical (1960)	Rat Female	Gavage 15.8, 126, 252 mg/kg in corn oil	1 day	Gross pathology		15.8		Uninformative
WIL Research (2004) (Guideline acute neurotoxicity (ACN) study OECD 424)	Crl:CD (SD)IGS BR rat Both	Gavage 0, 55, 95, 200 mg/kg	1 day	Neurotoxicity	55.0	95.0		High
Tyson et al. (1983)	SD Rats Male	Gavage 0, 46, 92, 228 mg/kg	1 day	Increased serum ALT and AST	46.0	92.0	Study with POD similar to ACN study (WIL Research, 2004)	Medium
White et al. (1985)	CD-1 mice Both	Gavage 200 to 600 mg/kg in 7 doses including 200, 450, 500, and 600 mg/kg and other doses were not specified	24 hours	Sedation		450.0	LD50 is 378 mg/kg in males and 491 mg/kg in females	Low
Xia and Yu (1992)	Wistar rat Female	Gavage 5 mmol/kg or 667 mg/kg	1 day	Increased serum SDH, GPT, and GDH with liver necrosis, liver		667.0		Medium
Moody et al. (1981)	SD rat Male	Gavage 0, 1,080 mg/kg	1 day	Microsomal changes		1,080.0		Medium
Dow Chemical (1956)	Rabbit Not Specified	Dermal 2,520, 5,000, 10,000, 20,000 mg/kg	24 hours	Skin burning, scabs and scarring		2,520.0	LD50 is 10,000 mg/kg	Low irritation Medium mortality
Kronevi et al. (1977)	Guinea pig Not Specified	Dermal 1 mL or 3,600 mg/kg	12 hours	Skin edema and vesicles; Reduced liver glycogen		3,600.0		Uninformative
Dow Chemical (1956)	Rabbit Not specified	Dermal 3,980, 7,950, 15, 800 mg/kg	24 hours	Skin edema		3,980.0	LD50 is 10,000 mg/kg	Low irritation Medium mortality
Dow Chemical (1960)	Rabbit Not specified	Dermal doses not specified	Not clear					Uninformative

Study	Species Sex	Doses	Acute Exposure Duration	Endpoint Target Organ	NOAEL mg/kg	LOAEL mg/kg	Comment	Study Data Quality Score from Systematic Review
Dow Chemical (1960)	Rabbit Not specified	Dermal 0.5 and 1 g/kg	1 day	No deaths occurred	1,000.0			Uninformative
Milman et al. (1988) (Tumor initiator mechanistic study)	Osborne- Mendel rats Male	Gavage 0, 70 mg/kg		Tumor initiation not statistically significant with a single dose	70.0			High
Kronevi et al. (1981)	Guinea pig Not specified	Dermal 1 mL	1–16 hours					Uninformative
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GPT = glutamic pyruvic transaminase; GDH = glutamate dehydrogenase; LD50 = lethal dose at which 50% of test organisms die; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; SDH = sorbitol dehydrogenase ^a Bolded and shaded entries indicate critical studies.								

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For the acute oral and dermal scenarios, the acute oral neurotoxicity study in rats by WIL Research ([WIL Research, 2004](#)) was selected for POD utilization having a NOAEL of 55 mg/kg (LOAEL = 95 mg/kg). It was selected because it is an OECD 424 guideline study with a high quality rating and this endpoint and POD is protective for all other non-cancer acute hazards identified via the oral and dermal routes. Large acute decreases in motor activity, by 24 to 76%, were measured with statistical significance. However, due to the shape of the dose-response curve BMD analysis was not successful (*i.e.*, plateau of responses) and a NOAEL/LOAEL approach was applied that has more uncertainty than a BMD approach. Decreased motor activity was not reported in an uninformative subchronic neurotoxicity study in rats dosed with an *ad libitum* drinking water at similar doses due to confounding factors by decreased water consumption in high-dose males and females ([Dow Chemical, 2005](#)). However, the acute POD ([WIL Research, 2004](#)) was based on the endpoint of greatly decreased acute motor activity (quantified by interruptions to ambulatory and fine motor skills), which matches the ADME profile and pharmacokinetics of the chemical and oral data described in ([WIL Research, 2004](#)).

PBPK model predictions indicate that maximum blood concentration is reached 46 minutes after gavage dosing, after which point it declines rapidly for about 3 hours post-dose when elimination phase slows—corresponding to the rapid transitory effects on motor activity seen in rats. Motor activity should be measured at the time of peak effect that matches the pharmacokinetic information for consistent results. Gait impairment occurred for the LOAEL of 95 mg/kg as well ($p < 0.05$); however, no significant effects were found after 7 days. Additionally, for consistency neurotoxicity is a common hazard for solvents such as 1,2-dichloroethane ([Zhong et al., 2022](#)). In support, other studies in the 1,1,2-trichloroethane toxicology database also indicated neurotoxicity (*i.e.*, Niklasson (1993)) and as described previously. The $NOAEL_{HED} = NOAEL \times \text{dosimetric adjustment factor (DAF)}$, the DAF is 0.229 based on the body weight $^{3/4}$ -conversion and animal body weight data in the study. These are presented in Table 2-7.

The acute oral literature study by Tyson ([Tyson et al., 1983](#)) had a similar NOAEL of 46 mg/kg (LOAEL = 92 mg/kg) based on increased serum ALT and AST transaminase levels. As shown, multiple studies were uninformative for POD selection with details in the systematic review files, based on non-sensitive endpoints such as death or had higher POD values than the Tyson ([Tyson et al., 1983](#)) and WIL Research ([WIL Research, 2004](#)) studies.

Table 2-7. Acute Oral and Dermal PODs for 1,1,2-Trichloroethane

Hazard Effect	Study POD	NOAEL HED	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Conclusion
Neurotoxicity, Decreased acute motor activity in rats	LOAEL = 95 mg/kg NOAEL = 55 mg/kg	NOAEL HED =12.6 mg/kg	UF _A = 3 UF _H = 10	30	(WIL Research, 2004) Sprague-Dawley Rats Acute Oral, Acute Neurotoxicity Guideline Study OECD 424	Oral – Robust
						Dermal – Moderate-to-Robust
HED = human equivalent dose; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; POD = point of departure; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor						

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Acute Inhalation Scenarios PODs for 1,1,2-Trichloroethane

The acute inhalation study by WIL Research (2001) was selected for the acute inhalation POD for 1,1,2-trichloroethane based on damage to the innervated olfactory epithelium in the nasal tissue with a LOAEC value of 58 ppm (316 mg/m³, no NOAEC). These are presented in Table 2-8. It was selected because it was performed in a guideline study with a high-quality rating. This study provides a route specific and duration specific endpoint relevant to solvents that is the best available science. Other evidence in the 1,1,2-trichloroethane toxicology database also indicated hazards to the upper respiratory tract such as the subchronic inhalation study by (WIL Research, 2002). The 4-hour WIL Research study (2001) has a duration that better matches worker exposures than the 1-hour (Niklasson et al., 1993) study.

Table 2-8. Acute Inhalation Scenarios PODs for 1,1,2-Trichloroethane

Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Conclusion
Olfactory epithelium necrosis	LOAEC = 316 mg/m ³ (58 ppm) in 4 hours	LOAECadj = 52.7 mg/m ³ (9.7 ppm) LOAECadj HEC = 6.1 mg/m ³ (1.1 ppm)	UF _A = 3 UF _H = 10 UF _L = 3	100	(WIL Research, 2001) F-344 Rats 4 hours, Whole body Inhalation, TSCA 799.9135 Guideline study High systematic review score	Robust
UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; Acute Scenario: Inhalation study is 4 hours in 1 24-hour day. Acute continuous is 24 hours in 1 day. POD Continuous = Study POD × (4 hours per day/24 hours per day); POD Continuous HEC = POD Continuous × RGDR; RGDR = 0.115 based on animal weight data in study. The confidence conclusion is based on the weight of scientific evidence for evidence integration.						

Table 2-9 below lists the complete acute inhalation toxicology database for 1,1,2-trichloroethane for POD and endpoint selection, sorted by ascending LOAEC values with critical studies in bold font and shaded gray. As shown, multiple studies had uninformative or low ratings for POD selection with details in the systematic review files, based on non-sensitive endpoints such as death or had much higher POD values than the WIL Research study (WIL Research, 2001).

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Table 2-9. Acute Inhalation Toxicology Studies for 1,1,2-Trichloroethane^a

Study	Species Sex	Doses	Exposure Duration	Target Organ	Endpoint	NOAEC mg/m ³	LOAEC mg/m ³	Comment	Systematic Review Rating
WIL Research (2001)	Fischer 344 rats Both	Inhalation vapor 0, 58, 181, 1,527 ppm	4 hours	Upper respiratory tract	Olfactory tissue necrosis		316.00	LOAEC is 316 mg/m ³ or 58 ppm	High
Niklasson et al. (1993)	Pigmented rats Both	Inhalation vapor 0, 1,900, 5,700, 7,500, 9,400 mg/m ³	1 hour		Neurotox, optokinetic test		1,900.00		High
Hobara et al. (1984)	Dogs Both	Inhalation vapor 0, 200, 500, 700, 1,000, 1,500 ppm	1 hour		Decreased WBC, Immune	1,092.00	2,730.00	NOAEC is 1102 mg/m ³ or 200 ppm LOAEC is 500 ppm	Uninformative
Mellon Institute (1946)	Rat Not specified	Inhalation vapor 500 ppm	4 hours		Death		2,756.40	1 of 6 rats died at 500 ppm	Low
Hobara et al. (1984)	Dogs Both	Inhalation vapor 0, 700 ppm	4 hours		Decreased WBC, Immune		3,859.00		Uninformative
WIL Research (2001)	Fischer 344 rat Female	Inhalation vapor 0, 45, 177, 840 ppm (0, 248, 976 or 4,631 mg/m ³)	4 hours		Neurotox, BW, BALF protein	976.00	4,631.00		High
WIL Research (2001)	Fischer 344 rats Male	Inhalation vapor 0, 60, 205, 1,474 ppm (0, 330, 1,130 or 8,159 mg/m ³)	4 hours		Neurotox, BW, BALF protein	1,130.00	8,159.00	NOAEC is 1,130 mg/m ³ or 205 ppm. LOAEC is 1,474 ppm.	High
Carlson (1973)	Albino rat Male	Inhalation vapor 0, 890, 2,080 ppm (0, 4,906 or 11,434 mg/m ³)	2 hours		Serum ALT	4,096.00	11,434.00		Medium
Gehring (1968)	Swiss Webster mice Female	Inhalation vapor 0, 3,750 ppm	17 hours		Serum ALT, anesthesia		20,673.00		Neurological/ Behavioral: Low, Hepatic/Liver: Medium, Mortality: Medium
Dow Chemical (1988)	SD rats Male	Inhalation aerosol 34,500 mg/m ³	4 hours		Gait, acoustic startle and activity changes		34,500.00	LC50 > 34,500 mg/m ³	Medium

Study	Species Sex	Doses	Exposure Duration	Target Organ	Endpoint	NOAEC mg/m ³	LOAEC mg/m ³	Comment	Systematic Review Rating
Gehring (1968)	Swiss Webster mice Female	Inhalation vapor 0, 13,500 ppm	17 hours		Serum ALT, anesthesia		74,423.00		Neurological/ Behavioral: Low, Hepatic/Liver: Medium, Mortality: Medium
Dow Chemical (1988)	Fischer 344 rats Both	Inhalation vapor 15,523, 18,425, 21,053 ppm	4 hours		Death			LC50 is 99,223 mg/m ³ or 18,000 ppm	Medium
Dow Chemical (1988)	Fischer 344 rats Male	Inhalation aerosol 16,200, 17,000, 17,200, 19,100, 19,300, 19,700, 36,700 mg/m ³	4 hours		Death			LC50 > 36,700 mg/m ³	Medium
Dow Chemical (1960)	Not specified	Inhalation vapor 30, 500 ppm	7 hours		Death			LC50 is 500 ppm	Uninformative
Stadler and Kennedy (1996)	Swiss Webster mice Male	Inhalation vapor 0, 1,000 ppm	1 hour		Respiratory rate	5,500.00			Uninformative
Moser and Balster (1986)	CD-1 mice Male	Inhalation vapor to 1,1,1-trichloroethane at 0, 1,800, 3,600, 7,200, 10,800 ppm	30 minutes			20,000.00		NOAEC is 3,600 ppm or 20,000 mg/m ³	Uninformative
LC50 = lethal concentration at which 50% of test organisms die; LOAEC = lowest-observed-adverse-effect concentration; NOAEC = no-observed-adverse-effect concentration; ppm = parts per million ^a Bolded and shaded entries indicate critical study									

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2.3.1.3.2 Non-Cancer PODs for Intermediate Exposures

The toxicology database for intermediate oral, dermal and inhalation exposures for 1,1,2-trichloroethane contains high quality studies with endpoints including neurotoxicity, immunotoxicity, upper respiratory tract tissue damage, reproductive toxicity, and death.

Intermediate Oral and Dermal POD Selection for 1,1,2-Trichloroethane

The subchronic Sanders (90-day oral drinking water dosing) study ([Sanders et al., 1985](#)) was selected for the intermediate oral and dermal scenarios POD based on immunosuppression in mice NOAEL at 3.9 mg/kg/day (LOAEL = 44 mg/kg/day) and is presented in Table 2-10. There was a large decrease of the immune response (by over 40% consistently in both sexes in 90 days of exposure) as measured by the specific hemagglutination titer assay which is one method for measuring humoral immunity via the T-cell dependent antigen response (TDAR) utilizing sheep red blood cells as the antigen. The TDAR was also shown to be decreased by the complementary TDAR method by 31% in male mice with a shorter 14-day dosing via gavage, utilizing the antibody forming cell assay. It should be noted that at least 28 days are typically necessary to characterize sensitive results. The 90-day drinking water study was conducted over 28 days and suppressed the immune response by 40 to 47%. The 14-day gavage study was less than 28 days and still suppressed the immune system but by a lesser amount of 31%. This study received a high systematic review ratings. Additionally, the ([Sanders et al., 1985](#)) study included both the antibody forming cells assay and the hemagglutination titer assay for measuring TDAR. These results from the ([Sanders et al., 1985](#)) are presented in Table 2-11. A White study via gavage dosing ([White et al., 1985](#)) with a medium data quality rating has similar findings with a NOAEL at 3.8 mg/kg/day (LOAEL = 38 mg/kg/day) based on changes in thymus (an immune system organ), brain, testes weights and a 31% decrease in the antibody forming cells in mice with 14 days of exposure.

Multiple studies in the 1,1,2-trichloroethane toxicology database indicated hazards to the immune system (*i.e.*, Hobara ([1984](#)), White ([1985](#))), as described previously (thymus hazard, decreased white blood cell counts), plus a similar solvent trans-dichloroethylene also produced immunotoxicity utilized for POD derivation ([ATSDR, 2025](#)). The Sanders study ([Sanders et al., 1985](#)) provides the best available science for POD selection and based on a weight of scientific evidence of immunotoxicity across studies and methods in the database. The data were not amenable to BMD modeling due to the steepness of the dose-response curve and lack of precise animal numbers, so the NOAEL/LOAEL approach was utilized ([ATSDR, 2021](#)). The NOAEL_{HED} NOAEL dosimetric adjustment factor or DAF, the DAF is 0.133 based on the body weight ³/₄-conversion and animal body weight data in the study.

Table 2-10. Intermediate Oral and Dermal POD Selection for 1,1,2-Trichloroethane

Hazard Effect	Study POD	NOAEL HED	Uncertainty Factors	Total Uncertainty Factors	Reference, Species, Duration, Route	Confidence Conclusion
Immunotoxicity, Decreased hemagglutination titers in mice	LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10	30	(Sanders et al., 1985) CD-1 Mice 90 days Oral High systematic review rating	Oral – Robust
						Dermal – Moderate-to-Robust
HED = human equivalent dose; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; POD = point of departure; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor;						

1873 Table 2-11 lists the complete intermediate oral and dermal toxicology database for 1,1,2-trichloroethane
1874 for POD and endpoint selection, sorted by ascending LOAEL values with critical studies in bolded and
1875 shaded font. Multiple studies had uninformative ratings for POD selection with details in the systematic
1876 review files, based on non-sensitive endpoints such as death or had much higher POD values than the
1877 Sanders and colleagues study ([Sanders et al., 1985](#)).

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Table 2-11. Intermediate Oral and Dermal Toxicity Studies Profile for 1,1,2-Trichloroethane^a

Study	Species Sex	Doses Duration	Endpoint(s)	NOAEL mg/kg/day	LOAEL mg/kg/day	Finding	Systematic Review Rating
(Al-Griw et al., 2016)	Swiss mice Not reported	IP 0, 0.1, 0.4 mg/kg-bw/day 3 weeks	Liver Apoptosis		0.10		Medium
(White et al., 1985)	CD-1 Mice Male	Gavage 0, 3.8, 38 mg/kg-bw/day 14 days	Brain, thymus, testes weight	3.80	38.00	Study with PODs similar to and supporting the Sanders immunotoxicity study	Medium
(Sanders et al., 1985)	CD-1 Mice Female	Drinking water 0, 3.9, 44, 384 mg/ kg-bw/day 90 days	Immunosuppression Over 40% decrease in T-cell dependent antigen response (TDAR) by the hemagglutination assay in 90 days of dosing	3.9	44.0	TDAR by hemagglutination assay	High
(Sanders et al., 1985)	Male	Gavage 0, 3.8, 38 mg/kg-bw/day 14 days	Immunosuppression 31% decrease in antibody forming cells (AFC) assay in T-cell dependent antigen response (TDAR) in 14 days of dosing	3.8	38.0	TDAR by AFC method is widely utilized	High
(Sanders et al., 1985)	CD-1 Mice Male	Drinking water 0, 4.4, 46, 305 mg/kg-bw/day 90 days	Immunosuppression TDAR by hemagglutination assay	4.40	46.00		High
(Wahlberg, 1984a)	Rabbit, Sex Not reported	Dermal 0, 48 mg/kg/day 10 days	Dermal irritation		48.00		Medium
(Milman et al., 1988) (Tumor promoter study)	Osborne-Mendel rats Male	Gavage 0, 70 mg/kg-bw/day	Tumor promotion		70.00		High
(Wahlberg, 1984a)	Guinea pig Not reported	Dermal 0, 238 mg/kg/day 10 days	Dermal erythma, edema, fissuring, scaling		238.00		Uninformative
(Plaa and Larson, 1965)	Swiss mice Male	IP 0, 0.2, 0.4 mL/kg 5 days	Kidney		288.00		Uninformative

Study	Species Sex	Doses Duration	Endpoint(s)	NOAEL mg/kg/day	LOAEL mg/kg/day	Finding	Systematic Review Rating
(White et al., 1985)	CD-1 Mice Both	Drinking water 0, 4.4, 46, and 305 mg/kg-bw/day 14 days	BW, drinking water consumption in males	46.00	305.00		Medium
(Seidenberg et al., 1986) (Developmental study)	ICR Mice Female	Gavage 0, 350 mg/kg/day GD 8–12	Mortality	N/A	350.00		Medium
(George et al., 1989) (Reproduction study)	SD Rats Both	Drinking water 0, 0, 3, 10, 30 ppm Tested 1,1,1-trichloroethane Subchronic	Parental	2.60	N/A		High
(George et al., 1989) (Reproduction study)	SD Rats Both	Drinking water 0, 0, 3, 10, 30 ppm Tested 1,1,1-trichloroethane Subchronic	Reproduction	3.50			High
(George et al., 1989) (Reproduction study)	SD Rats Both	Drinking water 0, 0, 3, 10, 30 ppm Tested 1,1,1-trichloroethane Subchronic	Developmental	5.90			High
(Sanders et al., 1985)	CD-1 Mice Male	Gavage 0, 3.8, 38 mg/kg-bw/ day 14 days	Immunosuppression	38.00			High
(WIL Research, 2005) (Developmental)	Crl:CD (SD) IGS BR Rats Female	Drinking water 0, 17, 48, 111 mg/kg-bw/day GD6–20		111.00		Several endpoints considered unacceptable	Low
(Dow Chemical, 2005) (Subchronic neurotoxicity)	F344/DUCRL Rats Male	Drinking water 0, 12.1, 37.6, 86 mg/kg-bw/day 13 weeks	Neurotoxicity	86.00			Uninformative
GD = gestation days; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level ^a Bolded and shaded gray entries indicate critical studies							

Intermediate Inhalation Scenarios PODs

The subchronic inhalation study by WIL Research (2002) was selected for the intermediate inhalation POD for 1,1,2-trichloroethane based on lesions to the innervated olfactory epithelium in the nasal tissue with a study BMC_{10} of 31.15 mg/m^3 ($BMCL_{10} = 22.11 \text{ mg/m}^3$). These are presented in Table 2-12. The continuous $BMCL_{10 \text{ HEC}}$ of 0.62 mg/m^3 is based on body weight data in the study used to calculate the RGDR value. It was selected because it was performed in a guideline study with a high-quality rating and this endpoint and POD is protective for all other non-cancer intermediate hazards identified via the inhalation route. The BMD modeling for this study and graphs are listed in 3.5Appendix B. Other evidence in the 1,1,2-trichloroethane toxicology database, also indicated hazards to the upper respiratory tract such as the acute inhalation study by (WIL Research, 2002).

Table 2-12. Intermediate Inhalation Scenarios PODs

Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Conclusion
Lesions in the olfactory epithelium	$BMC_{10} = 31.15 \text{ mg/m}^3$ (5.71 ppm) $BMCL_{10} = 22.11 \text{ mg/m}^3$ (4.05 ppm)	$BMCL_{10} = 3.95 \text{ mg/m}^3$ (0.72 ppm) $BMCL_{10 \text{ HEC}} = 0.62 \text{ mg/m}^3$ (0.11 ppm)	$UF_A = 3$ $UF_H = 10$	30	(WIL Research, 2002), F-344 Rats 13 weeks, 6 hours/day, 5 days/week, Whole body Inhalation, TSCA 799.9346 Guideline study, High systematic review rating	Robust
BMC = benchmark concentration; BMCL = benchmark concentration lower bound; ppm = parts per million; HEC = human equivalent concentration; POD = point of departure; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor Intermediate and Chronic Scenarios: Inhalation study is 6 hours per day and 5 days per week; POD is 168 hours per week; Intermediate and Chronic POD = Study POD $\times$ (6 hours per day/24 hours per day) $\times$ (5 days per week/7 days per week); POD Continuous HEC = POD Continuous $\times$ RGDR; RGDR = 0.157 based on animal weight data in study						

Table 2-13 lists the complete intermediate inhalation toxicology database for 1,1,2-trichloroethane for POD and endpoint selection, sorted by ascending LOAEC values with critical studies in bolded and shaded font. As shown, multiple studies had uninformative ratings for POD selection with details in the systematic review files, based on non-sensitive endpoints or had much higher POD values than the WIL Research (WIL Research, 2002) study.

1898 **Table 2-13. Intermediate Inhalation Toxicity Studies Profile for 1,1,2-Trichloroethane^a**

Study	Species Sex	Doses Exposure Duration	Endpoint Target Organ Endpoint	NOAEC mg/m ³	LOAEC mg/m ³	Finding	Data Quality Score
(WIL Research, 2002)	Fischer 344 rats Both	Inhalation 0, 15, 40, 100 ppm 13 weeks	Olfactory tissue lesions Upper respiratory tract		81.9	BMCL10 HEC = 0.11 ppm (0.62 mg/m ³), LOAEC is 15 ppm or 81.9 mg/m ³	High Guideline study TSCA 799.9346
(Kyrklund and Haglid, 1990)	SD Rat Male	Inhalation 0, 1,200 ppm 30 days continuously	Brain alterations Brain		6,547		Medium
(Mellon Institute, 1947)	Albino rat Both	Inhalation 0, 84 ppm 75 days		N/A	N/A	Lung infections limited value of this study	Uninformative
(Mellon Institute, 1947)	Dog	Inhalation 0, 84 ppm 75 days	Decreased BW gain	N/A	N/A		Uninformative
BMCL = benchmark concentration lower bound; BW = body weight; ppm = parts per million; HEC = human equivalent concentration; LOAEC = lowest observed adverse effect concentration; NOAEC = no observed adverse effect concentration; TSCA = Toxic Substance Control Act ^a Bolded and shaded gray entries indicate critical studies.							

1899 **2.3.1.3.3 Non-Cancer PODs for Chronic Exposures**

1900 ***Chronic Non-Cancer Oral and Dermal POD Selection for 1,1,2-Trichloroethane***

1901 The toxicology database for chronic oral and dermal exposures for 1,1,2-trichloroethane contains
 1902 medium-quality studies with endpoints including body weight changes. However, the high-quality
 1903 subchronic duration ([Sanders et al., 1985](#)) study was selected for the chronic oral and dermal scenarios
 1904 POD based on immunosuppression in mice NOAEL at 3.9 mg/kg/day (LOAEL = 44 mg/kg/day). These
 1905 are presented in Table 2-14. There was consistently a large 40% or greater decrease in the immune
 1906 response at the LOAEL value in both male and female mice. The White study ([White et al., 1985](#)) has
 1907 similar findings with a similar NOAEL at 3.8 mg/kg/day (LOAEL = 38 mg/kg/day) based on changes in
 1908 thymus (critical to the immune system), brain, and testes weight. It was selected because it was
 1909 performed in a study with a high-quality rating and this endpoint and POD are protective for all other
 1910 non-cancer hazards identified via the oral and dermal routes. Multiple studies in the 1,1,2-
 1911 trichloroethane toxicology database indicated hazards to the immune system (*i.e.*, ([White et al., 1985](#);
 1912 [Hobara et al., 1984](#))) as described previously. The Sanders study ([Sanders et al., 1985](#)) provides the best
 1913 available science for POD selection based on a weight of scientific evidence review of immunotoxicity
 1914 in the database. Conversely, while there is uncertainty in using a subchronic study, the chronic studies
 1915 provided cancer endpoints or were uninformative for dose-response; therefore, a high-quality subchronic
 1916 study was selected for the chronic oral and dermal scenarios with a UFs to provide confidence that the
 1917 subchronic POD is protective for chronic durations.

1918 **Table 2-14. Chronic Non-Cancer Oral and Dermal POD Selection for 1,1,2-Trichloroethane**

Hazard Effect	Study POD	NOAEL HED	Uncertainty Factors	Total Uncertainty Factors	Reference, Species, Duration, Route	Confidence Conclusion
Immunotoxicity, Decreased hemagglutination titers in mice	LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10 UF _S = 10	300	(Sanders et al., 1985) CD-1 Mice 90 days Oral, High systematic review score	Oral – Moderate-to- Robust
						Dermal – Moderate
HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse effect level; POD = point of departure; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; UF _S = subchronic-to-chronic uncertainty factor						

1919
1920 Table 2-15 lists the complete chronic oral and dermal toxicology database for 1,1,2-trichloroethane for
1921 POD and endpoint selection, sorted by ascending LOAEL values with critical studies in bold and shaded
1922 font. As shown, multiple studies had uninformative ratings for POD selection with details in the
1923 systematic review files, had inappropriate dosing scenarios (*i.e.*, injection) or had much higher POD
1924 values than the intermediate duration Sanders (Sanders et al., 1985) study.

1925

Table 2-15. Chronic Oral and Dermal Non-Cancer Toxicology Studies Profiles for 1,1,2-Trichloroethane

Study	Species Sex	Doses	Exposure Duration	Target Organ	Endpoint	NOAEL mg/kg/day	LOAEL mg/kg/day	Finding	Systematic Review Rating
(DuPont, 2006) (Reproduction study)	CD(SD)IGS BR Rats Both	Drinking water 0, 170, 570, 1350 ppm (0, 13.1, 40.6, and 82.2 mg/kg/day for P1 males during premating)	>91 days	Systemic	Parental BW, water consumption, food consumption, Pup BW	40.60	82.2	Nutritional, Developmental	Uninformative
(NCI, 1978) (Cancer study)	B6C3F1 Mice Both	Gavage 0, 0, 195, 390 mg/ kg-bw/day for 5 days/week	78 weeks	Liver, adrenal gland	Tumors	0	195.00	Cancer findings for OSF calculations. Lowest dose tested is 195 mg/kg/day so not a sensitive study for non-cancer endpoints with a non-cancer NOAEL of 390 mg/kg/day. Study did not evaluate important non-cancer endpoints like neurotoxicity or immunotoxicity	Medium, liver tumor dose- response had a high correlation coefficient of 0.99
(Norpoth et al., 1988)	SD Rats Both	Subcutaneous injection of 15.37 or 46.77 µmol once per week	104 weeks			None	None	No POD established	Uninformative
(NCI, 1978) (Cancer study)	Osborne Mendel Rats Both	Gavage 0, 0, 46, 92 mg/kg bw/day for 5 days/week	78 weeks			None	None	No POD established for cancer	Medium, mortality in control groups
BW = body weight; NOAEL = no-observed-adverse-effect level; OSF = oral slope factor; POD = point of departure									

1926

Chronic Inhalation Scenarios PODs for 1,1,2-Trichloroethane

The subchronic inhalation study by ([WIL Research, 2002](#)) was selected for the chronic inhalation POD for 1,1,2-trichloroethane based on lesions to the innervated olfactory epithelium in the nasal tissue with a BMC₁₀ of 31.15 mg/m³ (BMCL₁₀ = 22.11 mg/m³). These results are presented in Table 2-16. The continuous BMCL₁₀ HEC of 0.62 mg/m³ is based on body weight data in the study to calculate the RGDR value. It was selected because it was performed in a guideline study with a high-quality rating. Other evidence in the 1,1,2-trichloroethane toxicology database also indicated hazards to the upper respiratory tract such as the acute inhalation study by ([WIL Research, 2002](#)). Thus, this study is the best available science for POD selection based on a weight of scientific evidence evaluation. There are no chronic 1,1,2-trichloroethane inhalation studies available for POD selection for the chronic inhalation scenario, so a high-quality subchronic study was selected. Because the inhalation endpoint is a portal of entry effect, it was not appropriate to utilize the PBPK model to extrapolate a POD from chronic oral data.

Table 2-16. Chronic Inhalation Non-Cancer Scenarios PODs for 1,1,2-Trichloroethane

Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Conclusion
Lesions in the olfactory epithelium	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm) BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm) BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm)	UF _A = 3 UF _H = 10 UF _S = 10	300	(WIL Research, 2002), F-344 Rats 13 weeks, 6 hours/day, 5 days/week, Whole body Inhalation, TSCA 799.9346 Guideline Study, High systematic review rating	Moderate-to-Robust
BMC = benchmark concentration; BMCL = benchmark concentration lower bound; TSCA = Toxic Substances Control Act; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _S = subchronic-to-chronic uncertainty factor Intermediate and Chronic Scenarios: Inhalation study is 6 hours per day and 5 days per week; POD is 168 hours per week; Intermediate and Chronic POD POD = Study POD × (6 hours per day/24 hours per day × (5 days per week/7 days per week)); POD HEC = POD Continuous × RGDR; RGDR = 0.157 based on animal weight data in study						

There are no chronic 1,1,2-trichloroethane inhalation studies available for listing the chronic inhalation toxicology profile.

2.3.1.4 Dose-Response Derivation for Non-Cancer Hazard Values

The animal study PODs were analyzed by BMD analysis as feasible to refine the values from the NOAEL/NOAEC and LOAEL/LOAEC approach. The studies analyzed by BMD software are listed in Appendix B and studies not listed were unable to be modeled by the BMD software, were uninformative for dose-response, or their POD values were very high as not to be human health protective relative to the studies selected. For oral and dermal routes, the PODs were scaled by the body weight (³/₄) methodology for dosimetric calculation of the HED values utilizing the animal body weights in the study (not default animal body weights) as compared to the human body weight of 80 kg. For inhalation route, the PODs were analyzed by the regional gas dosimetric ratio (RGDR) methodology to calculate the HEC values. The animal body weights from the study are considered the best available science for the RGDR and POD derivations, since default animal body weights can deviate from the empirical data. The PODs were duration adjusted from the animal study values to calculate the HED and HEC values for the general population (continuous adjusted basis) in which case the UF_A value was reduced from the default value of 10 to the refined value of 3. For inhalation scenarios, Haber's Law ([Haber, 1924](#)) was

applied to calculate the duration adjusted POD based on the animal study duration relative to the general population exposure duration specific to each exposure scenario (acute, intermediate, chronic), where the adjusted POD is inversely proportional to the relative exposure duration. The PBPK model was not utilized for converting non-cancer oral data to the inhalation route since there exists a high-quality inhalation study based on portal of entry effects, which are not possible to model from oral data.

As described in Section 2.3.1.3, EPA identified the best available studies for 1,1,2-trichloroethane for quantitative dose-response analysis. The sections below describe the steps used to derive the hazard values used to calculate risks for 1,1,2-trichloroethane.

2.3.1.4.1 Duration, Dosimetric, and Unit Adjustments

Duration, Dosimetric, and Unit Adjustments for Inhalation Hazard Values

Inhalation PODs were adjusted for duration according to Haber's Law for the general population (continuous basis) for each specific scenario (acute, intermediate, chronic). The RGDR analysis was also performed to allow calculation of the HEC values.

Unit Conversion

It is often necessary to convert between ppm and mg/m³ due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all inhalation hazard values in both units. The following equations presents the conversion of the HEC from mg/m³ to ppm (Equation 2-1) and the HEC to a HED (Equation 2-2).

Equation 2-1. Converting ppm to mg/m³

$$HEC \text{ (mg/m}^3\text{)} = HEC \text{ (ppm)} \times \text{Molecular Weight}/24.45^1$$

Equation 2-2. Converting HEC to HED

$$HEC \text{ (mg/kg)} = HEC \text{ (mg/m}^3\text{)} \times \text{daily inhalation rate/body weight}$$

Where:

$$\begin{aligned} \text{Daily inhalation rate} &= 14.7 \text{ m}^3 \text{ for a continuous exposure (equivalent to } 0.6125 \text{ m}^3/\text{hour)} \\ \text{Body weight} &= 80 \text{ kg for an average adult} \end{aligned}$$

Gases with Systemic Effects

In the absence of human data to parameterize a human PBPK model, HECs can be calculated from the rodent inhalation equivalent concentration (POD_{Continuous}). Gases leading to systemic health effects were calculated using the the default methodology which adjusts the average exposure concentration by the regional gas dose ratio (RGDR), which for systemically acting gases is assumed to be the ratio of the animal blood:air partition coefficient (Hb/g)_A to the human blood-to-air partition coefficient (Hb/g)_H; that is, RGDR_{systemic} = (Hb/g)_A / (Hb/g)_H. The following formulae describe the calculation of the HEC (Equation 2-3):

¹ The Ideal Gas Law can be used to convert between ppm and mg/m³. At standard temperature and pressure (STP; 25°C and 760 mm Hg), 1 mole of gas occupies 24.45 L. However, when conditions differ from STP, a different gas conversion factor can be calculated using the reported experimental temperature or pressure.

Equation 2-3. Converting $POD_{Continuous}$ to HEC for Gases with Systemic Effects

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

The blood-to-air partition coefficients for rats and mice, respectively, are $\left(\frac{HB}{g}\right)_{A, rat} = 58$ and

$\left(\frac{HB}{g}\right)_{A, mouse} = 71$; the blood-to-air partition coefficient for humans $\left(\frac{HB}{g}\right)_H = 44.2$. When $\frac{\left(\frac{HB}{g}\right)_A}{\left(\frac{HB}{g}\right)_H} > 1$

for volatile organic compounds such as 1,1,2-trichloroethane, then a default ratio of 1 is used in

accordance with ([U.S. EPA, 1994](#)); *i.e.*, $RGDR_{systemic} = 1$. Because $\frac{\left(\frac{HB}{g}\right)_A}{\left(\frac{HB}{g}\right)_H} > 1$ for rats and mice, the HEC

values are the same as the rodent $POD_{Continuous}$ values.

Dosimetric and Unit Adjustments for Oral Hazard Values

Dosimetric Adjustments: Allometric scaling accounts for differences in physiological and biochemical processes, mostly related to kinetics.

For application of allometric scaling in risk evaluations, EPA uses dosimetric adjustment factors (DAFs), which can be calculated using Equation 2-4.

Equation 2-4. Dosimetric Adjustment Factor (DAF)

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

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)

2.3.1.4.2 Uncertainty Factors Used for Non-Cancer Endpoints

For the non-cancer health effects, the Agency applied specific uncertainty factors (UF) to identify benchmark MOEs for acute, intermediate, and chronic exposure durations for each exposure route among studies used to estimate risks. EPA used a total default UF of 100 for the benchmark MOEs for acute, intermediate, and chronic exposure durations for all exposure routes among studies that are used to estimate risks when utilizing NOAEL/NOAEC values and a total UF of 30 when the inter-species dosimetric adjustment is performed utilizing HED and HEC values for PODs. EPA guidance ([U.S. EPA, 2012a, 2002a, 1993](#)) further discuss considerations for application of uncertainty factors in human health hazard dose-response assessment and whether the database supports refining the values. A total uncertainty factor for each POD is calculated by multiplication of each of the applied UFs ([U.S. EPA, 2025b](#)).

2036 **1. *Interspecies Uncertainty Factor (UF_A) of 3***

2037 For 1,1,2-trichloroethane, all oral/dermal and inhalation PODs utilized inter-species dosimetric
2038 adjustments so that the default UF_A of 10 is reduced to 3. EPA uses data from oral toxicity
2039 studies in animals to derive relevant HEDs, and U.S. EPA (2011b) recommends allometric
2040 scaling (using the ³/₄ power of body weight) to account for interspecies toxicokinetics differences
2041 for oral data. When applying allometric scaling, EPA guidance (U.S. EPA, 2011b) recommends
2042 reducing the UF_A of 10 down to 3. The remaining uncertainty is associated with interspecies
2043 differences in toxicodynamics. EPA also uses a UF_A of 3 for the dermal HED values because
2044 these values are derived from the oral HED and a UF_A of 3 when HEC values are based on
2045 inhalation dosimetric modeling (*i.e.*, RGDR).
2046

2047 **2. *Intraspecies Uncertainty Factor (UF_H) of 10***

2048 For all PODs, the default UF_H of 10 was utilized in the absence of specific information to refine
2049 this value. EPA uses a default UF_H of 10 to account for variation in sensitivity within human
2050 populations due to limited information regarding the degree to which human variability may
2051 impact the kinetics disposition or impact the hazard response to 1,1,2-trichloroethane and its
2052 metabolites, which is consistent with the 95th percentile value published in recent literature
2053 (Schneider et al., 2022). In support for 1,1,2-trichloroethane, one metabolite is a reactive
2054 chlorinated aldehyde which can be a susceptibility consideration for people with the aldehyde
2055 dehydrogenase-2 polymorphism with decreased clearance for aldehydes (Gross et al., 2015) and
2056 there is no 1,1,2-trichlorethane toxicology or ADME data utilizing an animal model for this
2057 polymorphism (U.S. EPA, 2025b).
2058

2059 **3. *LOAEL-to-NOAEL Uncertainty Factor (UF_L) of 3***

2060 For the acute inhalation scenario, the POD was based on a study LOAEC value and considering
2061 the dose-response in the data, a UF_L of 3 was considered appropriate.
2062

2063 **4. *Subchronic-to-Chronic Uncertainty Factor (UF_S) of 10***

2064 For 1,1,2-trichloroethane, the default subchronic to chronic uncertainty factor of 10 was utilized
2065 in the absence of specific information to refine this value and it is consistent within the range of
2066 UFS values published (U.S. EPA, 2002a). There are no suitable chronic studies to estimate a
2067 refined UF_S value below a factor of 10 to account for extrapolating from data obtained in a study
2068 with less-than lifetime (short-term/subchronic) exposure to lifetime (chronic) exposure. This
2069 UFS was applied to the BMDL/BMCL from the subchronic studies identified for the
2070 intermediate oral and inhalation PODs, respectively. As chronic studies from the 1,1,2-
2071 trichloroethane database were not identified as suitable for the chronic duration POD, the
2072 assumption that effects from a given compound in a subchronic study occur at a 10-fold higher
2073 concentration than in a corresponding (but absent) chronic study was applied. This assumption is
2074 based on the U.S EPA guidance (U.S. EPA, 2002a). The lack of suitable chronic studies
2075 prevented POD selection from a chronic study as well as prevented the estimation of a refined
2076 UF_S value. For inhalation, the PODs follow Haber's Rule, for the same endpoint of nasal tissue
2077 damage, the subchronic POD is less than the acute POD. There is no chronic inhalation data to
2078 calculate an alternate UF_S value or supply an alternate chronic POD value. As the chronic oral
2079 and dermal scenarios PODs were based on a 90-day subchronic study, the application of the UF_S
2080 of 10 for the subchronic-to-chronic duration is considered reasonable and appropriate. The oral
2081 and dermal PODs did decrease from the acute to the intermediate duration. The acute oral
2082 NOAEL was 55 mg/kg based on neurotoxicity and the subchronic oral NOAEL was 3.9
2083 mg/kg/day based on immunotoxicity. As the chronic inhalation scenario was based on a 13-week
2084 subchronic study, the application of the UF_S of 10 for the subchronic-to-chronic duration is

considered appropriate. The inhalation adverse concentration did decrease from the acute to the intermediate duration, from 316 mg/m³ to 31 mg/m³, both with adverse effects in olfactory tissue. As the duration adjustment is being applied to a chronic exposure duration that is longer than the subchronic duration the uncertainty factor is intended, thus lowering of the uncertainty factor was not seen as justifiable without empirical data ([U.S. EPA, 2025a, b](#)).

2.3.1.4.3 Summary of Non-Cancer Hazard Values Used for Risk Estimation

Table 2-17 and Table 2-18 summarize the non-cancer oral/dermal and inhalation PODs for 1,1,2-trichloroethane for the acute, intermediate, and chronic exposure scenarios.

2093

Table 2-17. Oral and Dermal Non-Cancer PODs for 1,1,2-Trichloroethane

Duration	Effect	Study POD	NOAEL HED	Uncertainty Factors	Total Uncertainty Factors	Reference, Species, Duration, Route	Confidence Conclusion
Acute	Neurotoxicity, decreased acute motor activity in rats	LOAEL = 95 mg/kg NOAEL = 55 mg/kg	NOAEL HED = 12.6 mg/kg	UF _A = 3 UF _H = 10	30	(WIL Research, 2004) Sprague-Dawley Rats	Oral – Robust
						Oral, Acute Neurotoxicity Guideline Study OECD 424, High systematic review rating	Dermal – Moderate-to-Robust
Intermediate	Immunotoxicity, decreased hemagglutination titers in mice	LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10	30	(Sanders et al., 1985) CD-1 Mice 90 days Oral, High systematic review rating	Oral – Robust
							Dermal – Moderate-to-Robust
Chronic	Immunotoxicity, decreased hemagglutination titers in mice	LOAEL = 44 mg/kg NOAEL = 3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10 UF _S = 10	300	(Sanders et al., 1985) CD-1 Mice 90 days Oral, High systematic review rating	Oral – Moderate-to-Robust
							Dermal – Moderate

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor

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Table 2-18. Inhalation PODs for 1,1,2-Trichloroethane

Duration	Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Conclusion
Acute	Olfactory epithelium necrosis	LOAEC = 316 mg/m ³ (58 ppm) in 4 hours	LOAECadj = 52.7 mg/m ³ (9.7 ppm) LOAECadj HEC = 6.1 mg/m ³ (1.1 ppm)	UF _A = 3 UF _H = 10 UF _L = 3	100	(WIL Research, 2001) F-344 Rats 4 hours Inhalation, TSCA 799.9135 High systematic review rating	Robust
Intermediate	Lesions in the olfactory epithelium	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm)	UF _A = 3 UF _H = 10	30	(WIL Research, 2002) F-344 Rats	Robust

Duration	Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Conclusion
		BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ HEC= 0.62 mg/m ³ (0.11 ppm)			13 weeks, 6 hours/day, 5 days/week, Whole body Inhalation, TSCA 799.9346 High systematic review rating	
Chronic	Lesions in the olfactory epithelium	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm) BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm) BMCL ₁₀ HEC= 0.62 mg/m ³ (0.11 ppm)	UF _A = 3 UF _H = 10 UF _S = 10	300	(WIL Research, 2002), F-344 Rats 13 weeks, 6 hours/day, 5 days/week, Whole body Inhalation, TSCA 799.9346 High systematic review rating	Moderate-to-Robust
BMC = benchmark concentration; BMCL = benchmark concentration lower bound; HEC = human equivalent concentration; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor Acute Scenario: Inhalation study is 4 hours in one 24-hour day. Acute POD is 24 hours in 1 day. POD = Study POD × (4 hours per day/24 hours per day); POD HEC = POD × RGDR; RGDR = 0.115 based on study animal weight data Intermediate and Chronic Scenarios: Inhalation study is 6 hours per day and 5 days per week; POD is 168 hours per week; Intermediate and Chronic POD = Study POD × (6 hours per day/24 hours per day) × (5 days per week/7 days per week); POD HEC = POD × RGDR; RGDR = 0.157 based on animal weight data in study							

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2.3.2 Non-Cancer Weight of Scientific Evidence and Confidence Summaries

The 1,1,2-trichloroethane human health toxicology database includes medium and high-quality literature studies and standard guideline studies that were evaluated by the EPA systematic review process for endpoint selection and POD derivation that provided confidence in these decisions based on the weight of scientific evidence using the best available science. The hazards identified for 1,1,2-trichloroethane were neurotoxicity, respiratory tract pathology, immunotoxicity, liver pathology, irritation, male reproductive toxicity, body weight changes and mortality. Metabolism of 1,1,2-trichloroethane produces reactive metabolites such as a free radical, a chlorinated aldehyde, an acyl chloride and hydrochloric acid. Upon evaluating the reasonably available information for the oral, dermal, and inhalation scenarios, dose-response analysis identified human hazard endpoints and PODs that were derived for acute, intermediate, and chronic exposures, as well as derivation of oral, dermal, and inhalation cancer slope values. The selected endpoints and PODs are presented above in Table 2-16 and Table 2-17. The PBPK model produced confidence in the oral to inhalation route refinement of the cancer inhalation unit risk calculations. EPA considered all information that was reasonably available for 1,1,2-trichloroethane identified through the OPPT systematic review process under the TSCA up to April 2025 to characterize human health hazard endpoints and PODs. Overall, there is moderate-to-robust confidence in the non-cancer endpoints and PODs selected for the risk evaluation are sensitive and human health protective. The weight of scientific evidence for the POD selection confidence conclusions are listed below.

For the acute inhalation scenario, there is robust confidence in this endpoint and POD selection. The acute WIL inhalation study selected ([WIL Research, 2001](#)) has a high systematic review score for a route specific POD from a guideline study which has the common hazard in olfactory tissue as the subchronic inhalation study ([WIL Research, 2002](#)). The conversion of the oral toxicology studies systemic PODs to the corresponding inhalation PODs by the PBPK model ([Sapphire Group, 2002](#)) were not as protective as PODs based on the portal of entry hazard identified in the WIL study ([WIL Research, 2001](#)), which accounts for local effects as well as systemic effects. The PBPK model did not assess portal of entry effects. There were no epidemiology studies identified that could be used for POD derivation for the acute inhalation scenario.

For the acute oral scenario, there is robust confidence in this endpoint and POD selection. The acute WIL acute neurotoxicity study selected ([WIL Research, 2004](#)) has a high systematic review score for a route specific POD from a guideline study which has the common hazard of neurotoxicity for solvents. Neurotoxicity hazards were also observed in other 1,1,2-trichloroethane studies such as sedation and optokinetic test alterations (([White et al., 1985](#)), ([Niklasson et al., 1993](#)), respectively) and for other chlorinated solvents such as 1,2-dichloroethane also having decreased motor activity ([Zhong et al., 2022](#)). For the acute dermal scenario, the confidence is moderate-to-robust due to a route-to-route extrapolation uncertainty. There were no epidemiology studies identified which could be used for POD derivation for the acute oral or dermal scenarios.

For the intermediate inhalation scenario, there is robust confidence in this endpoint and POD selection. The subchronic WIL inhalation study selected ([WIL Research, 2002](#)) has a high systematic review score for a route specific POD from a guideline study which has the common hazard in olfactory tissue as the acute inhalation study ([WIL Research, 2001](#)). The conversion of the oral toxicology studies systemic PODs to the corresponding inhalation PODs by the PBPK model ([Sapphire Group, 2002](#)) were not as protective as PODs based on the portal of entry hazard identified in the WIL study ([WIL Research, 2001](#)), which accounts for local effects as well as systemic effects. For the chronic inhalation POD, there is moderate-to-robust confidence due the chronic extrapolation uncertainty from a subchronic study and based on a weight of scientific evidence and the best available science across toxicology studies,

chemicals, study quality and authoritative assessments. The PBPK model did not assess portal of entry effects. There were no epidemiology studies identified which could be used for POD derivation for the intermediate and chronic inhalation scenarios.

For the intermediate oral POD, there is robust confidence in this endpoint and POD selection. The POD was selected from a high-quality subchronic mouse immunotoxicity study based on decreased TDAR assay as measured by hemagglutination titers decreased by over 40% ([Sanders et al., 1985](#)) evaluated in both sexes. In support, the TDAR assay based on antibody forming cells also decreased the immune response by 31% at the same doses ([Sanders et al., 1985](#)). For the intermediate dermal POD there is moderate-to-robust confidence due to the uncertainty of the oral to dermal route extrapolation from the oral Sanders and colleagues study. For the chronic oral POD, there is moderate-to-robust confidence due to the chronic extrapolation uncertainty from a subchronic study ([Sanders et al., 1985](#)) and based on a weight of scientific evidence and the best available science across toxicology studies, chemicals, study quality and authoritative assessments. For the chronic dermal scenario, there is moderate confidence utilizing the Sanders study ([Sanders et al., 1985](#)) due to the uncertainty in the oral to dermal route extrapolation. There were no epidemiology studies identified which could be used for POD derivation for the intermediate and chronic oral and dermal scenarios.

2.4 Cancer Hazard Assessment

2.4.1 Hazard Identification

The following sections summarize the human evidence and animal study data that were assessed by EPA systematic review for 1,1,2-trichloroethane.

2.4.1.1 Human Evidence

Two case-control studies evaluated associations between 1,1,2-trichloroethane exposure and cancer in humans. In a large case-control study in the United States, investigators evaluated occupations/industries and work-related exposures to 1,1,2-trichloroethane and the risk of dying from pancreatic cancer. The study identified 63,097 cases of death from pancreatic cancer from the general population of 24 U.S. states between 1984 and 1993, and 252,386 individuals dying from noncancer causes from the same population served as controls. A high probability of occupational exposure to 1,1,2-trichloroethane based on usual job and industry data from death certificates and a job-exposure matrix was associated with an increased odds of death from pancreatic cancer compared to those with zero probability of exposure to 1,1,2-trichloroethane in black men, but not in black women, white men, or white women ([Kernan et al., 1999](#)). Although the odd ratio (OR) comparing high probability of exposure to zero probability of exposure in black men was statistically significantly greater than the null (OR = 3.0, 95% CI: 1.2–7.6), the association was based on only eight cases with high probability of exposure. Increased exposure intensity for 1,1,2-trichloroethane based on the job-exposure matrix was not associated with increased odds of death from pancreatic cancer in any of the aforementioned sex/race groups. Covariate adjustments included age, marital status, metropolitan/non-metropolitan residential status, and region of residence. In a population-based case-control study in Minnesota, exposure to 1,1,2-trichloroethane as identified by participants' occupational history and job-exposure matrix was not associated with an increased odds of developing renal cell cancer (438 cases, 687 controls) ([Dosemeci et al., 1999](#)). Covariate adjustments included age, smoking, hypertension status and/or use of diuretics and/or anti-hypertension drugs, and body mass index.

2.4.1.2 Laboratory Animal Evidence

The carcinogenic effects of 1,1,2-trichloroethane have been evaluated in two medium quality 78-week bioassays of rats and mice exposed by gavage administration ([NCI, 1978](#)) and in a 2-year bioassay of rats exposed by subcutaneous injection ([Norpoth et al., 1988](#)). The rat bioassay by Norpoth was rated uninformative for dose-response due to the lack of dose normalization based on body weight ([Norpoth et al., 1988](#)). A high-quality study testing whether 1,1,2-trichloroethane acts as a cancer initiator or promoter was conducted in rats exposed by gavage for 7 weeks ([Milman et al., 1988](#)). No chronic carcinogenicity assay in animals exposed to 1,1,2-trichloroethane via inhalation was identified.

Oral Study in Mice

The medium quality 1978 NCI cancer study ([NCI, 1978](#)) in B6C3F1 mice dose-response for liver hepatocellular carcinoma had a high correlation of 0.994 for male mice and 0.989 for female mice (EPA CORREL function in Excel), with similar results for both male and female mice, as shown in Figure 2-11. The study was rated as medium. The liver carcinomas incidences in female mice had high differential values across doses with 0% incidence in the vehicle controls, 33% incidence in the low-dose and 89% incidence in the high-dose group. By two statistical tests in both male and female mice (Fisher exact test and Cochran-Armitage test), there was a highly statistically significantly increased incidence of hepatocellular carcinomas in all groups which were dose related ($p < 0.0001$). The study authors reported adrenal pheochromocytomas were also confirmed in both sexes which had a positive dose-related association by the Cochran-Armitage test, with 0% incidence in controls with 17 and 28% incidences in the high-dose group in male and female mice, respectively. The Sapphire Group ([Sapphire Group, 2004b](#)) concluded that the liver tumors indicated in the NCI mouse study ([NCI, 1978](#)) were an appropriate endpoint for the development of the PBPK model for the HAP Task Force (2004). As described in Section 2.3.1.1.4, the liver was also the target organ in other shorter duration studies, such as an acute study demonstrating elevated serum ALT/AST transaminase levels with a NOAEL of 46 mg/kg and LOAEL of 92 mg/kg in the Tyson study ([Tyson et al., 1983](#)) which was utilized as for POD selection by ATSDR. The Milman study in rats ([Milman et al., 1988](#)) produced liver tumor foci in 7 weeks of dosing at 70 mg/kg/day.

In the NCI cancer study ([NCI, 1978](#)), B6C3F1 mice were treated with 1,1,2-trichloroethane in corn oil at 5 days/week for 78 weeks via gavage with time-weighted doses of 0 mg/kg/day for controls, 195 mg/kg/day for the low dose and 390 mg/kg/day for the high dose (corresponding to 0, 139 and 279 mg/kg/day on a 7-day per week continuous basis). Twenty animals per sex were in the control groups. The initial doses were 150 and 300 mg/kg/day; however, the study authors concluded these doses were being tolerated in this strain of mice so the doses were increased to 200 and 400 mg/kg/day in week 9 of the study. There is confidence in utilizing the 1,1,2-trichloroethane mouse cancer study for the 1,1,2-trichloroethane cancer assessment, as described below. The dose-response for liver tumors is linear and has a high correlation coefficient and highly significant ($r = 0.99$, $p < 0.001$, see Figure 2-11). The linear tumor dose-response in both male (square symbols in Figure 2-11) and female mice (circle symbols in Figure 2-11) supports the linear low dose liver cancer model with robust 77% to 89% tumor incidence in the high-dose group and significant 33 to 37% tumor incidence in the low-dose group. The study authors concluded that in mice the maximum tolerated dose was over 400 mg/kg/day, which supports that the biology was not overwhelmed at the highest dose doses ([NCI, 1978](#)). Shorter-term studies did have liver pathology as well. The chemical administration was by gavage dosing, so doses are well quantified and no co-exposure to other chemicals due to volatilization from other dosing types such as from food or water. The 1,1,2-trichloroethane mouse cancer study is the best available science using a cancer study that tested the target chemical, 1,1,2-trichloroethane.

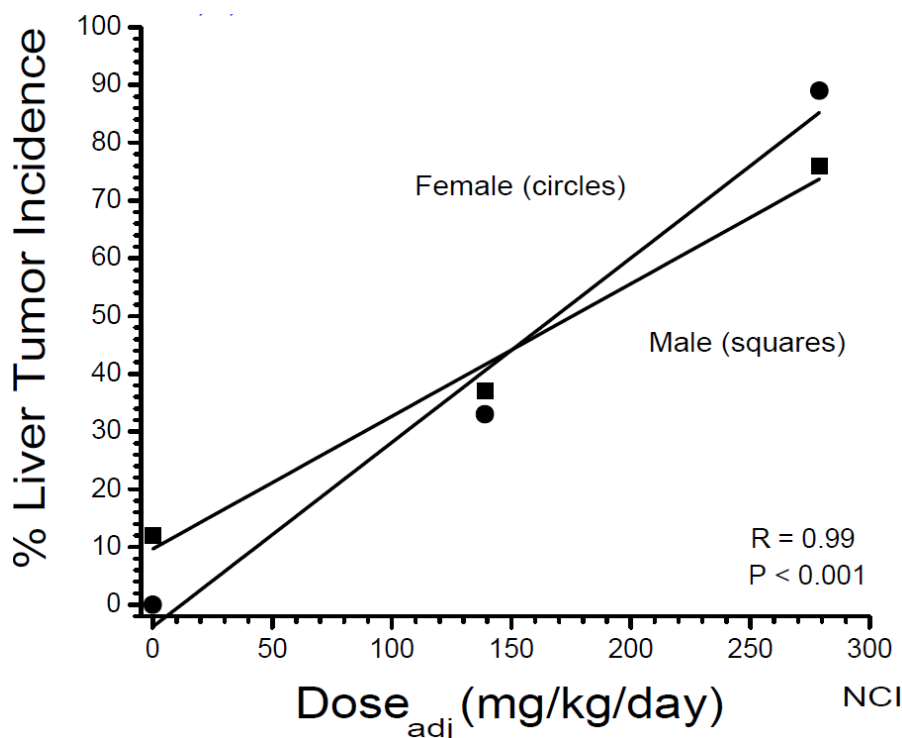


Figure 2-11. Liver Tumor Dose-Response in Mice for 1,1,2-Trichloroethane (NCL, 1978)

The PBPK model indicates that liver metabolism in mice exposed to oral daily gavage doses is expected to be linear for doses up to approximately 300 mg/kg (5 days a week for 78 weeks), at which point metabolism starts to become non-linear (see Figure 2-7 from the PBPK Modeling Approach discussed in Section 2.2.5.2). The lower doses from the (NCL, 1978) cancer study (≈ 195 mg/kg/day for 5 days for 78 weeks) did not saturate metabolism, which is also supported by the high linear tumor dose-response ($r = 0.99$). While PBPK simulations based on cytochrome P450 metabolism suggested deviations from linearity at the highest dose in the cancer study (≈ 390 mg/kg/day for 5 days, over 78 weeks), the body weights of male and female mice were not markedly affected by treatment, supporting that the high dose did not exceed the maximum tolerated dose as the study authors concluded. The study authors increased the high dose from 300 mg/kg/day to 400 mg/kg/day because the initial dose was considered to be insufficient. It should be noted that metabolic enzymes other than the cytochrome P450 metabolism are involved in 1,1,2-trichloroethane bioactivation and clearance. The 10% increase in tumor incidence occurred at lower doses of 20 mg/kg/day or less in the linear region of the PK response. 1,1,2-Trichloroethane is a reactive alkyl halide and produces four reactive metabolites that can damage DNA. The chemical species to which tumor formation is most important is not separately quantified by the PBPK model, which calculates total amount of 1,1,2-trichloroethane metabolized in the liver by the CYP pathway. Overall, this information does not preclude the use of a linear cancer slope factor because the data support linear modeling, despite not fully capturing the uncertain MOA through the PBPK model. There is confidence in the 1,1,2-trichloroethane tumor dose-response and the cancer slope factor calculations across assessments.

The PBPK-predicted amount of 1,1,2-trichloroethane metabolized in the liver is a partial metric. The non-linearity of cytochrome P450 metabolism indicated by the PBPK model at higher doses, while cancer response increases approximately linear with doses, indicates complex, dynamic cancer biology, concurrent damage formation and progression alongside recovery or protective mechanisms such as glutathione conjugation of reactive intermediates. As such, the dose metric does not capture the complexity of the MOA, including the formation of reactive intermediates, DNA-adduct formation, the

2266 impact of glutathione, or the relevance of the unknown biologically effective dose metric. 1,1,2-
2267 Trichloroethane and its active metabolites are reactive, indicating that multiple compounds may
2268 contribute to different stages of carcinogenesis (*i.e.*, tumor initiation and tumor progression steps). A
2269 portion of the 1,1,2-trichloroethane is eliminated through the lungs via exhalation by either oral or
2270 inhalation dosing. Although these processes can function differently between species, there is no direct
2271 evidence that metabolism formation in mice is absent in humans, both species have cytochrome P450
2272 and aldehyde dehydrogenase-2 enzymes. And consistent dose-response trends indicate that tumor
2273 formation increases linearly with the doses tested, the application of the cancer linear slope factor is
2274 appropriate under these conditions.

2275
2276 It is important to note that clearance of the reactive 2-chloroacetaldehyde metabolite by aldehyde
2277 dehydrogenase-2 is not specifically represented and its decreased clearance at higher doses can increase
2278 tumor incidence. At high doses, reactive aldehydes can inhibit aldehyde dehydrogenase activity and
2279 decrease protective glutathione levels. The similar chemical 1,2-dichloroethane also produces the 2-
2280 chloroacetaldehyde metabolite. The aldehyde dehydrogenase-2 inhibitor disulfiram was shown to
2281 increase the tumor incidences rates based on co-exposure with 1,2-dichloroethane, but not by 1,2-
2282 dichloroethane or disulfiram exposure alone. Additionally, increased blood levels of 1,2-dichloroethane
2283 by 5-fold resulted from this co-exposure and decreased clearance through this pathway supporting 1,2-
2284 dichloroethane and metabolite accumulation before this enzyme in the rodent models ([Cheever et al., 1990](#)).
2285

2286
2287 Additionally, inhalation exposures that were extrapolated from the oral doses via the PBPK model occur
2288 in dose ranges for which metabolism is linear. As a result, internal dose metrics relevant to tumor
2289 formation are expected to scale proportionately with exposure under inhalation conditions. Given lack of
2290 evidence to establish a threshold or nonlinear response, the absence of a well-defined MOA, and that the
2291 highest dose did not exceed that of the MTD, small deviations from linearity at higher doses do not
2292 conflict with the use of linear extrapolation to predict cancer incidence in mice.
2293

2294 This cancer study ([NCL, 1978](#)) also found tumors in the adrenal gland. The mouse cancer study has a
2295 medium quality systematic review, providing confidence in the study. The mouse cancer study was
2296 utilized in multiple documents from other state and federal programs: U.S. EPA IRIS report ([U.S. EPA, 1987](#)),
2297 U.S. EPA PPRTV report ([U.S. EPA, 2011a](#)), California EPA Office of Environmental Health
2298 Hazard Assessment (OEHHA) report ([OEHHA, 2006](#)) and the HAP Task Force PBPK report ([Sapphire Group, 2004b](#)).
2299

2300
2301 Body weights and survival of male mice were not affected by treatment ([NCL, 1978](#)). Body weights of
2302 female mice were not affected by treatment. Female mice exhibited a statistically significant decrease in
2303 survival largely due to early deaths in the low-dose group that were not associated with tumor
2304 development. However, ([NCL, 1978](#)) reported that sufficient numbers of low-dose females survived for
2305 evaluation of late-developing tumors. Statistically significant, dose-related trends in the incidences of
2306 hepatocellular carcinoma were identified in both male and female mice (regardless of control group),
2307 and the incidences were statistically significantly increased at both doses relative to the untreated and
2308 vehicle control groups. The incidences of hepatocellular carcinoma in male mice were 2/17 for the
2309 untreated control, 2/20 for the vehicle control, 18/49 for the low-dose, and 37/49 for the high-dose
2310 groups, respectively. The incidences of hepatocellular carcinomas in female mice were 2/20 for the
2311 untreated control, 0/20 for the vehicle control, 16/48 for the low-dose, and 40/45 for the high-dose
2312 groups, respectively. These results are presented in Table 2-19.
2313
2314

Additionally, statistically significant trends in the incidences of adrenal pheochromocytomas were observed for male and female mice (Table 2-19). The incidences in treated males were not statistically significantly different from either control group. In males, the incidences of adrenal pheochromocytomas were 0/18, 0/20, 0/49, and 8/48 for the untreated control, vehicle control, low-dose, and high-dose groups, respectively. The incidence of these neoplasms in high-dose females was statistically significantly increased relative to the untreated and vehicle control groups. In females, the incidences were 0/20, 0/20, 0/48, and 12/43 in the untreated control, vehicle control, low-dose, and high-dose groups, respectively.

Table 2-19. Neoplasm Incidences in Mice Exposed to 1,1,2-Trichloroethane by Gavage for 78 Weeks followed by 13-Week Recovery Period (NCI, 1978)

Tumor Site	0 (Untreated)	0 (Vehicle)	195 mg/kg-day	390 mg/kg-day
Male mice				
Hepatocellular carcinomas	2/17 ^a (12%)	2/20 ^a (10%)	18/49 ^{b c} (37%)	37/49 ^{b c} (76%)
Adrenal pheochromocytomas	0/18 ^a	0/20 ^a	0/49	8/48 (17%)
Female mice				
Hepatocellular carcinomas	2/20 ^a (10%)	0/20 ^a	16/48 ^{b c} (33%)	40/45 ^{b c} (89%)
Adrenal pheochromocytomas	0/20 ^a	0/20 ^a	0/48	12/43 ^{b c} (28%)
^a Significant dose-related trend as reported by the study authors; the trend test was performed separately with each control group. ^b Significantly different from the untreated control group (p < 0.05) as reported by the study authors. ^c Significantly different from the vehicle control group (p < 0.05) as reported by the study authors.				

Oral Study in Rats

The 1978 NCI cancer study in Osborne-Mendel rats (NCI, 1978) did not find statistically significant increase in tumor incidence as a function of treatment. However, multiple tumors were indicated in treated, but not control rats, including renal tubular adenomas, transitional-cell carcinomas of kidney, adrenal cortical carcinomas as well as hemangiosarcomas of abdomen, pancreas, spleen, and subcutaneous tissue. The study was rated as medium and results are summarized in Table 2-20.

In the 1978 NCI cancer study 50 animals per sex of male and female Osborne-Mendel rats (NCI, 1978) were treated with 1,1,2-trichloroethane in corn oil at 5 days/week for 78 weeks via gavage with time-weighted doses of 0, 46 and 92 mg/kg/day (corresponding to 0, 32.9, and 65.7 mg/kg/day on a 7-day per week continuous basis). Twenty animals per sex were in the control groups. The initial doses were 35 and 70 mg/kg/day; however, the study authors concluded these doses were being tolerated in this strain of rats so the doses were increased to 50 and 100 mg/kg/day in week 21 of the study. In context, the acute oral LD₅₀ in Wistar rats is a higher dose of 837 mg/kg. Adrenal cortical carcinomas occurred in 1/50 high-dose males, 2/50 low-dose females, and 1/50 high-dose females with no tumors detected in the untreated or vehicle control groups. Renal tubular adenomas were present in 1/50 of low-dose and in 1/50 of high-dose males. Transitional-cell carcinoma of the kidney occurred in 1/50 of low-dose males. Hemangiosarcomas of the spleen occurred in 3/49 of low-dose males, in the pancreas in 1/49 of low-dose males and as a tissue mass in the abdomen in 1/50 of low-dose males. In one high-dose male and one low-dose female, hemangiosarcoma occurred as a subcutaneous tissue mass. This rat study was only 78 weeks in duration—not the typical 104 weeks cancer study for rats and the top continuous dose tested was only 65.7 mg/kg/day (8% of the rat LD₅₀ value), which introduces uncertainty into the

interpretation of these results and the study duration can influence endpoint incidences and false negative responses.

Table 2-20. 1,1,2-Trichloroethane Rat Cancer Study Results (Summarized from [\(NCI, 1978\)](#))

Tumor Site	0 (Untreated)	Low-Dose 46 mg/kg/day	High-Dose 92 mg/kg/day
Male rats			
Adrenal Cortical Carcinomas	0	0	1/50 (2%)
Renal Tubular Adenomas	0	1/50 (2%)	1/50 (2%)
Pancreas Hemangiosarcoma	0	1/49 (2%)	0
Abdominal Hemangiosarcoma	0	1/50 (2%)	0
Subcutaneous Tissue Hemangiosarcoma	0	0	1/50 (2%)
Spleen Hemangiosarcoma	0	3/49 (6%)	0
Pituitary Adenoma	0	5/47 (11%)	1/46 (2%)
Malignant Lymphoma	1/20 (5%)	1/50 (2%)	3/50 (6%)
Kidney Carcinoma	0	1/50 (2%)	0
Female rats			
Adrenal Cortical Carcinomas	0	2/50 (4%)	1/50 (2%)
Subcutaneous Tissue Hemangiosarcoma	0	1/50 (2%)	0
Subcutaneous Fibroma	2/20 (10%)	0	1/50 (2%)
Pituitary Adenoma	2/20 (10%)	9/48 (19%)	5/48 (10%)
Thyroid Adenoma or Carcinoma	0	3/50 (6%)	1/50 (2%)
Mammary Gland Adenocarcinoma	1/20 (5%)	0	4/50 (8%)
Mammary Gland Fibroadenoma	6/20 (30%)	16/50 (32%)	9/50 (8%)
Mammary Gland Adenocarcinoma or Fibroadenoma	7/20 (35%)	16/50 (32%)	13/50 (26%)
Endometrial Stromal Polyp	0	5/50 (10%)	0

The 1978 NCI cancer study ([NCI, 1978](#)) conducted a chronic cancer bioassay in Osborne-Mendel rats and B6C3F1 mice (20/sex/species in control groups, 50/sex/species in treatment groups) exposed by gavage 5 days/week. The control groups consisted of untreated controls (not intubated) and vehicle controls (intubated with corn oil). Treated rats were given 1,1,2-trichloroethane at doses of 30 or 70 mg/kg-day for 20 weeks. As these doses were well tolerated, the doses were increased to 50 and 100 mg/kg-day, respectively, for the remaining 58 weeks. After a 78-week exposure period, the rats were maintained without treatment for an additional 34 to 35 weeks. The time-weighted average doses calculated by the study authors were 0, 46, and 92 mg/kg-day for rats and 0, 195, and 390 mg/kg-day for mice. Histopathology of a comprehensive set of organs was evaluated. However, [NCI \(1978\)](#) did not evaluate histopathology of the clitoral gland, eyes, Harderian gland, nasal cavity, preputial gland, seminal vesicle, or vagina in either species.

Survival and body weights of male and female rats were not affected by treatment ([NCI, 1978](#)). The concurrent vehicle control group exhibited low survival, with only 1/20 males and 4/20 females surviving until study termination; therefore, no statistical comparison could be performed between tumor incidences in the concurrent vehicle control group and treatment groups. There was no statistically significant, exposure-related increase in neoplasm incidence in male or female rats relative to the untreated controls or historical vehicle controls (as reported by the study authors). However, the study authors acknowledged that rats may not have received the maximum tolerated dose based on the lack of treatment-related effects on survival and body weight. Additionally, a rat study is typically done for 104 weeks, but this study was only done for 78 weeks. Dosing was also only conducted for 5 days per week rather than 7 days per week; therefore, providing 2 days recovery before the next series of dosing. While EPA cannot confirm potential impacts on the findings without a full study over the entire duration of 104 weeks and 7 days a week dosing, it is possible this decreased study time for the rats is why no statistically significant exposure-related increase in neoplasm incidence was reported. Although these discrepancies occurred for the rat study, the mouse study did show statistically significant impacts with a clear dose-response. Taken together, along with confidence in the PBPK model for extrapolating animal to human data based on readily available animal data from this study, EPA retains a moderate confidence in the IUR derived from the mouse study.

Dermal Study in Rats

In the study rated uninformative for dose-response, Norpoth ([1988](#)) conducted a 2-year cancer bioassay in Sprague-Dawley rats (35 control males, 50 control females, 50/sex in treatment groups) exposed by subcutaneous injection once per week at 15.37 or 46.77 μmol . The control groups consisted of untreated controls (not injected) and vehicle controls (injected with dimethyl sulfoxide, DMSO). The specific tissues evaluated were not identified, and results were not reported by organ site. The incidences of sarcomas in male (8 total) and female (5 total) rats dosed with 46.77 μmol was statistically significantly greater than untreated controls (no sarcomas), but the incidences were not statistically different from vehicle controls (2 in males, 3 in females). The incidences of mesenchymal and epithelial tumors, carcinomas (not otherwise specified), all tumors, malignant tumors, and benign tumors did not increase with treatment.

2.4.1.3 Mechanistic and Supporting Evidence

Tumor Promoter Information

In the 1988 EPA Milman *in vivo* tumor study in male Osborne Mendel rats ([Milman et al., 1988](#)), 1,1,2-trichloroethane (listed as 1,1,2-TCE in study), indicated that when administered in the promotion protocol after initiation with diethylnitrosamine (DEN) 1,1,2-trichloroethane induced significant increases in abnormal liver findings of the gamma glutaryltranspeptidase positive (GGT+)-foci above control levels. GGT is not normally expressed in adult rat liver and it is a marker of pre-neoplastic lesions. 1,1,2-Trichloroethane also induced significant increases in GGT+/-foci when administered in the promotion protocol without DEN initiation. Tumor initiation is before the promotion phase of tumorigenesis. The Sapphire Group report ([Sapphire Group, 2002](#)) concluded that 1,1,2-trichloroethane was positive as a potent liver tumor promoter and was identified as a weak liver tumor initiator. In the presence of the DEN tumor initiator, 1,1,2-trichloroethane produced statistically significant abnormal liver findings at 6.27 foci/cm² relative to the corn oil control with 1.62 GGT+ liver foci/cm², which was higher GGT+ foci induction than the phenobarbital control tumor promoter value of 4.04 GGT+ foci/cm² ($p < 0.05$). Even in the absence of the DEN tumor initiator, 1,1,2-trichloroethane still induced statistically significant abnormal liver findings at 4.43 GGT+ foci/cm² relative to the corn oil control at 0.37 foci/cm² and the phenobarbital control at 0.27 foci/cm² ($p < 0.01$). In the development of the mouse cancer study PBPK model for the HAP Task Force, from these EPA Milman toxicology study ([Milman et al., 1988](#)) findings The Sapphire Group concluded, “[t]aken as a whole, these studies

indicated that 1,1,2-TCE may be a complete carcinogen with weak initiating activity and stronger promoting activity” ([Sapphire Group, 2004b](#)).

In the rat liver tumor promoter study ([Milman et al., 1988](#)), 1,1,2-trichloroethane was dosed at 70 mg/kg/day via oral gavage in corn oil for 5 days/week for 7 weeks after a single 30 mg intraperitoneal dose by injection of the tumor initiator DEN and the livers were examined for abnormal liver foci based on gamma glutamyltranspeptidase histopathology.

([Milman et al., 1988](#)) performed a cancer initiation/promotion study in male Osborne-Mendel rats (10/group). Two protocols were used. During the initiation protocol, rats were given a two-thirds partial hepatectomy and, 24 hours later, a gavage dose of 1,1,2-trichloroethane at 70 mg/kg in corn oil. Tumor promotion was achieved via feeding the animals a diet containing the known tumor promoter phenobarbital for 7 weeks. A complete carcinogen requires both tumor initiation followed by tumor promotion to form GGT+ liver foci. The animals were then sacrificed and GGT-positive foci in the liver were quantified.

During the promotion protocol, partially hepatectomized rats were given an intraperitoneal initiation dose of water or diethylnitrosamine (DEN) and then received 1,1,2-trichloroethane at 70 mg/kg in corn oil via gavage 5 days/week for 7 weeks ([Milman et al., 1988](#)). After the promotion phase, the animals were sacrificed and hepatic GGT-positive foci were quantified. Relative to the vehicle control, 1,1,2-trichloroethane increased the number of hepatic GGT-positive foci following initiation with water (4.4 vs. 0.4 foci/cm²) and initiation with DEN (6.3 vs. 1.6 foci/cm²).

Immunotoxicity Mechanistic Information

Immunotoxicity is a recognized general mechanism to contribute to cancer development in various tissues including the liver and chemicals that cause suppression of the immune system should be considered a human-relevant risk factor for the development of cancer ([Hilton et al., 2022](#); [Smith et al., 2016](#)). Sanders (1985) has indicated that 1,1,2-trichloroethane causes the immunotoxicity key event in mammals at 13 weeks with a LOAEL of 44 mg/kg/day and a NOAEL of 3.9 mg/kg/day in mice, which precedes liver tumorigenesis at 49 weeks at a LOAEL dose of 195 mg/kg/day in mice, however at elevated tumor incidences of 33% to 37% ([NCI, 1978](#)), thus an reference dose (RfD) threshold approach can be considered for 1,1,2-trichloroethane cancer assessment. However, there is not sufficient evidence that an immunotoxicity mechanism-based POD is human health-protective for liver cancer and to adequately perform a Bradford-Hill analysis for causation as a key event for 1,1,2-trichloroethane tumorigenesis (*i.e.*, strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence, and analogy). In support, the LOAEL for immunotoxicity is 44 mg/kg/day (NOAEL = 3.9 mg/kg/day) and the BMD value for liver tumors is a much lower value of 3.72 mg/kg/day (BMDL = 2.87 mg/kg/day; see BMD Appendix B). Thus, the linear cancer approach is utilized based on the sufficient evidence of genotoxicity listed in Section 2.4.2, also considering the liver tumor dose-response ($r = 0.99$ with $r = 1.00$ being a perfect correlation).

U.S. EPA OncoLogic Results

The U.S. EPA OncoLogic tool predicts the carcinogenic potential of compounds based on the chemical structure and reactivity mechanisms ([U.S. EPA, 2021b](#)). For 1,1,2-trichloroethane, OncoLogic classifies it as a Moderate concern for cancer, the same rating as a similar chemical, 1,2-dichloroethane, based on the following rationales (OncoLogic; accessed August 15, 2025). Haloalkanes and haloalkenes can be direct-acting alkylating agents and others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Some haloalkanes are known or suspected carcinogens with multiple mechanisms involved in their carcinogenic activity is believed to be related to genotoxicity, cytotoxicity

and various epigenetic mechanisms. The potential of haloalkanes and haloalkenes to alkylate cellular nucleophiles such as DNA is the basis of concern for their carcinogenicity. Alkylation of DNA can cause critical genetic mutations (such as G to A) transitions and instabilities that can lead to tumor formation (*i.e.* the p53 gene and other oncogenes, cell cycle control genes, etc).

1,1,2-Trichloroethane Role of Metabolism on Mode of Action Information

1,1,2-trichloroethane is extensively metabolized in the liver to produce multiple reactive metabolites which have the potential to alkylate DNA ([Mazzullo et al., 1986](#)). Alkyl halides such as 1,1,2-trichloroethane and its metabolites are known to alkylate DNA, which can promote increases in genomic mutations. As shown in Figure 2-12, these reactive species created through oxidative metabolism and dechlorinations include a dichloroethane free radical, 2-chloroacetaldehyde, a dichloro acyl chloride, and hydrochloric acid (HCl) based on empirical data ([Mazzullo et al., 1986](#)). Haloalkanes have the potential to alkylate cellular nucleophiles such as DNA and glutathione (an important free radical buffer in cells). The 1,1,2-trichloroethane generates a free radical and free radicals can fragment and damage DNA. In support, the oral cancer slope factor for 2-chloroacetaldehyde metabolite is 0.27 per mg/kg/day also based on hepatocellular adenomas and carcinomas in mice ([Daniel et al., 1992](#)). The 2-chloroacetaldehyde metabolite is cleared by aldehyde dehydrogenase-2 ([Sharpe and Carter, 1993](#)), so for people with the ALDH-2 enzyme mutation (several million Americans, ([Gross et al., 2015](#))) this data has relevance to susceptibility for people with the mitochondrial ALDH gene polymorphism having decreased aldehyde clearance activity with increased rates of multiple diseases such as cancer, heart disease and neurological diseases.

In a study by Cheever ([1990](#)), the oral administration of the ALDH-2 inhibitor disulfiram increased the blood levels of a similar solvent 1,2-dichloroethane in rats by five-fold when administered via inhalation (2-chloroacetaldehyde is also a metabolite of 1,2-dichloroethane). ALDH-2 inhibition also significantly increased the incidences of tumors and carcinomas by 1,2-dichloroethane, which also indicates that ALDH-2 activity is important for 1,2-dichloroethane clearance *in vivo* to protect from adverse outcomes. It should be noted that there is no 1,1,2-trichloroethane toxicology data on animal models with the ALDH-2 deficiency to assess this potentially susceptible subpopulation.

Metabolism to reactive intermediates may play a role in the carcinogenicity of 1,1,2-trichloroethane observed in mice. Following oral dosing of rats and mice, 1,1,2-trichloroethane is metabolized to chloroacetic acid, thiodiacetic acid, and S-carboxymethylcysteine (([Mitoma et al., 1985b](#)) as cited in ([ATSDR, 2021](#))). Chloroacetic acid is produced via hepatic CYP450 activity (([Ivanetich and Van den Honert, 1981](#)) as cited in ([ATSDR, 2021](#))), while thiodiacetic acid and S-carboxy-methyl-cysteine are formed following conjugation of 1,1,2-trichloroethane with glutathione (([Yllner, 1971](#)) as cited in ([ATSDR, 2021](#))). Cytochrome P450 (CYP450)-mediated metabolism of 1,1,2-trichloroethane can also produce free radicals, which can lead to lipid peroxidation or covalent binding to macromolecules ([Mazzullo et al., 1986](#); [Tyson et al., 1983](#)) as cited in ATSDR ([2021](#)). Chloroacetic acid can also form covalent bonds with macromolecules, potentially resulting in altered protein function or DNA adducts. Covalent binding by reactive metabolites may be an important initial step in the carcinogenesis observed in mice.

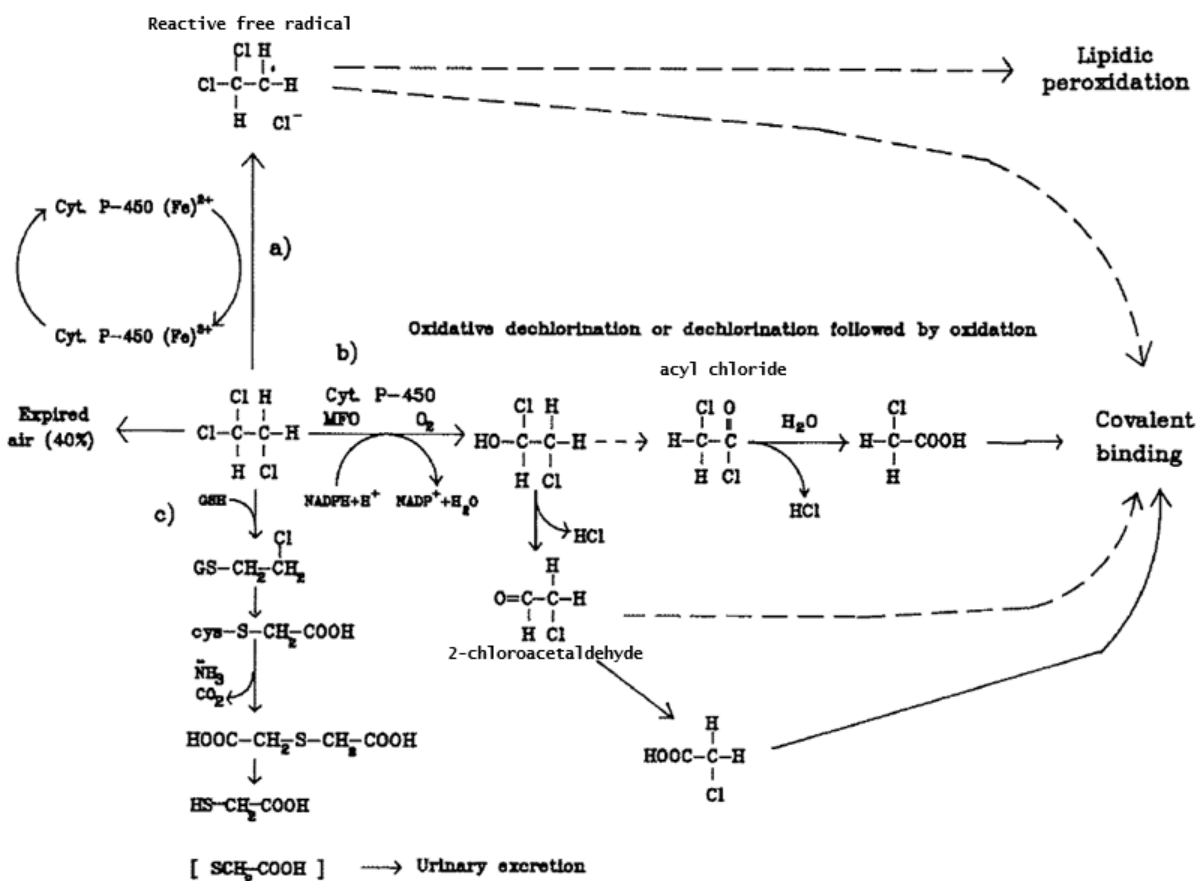


Figure 2-12. Metabolic Diagram for 1,1,2-Trichloroethane (Mazzullo et al., 1986).

Proven pathways in this specific study are depicted by solid arrows, with several reactive metabolites labeled.

2.4.1.3.1 Cancer Classification and Evidence Integration Conclusions

The evidence integration tables for cancer are listed in 3.5 Appendix A, considering factors that increase strength and factors that decrease strength that led to an overall judgment based on the summary of key findings as well as the within-stream strength of the evidence judgement. A summary table of the evidence judgement for the various tumor types is shown below (Table 2-21). 1,1,2-Trichloroethane has been classified as a complete carcinogen in the Sapphire Group PBPK report having both tumor initiator and tumor promoter activities. Qualitatively, 1,1,2-trichloroethane causes tumors in multiple tissues in both sexes and in two species (rats and mice) dosed orally for 78 weeks. The liver tumors in mice in both sexes quantitatively have an excellent dose-response with statistical significance.

The OEHHHA 2006 report (OEHHHA, 2006) concluded that 1,1,2-trichloroethane should be treated as a potential human carcinogen based on the development of pheochromocytomas in both sexes of mice as well as upon the increased incidence of liver tumors observed in both male and female mice treated at two doses of 1,1,2-trichloroethane. Both the EPA 1987 IRIS (U.S. EPA, 1987) and the EPA 2011 PPRTV (U.S. EPA, 2011a) documents reported that 1,1,2-trichloroethane is a possible human carcinogen based on liver cancer in mice and that the structurally related chemical 1,2-dichloroethane is a probable human carcinogen. The medium quality 1978 NCI oral mouse cancer study was the basis of

the oral cancer slope factor (CSF) reported by EPA IRIS, EPA PPRTV and the California OEHHA (OEHHA, 2006). Also, the 1978 NCI 1,1,2-trichloroethane mouse oral cancer study was the basis of the inhalation unit risk reported by IRIS and PPRTV, as well as the basis of the Sapphire Group development of the PBPK model (for the HAP Task Force).

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), 1,1,2-trichloroethane is considered “Likely to be Carcinogenic to Humans” based on evidence of increased tumor incidences in both sexes of one species (mice) in the liver and adrenal gland in a medium-quality cancer bioassay (NCI, 1978) and inadequate human evidence of carcinogenicity in two case-control studies (Dosemeci et al., 1999; Kerner et al., 1999). 1,1,2-Trichloroethane qualitatively produced tumors in two species, mice and rats, and quantitatively produced tumors in mice. The liver tumors in mice (incidences of 33–37% at the low dose of 195 mg/kg/day and 76–89% at the high dose of 390 mg/kg/day) had a high correlation to dose of 0.99 in both sexes with $p < 0.001$ significance at an incidence of 89% in females at the high dose of 390 mg/kg/day, which is below the maximum tolerated dose (NCI, 1978). Male and female rats exhibited increased liver and adrenal gland tumor incidences (NCI, 1978). A positive tumor study in mice has been demonstrated with high tumor incidences in both sexes and at both doses, plus a weight of scientific evidence in experimental animals that the agent causes events generally known to be associated with tumor formation, which for 1,1,2-trichloroethane specifically are genotoxicity *in vivo* in Section 2.4.2 below and immunotoxicity *in vivo* (Sanders et al., 1985).

In case-control studies, no association was identified for kidney tumors and 1,1,2-trichloroethane exposure (Dosemeci et al., 1999), however an association between pancreatic tumors and working a job with a high probability of 1,1,2-trichloroethane exposure was observed in black men but not in other demographic groups (Kerner et al., 1999). The evidence for each tumor type observed in epidemiological and animal studies of 1,1,2-trichloroethane is shown in Table 2-21. The inhalation unit risk was calculated using the peer-reviewed Sapphire Group PBPK model (Sapphire Group, 2002), which produced HEC values that were utilized as inputs for the benchmark dose analysis (Sapphire Group, 2002). The PBPK model was validated against multiple routes of exposure, supporting both oral and inhalation dosing for various exposure regimens, which provides high confidence in the PBPK model to predict internal kinetics for systemic hazard across routes. As such, when performing route-to-route extrapolation, the moderate confidence in the oral study POD should be preserved across to the inhalation POD. Because the PBPK model predicts the internal concentrations associated with biological responses, uncertainty for different routes of exposure decreases; the route-specific uptake processes are accounted for, so the focus is on the hazard occurring inside the body. As such, the HEC and corresponding IUR should be considered to have moderate confidence as well.

Table 2-21. Evidence Integration Judgements for Each Cancer Type

Cancer Type	Human	Animal	Mechanistic
Liver	Indeterminate	Moderate (mice)	Moderate
Adrenal gland	Indeterminate	Slight (mice)	Indeterminate
Pancreas	Indeterminate	Indeterminate (rats)	Indeterminate
Kidney	Indeterminate	Indeterminate (rats)	Indeterminate

1,1,2-Trichloroethane produces multiple reactive metabolites that can damage DNA (as noted previously, a free radical, an aldehyde, an acyl chloride, etc.). One metabolite 2-chloroacetaldehyde is recognized as causing persistent DNA crosslinks, carcinogen and people with the aldehyde dehydrogenase-2 mutation are a PESS group (several million Americans). There are 22 positive genotoxicity assays based on the 2021 ATSDR report ([ATSDR, 2021](#)) and the Sapphire Group PBPK report ([Sapphire Group, 2004b](#)) supporting a linear low dose cancer assessment, also supported by the linear liver tumor dose-response in mice ($r = 0.99$). 1,1,2-Trichloroethane is immunotoxic, which is a recognized cancer mechanism, so the RfD threshold cancer approach is also a consideration; however, there lacks sufficient data to conduct a Bradford-Hill analysis for causation for this mechanism.

Overall, qualitatively 1,1,2-trichloroethane caused multiple tumors in two species (mouse and rat) ([NCI, 1978](#)). The liver tumor and adrenal gland tumor findings in the mouse study ([NCI, 1978](#)) were statistically significant in two sexes. The mouse study was rated medium quality under EPA's systematic review process. The rat study had several limitations (including shorter exposure duration and low dosing levels) but still found tumors in multiple tissues although not statistically significant (medium systematic review rating). However, the limitations of rat study design may have hindered its ability to reach statistical significance.

The immunotoxicity findings raise concerns for 1,1,2-trichloroethane to be tumorigenic in humans since immunotoxicity is a recognized mechanism for tumorigenesis ([Smith et al., 2016](#)). However, it is not proven that all immunotoxic chemicals can cause cancer. Based on 22 positive genotoxicity findings *in vitro* and *in vivo* (see Section 2.4.2), multiple reactive metabolites which can damage DNA, positive *in vivo* tumor promoter/initiation results and *in vivo* cancer study results, EPA is using the default linear low-dose approach to model the oral cancer data. This approach is used in conjunction with the use of the PBPK modeling developed by the Sapphire Group ([Sapphire Group, 2004b](#)).

Both the oral and inhalation cancer slope factors were based on the extrapolation method utilizing the linearized multistage procedure for extra risk as described in Appendix B utilizing the medium-quality NCI mouse oral cancer study and are presented in Table 2-22.

Table 2-22. Oral and Inhalation Cancer Slope Factors Across Existing Quantitative Assessments

1,1,2-Trichloroethane Mouse Study Cancer Factor	EPA 1987 IRIS (U.S. EPA, 1987)	EPA 2011 PPRTV (U.S. EPA, 2011a)	2006 OEHHHA (OEHHHA, 2006)	EPA 2026 OPPT
Oral/dermal slope factor (per mg/kg/day)	5.7E-02	5.7E-02	5.7E-02	3.48E-02
Inhalation unit risk (per $\mu\text{g}/\text{m}^3$)	1.60E-5	1.60E-5	N/A	2.98E-6
Carcinogenic in humans	Possible	Possible	Potential	Likely
EPA = Environmental Protection Agency; IRIS = Integrated Risk Information System; OEHHHA = Office of Environmental Health Hazard Assessment; OPPT = Office of Pollution Prevention and Toxics				

2.4.2 Genotoxicity Hazard Identification and Evidence Integration

Genotoxicity Mechanistic Information

The genotoxicity data regarding 1,1,2-trichloroethane describe both positive and negative findings. Across the various *in vitro* and *in vivo* methods, 22 assays reported positive findings. As discussed previously, several 1,1,2-trichloroethane *in vivo* studies with dosing in water-based systems such as drinking water dosing did not identify hazards indicated in gavage studies; thus, for 1,1,2-trichloroethane *in vitro* studies also with water-based dosing may also have false negative results. Also, *in vivo* micronucleus assays can be a single dose specifically for 1,1,2-trichloroethane ([Crebelli et al., 1999](#)), which may have challenges to reach the bone marrow, and have reported negative results for known carcinogens, while other *in vitro* micronucleus assays in mammalian cells are positive for 1,1,2-trichloroethane ([Crebelli et al., 1999](#); [Doherty et al., 1996](#); [Tafazoli and Kirsch-Volders, 1996](#)); however, based on its physical and chemical properties, 1,1,2-trichloroethane is a volatile substance and therefore *in vitro* genotoxicity results in water-based dosing for 1,1,2-trichloroethane may be false negatives. Furthermore, the mechanistic information shows more positive genotoxicity findings than negative findings.

Most *in vivo* studies listed below were positive for genotoxicity, such as the mitotic recombination assay in drosophila ([Vogel and Nivard, 1993](#)), DNA adduct formation with mouse liver DNA ([Mazzullo et al., 1986](#)), DNA adduct formation with rat liver DNA ([Mazzullo et al., 1986](#)), S-phase DNA synthesis in mouse hepatocytes ([Mirsalis et al., 1989](#)), replicative DNA synthesis in mouse hepatocytes ([Miyagawa et al., 1995](#)) and inhibition of DNA synthesis in mouse testis ([Borzelleca and Carchman, 1982](#)). Negative *in vivo* results reported by ATSDR ([2021](#)) were sex-linked recessive lethal assay in *Drosophila* ([Foureman et al., 1994](#)), micronuclei in mouse bone marrow cells single dose at 200 to 400 mg/kg ([Crebelli et al., 1999](#)), DNA unwinding in mouse hepatocytes ([Taningher et al., 1991](#)) and unscheduled DNA synthesis in mouse hepatocytes ([Mirsalis et al., 1989](#)). A summary of this information is provided in Table 2-23.

Table 2-23. *In vivo* Genotoxicity Tests of 1,1,2-Trichloroethane

Reference	Species	Tissue/Cell Type	Dose, Frequency, and Route	Endpoint	Result
Mammalian assays					
Taningher et al. (1991)	Mouse (BALB/c)	Liver/hepatocytes	900 mg/kg by single i.p. injection	DNA damage (unwinding)	Negative
Mazzullo et al. (1986)	Rats (Wistar)	Liver	6.35 µmol/kg bw by single i.p. injection	DNA adducts	Weakly positive
Mazzullo et al. (1986)	Mouse (BALB/c)	Liver	6.35 µmol/kg bw by single i.p. injection	DNA adducts	Moderately to weakly positive
Mirsalis et al. (1989)	Mouse (B6C3F1)	Liver/hepatocytes	50, 200, 1,000 mg/kg by single gavage	Unscheduled DNA synthesis	Negative for UDS
Mirsalis et al. (1989)	Mouse (B6C3F1)	Liver/hepatocytes	200, 500, 600 mg/kg by single gavage	S-phase and replicative DNA synthesis	Positive
Miyagawa et al. (1995)	Mouse (B6C3F1)	Liver/hepatocytes	200 mg/kg by single gavage	Spontaneous replicative DNA synthesis	Positive

Reference	Species	Tissue/Cell Type	Dose, Frequency, and Route	Endpoint	Result
Crebelli et al. (1999)	Mouse (CrI: CD-1 (ICR) BR)	Bone marrow	200, 400, 600 mg/kg by single i.p. injection	Micronuclei	Negative
Borzelleca (1983) ^a	Mouse	Testes	Not reported	Inhibition of DNA synthesis	Positive
Insect assays					
Foureman et al. (1994) ^a	<i>Drosophila melanogaster</i>	Whole organism	1,000 ppm ppm by feeding for 3 days or 3,300 ppm by single injection	Sex-linked recessive lethality	Negative
Vogel and Nivard (1993) ^a	<i>D. melanogaster</i>	Eye	1,000, 2,000 ppm by inhalation in sealed bottles for 17 hours	Mitotic recombination	Weakly positive; occurring at doses that were cytotoxic to developing larvae
DNA = deoxyribonucleic acid; UDS = unscheduled DNA synthesis					
^a As cited in ATSDR (2021) .					

Most *in vitro* genotoxicity assays reported by ATSDR (2021) were negative in bacterial systems with dosing in a water based media. As stated previously, multiple *in vivo* 1,1,2-trichloroethane studies dosed in water may miss important toxicology endpoints observed in gavage dosing studies, thus there is evidence that dosing in open water-based systems have decreased sensitivity for this volatile chemical. However, bacteria are procaryotes with different biological structure and metabolism than eukaryotic cells such as mammals (*i.e.* lack endoplasmic reticulum with mammalian cytochrome P450 enzymes) and bacteria lack a nucleus with complex DNA organization of eukaryotic cells. Furthermore, bacteria have decreased metabolic capacity than humans and 1,1,2-trichloroethane produces multiple reactive metabolites inside the liver cells which have great concerns for causing DNA alkylation and damage. Bacterial genotoxicity assays have employed metabolic systems such as the S9 fraction derived from the endoplasmic reticulum from rat livers; however, these metabolizing systems are outside of the bacteria which is in contrast to eukaryotic cells with metabolizing enzymes within the cell near the nucleus. Charged and reactive metabolites generated with the S9 system might not readily cross the bacterial cell membrane nor cell wall (a structure not present in mammalian cells). As described in ATSDR (2021) gene mutation assays that were negative in bacterial systems *in vitro* include studies by [Barber and Donish \(1982\)](#), [Milman et al. \(1988\)](#), [Mitoma et al. \(1985a\)](#), [Rannug et al. \(1978\)](#), [Roldán-Arjona et al. \(1991\)](#), [Simmon et al. \(1977\)](#), [Zeiger et al. \(1988\)](#) and [Mersch-Sundermann \(1989\)](#). A summary of this information is provided in Table 2-24.

Most *in vitro* genotoxicity assays based on eukaryotic models reported by ATSDR (2021) were positive (11/15 studies). These positive results include mitotic gene conversion in saccharomyces ([Bronzetti et al., 1987](#)), chromosome malsegregation in aspergillus ([Crebelli et al., 1988](#)), micronuclei in human lymphocytes ([Tafazoli and Kirsch-Volders, 1996](#)), micronuclei in human MCL-5 cells ([Doherty et al., 1996](#)), micronuclei in human lymphoblastoid cells ([Doherty et al., 1996](#)), DNA damage in human lymphocytes ([Tafazoli and Kirsch-Volders, 1996](#)), DNA synthesis in rat hepatocytes ([Reddy et al., 1993](#)), DNA repair in rat hepatocytes ([Milman et al., 1988](#)); DNA adduct formation in calf thymus cells ([DiRenzo et al., 1982b](#)) and cellular transformation in mouse BALB/c-3T3 cells ([Milman et al., 1988](#)). *In vitro* eukaryotic assays which had negative results were micronuclei in human AHH-1 cells ([Doherty et al., 1996](#)), DNA repair in mouse hepatocytes ([Milman et al., 1988](#)) and cellular transformation in mouse BALB/c-3T3 cells ([Tu et al., 1985](#)). A summary of this information is provided in Table 2-24.

Genotoxicity data are available for endpoints evaluated in the liver *in vivo* and in hepatocytes *in vitro*. No evidence of unwinding DNA damage was detected in mouse hepatocytes following intraperitoneal injection ([Taningher et al., 1991](#)) as cited in ATSDR (2021). In mice and rats administered equivalent intraperitoneal doses of 1,1,2-trichloroethane, DNA adducts were detected in the livers of both species, with significantly greater levels of DNA binding occurring in mice ([Mazzullo et al., 1986](#)) as cited in ATSDR (2021). Following gavage dosing of mice, 1,1,2-trichloroethane did not elicit unscheduled DNA synthesis but did cause S-phase and replicative DNA synthesis in hepatocytes [Mirsalis et al. \(1989\)](#) and [Miyagawa et al. \(1995\)](#) as cited in ATSDR (2021). Induction of DNA synthesis may be an important factor in liver tumor formation (2021). DNA synthesis or repair was observed after *in vitro* exposure in rat hepatocytes (([Reddy et al., 1993](#); [Milman et al., 1988](#)) as cited in ATSDR (2021)), but not in mouse hepatocytes (([Milman et al., 1988](#)) as cited in ATSDR (2021)). EPA concurs that these results in hepatocytes suggest that DNA adducts and/or damage may be involved in the liver tumors identified in mice after oral dosing with 1,1,2-trichloroethane ([ATSDR, 2021](#)). A summary of this information is provided in Table 2-24.

Data from genotoxicity assays in cells or tissues from the mouse adrenal gland were not located. Results of additional genotoxicity studies of 1,1,2-trichloroethane indicate that it is not mutagenic but may induce micronuclei and DNA damage. 1,1,2-Trichloroethane was not mutagenic in a series of bacterial mutation assays in the presence or absence of metabolic activation (([Roldán-Arjona et al., 1991](#); [Mersch-Sundermann, 1989](#); [Milman et al., 1988](#); [Zeiger et al., 1988](#); [Mitoma et al., 1985a](#); [Barber and Donish, 1982](#); [Rannug et al., 1978](#); [Simmon et al., 1977](#)) as cited in ATSDR (2021)) or in a sex-linked recessive lethal test in *Drosophila melanogaster* exposed via feed (([Foureman et al., 1994](#)) as cited in ATSDR (2021)). Although no micronucleus induction was detected in bone marrow cells of mice exposed to 1,1,2-trichloroethane via intraperitoneal injection (([Crebelli et al., 1999](#)) as cited in ATSDR (2021)), micronuclei were formed in several human cell types exposed *in vitro* without metabolic activation (([Doherty et al., 1996](#)) and ([Tafazoli and Kirsch-Volders, 1996](#)) as cited in ATSDR (2021)). DNA damage was identified in human lymphocytes exposed *in vitro* in the presence or absence of metabolic activation (([Tafazoli and Kirsch-Volders, 1996](#)) as cited in ATSDR (2021)). A summary of this information is provided in Table 2-24.

1,1,2-Trichloroethane was weakly positive for mitotic recombination in *D. melanogaster* exposed via inhalation, but only at a cytotoxic concentration ([Vogel and Nivard, 1993](#)) as cited in ATSDR (2021)). Limited data indicate that 1,1,2-trichloroethane may cause chromosome malsegregation, mitotic gene conversion, or induction of dormant λ prophage DNA replication in *E. coli in vitro* ([Bronzetti et al. \(1987\)](#), [Crebelli et al. \(1988\)](#) and [Demarini and Brooks \(1992\)](#) as cited in ATSDR (2021)). Mixed results were obtained for cellular transformation in mouse BALB/c-3T3 cells without activation ([Milman et al. \(1988\)](#) and [Tu et al. \(1985\)](#) as cited in ATSDR (2021)). A summary of this information is provided in Table 2-24.

2695 **Table 2-24. *In Vitro* Genotoxicity Tests of 1,1,2-Trichloroethane**

Reference	Test System	Doses and Exposure Conditions	Endpoints	Results
Bacteria				
Barber and Donish (1982)	<i>Salmonella typhimurium</i> (TA98, TA100, 1535)	Not reported; 48 hours in a closed, vapor-phase system (plate incorporation)	Gene mutation (Ames test)	Negative (+/-S9)
Milman et al. (1988)	<i>S. typhimurium</i> (TA98, TA100, TA1535, 1537)	Not reported; plates enclosed in 9 L desiccators	Gene mutation (Ames test)	Negative (+/-S9)
Mitoma et al. (1985b) ^a	<i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537)	Not reported	Gene mutation	Negative (+/-S9)
Rannug et al. (1978)	<i>S. typhimurium</i> (TA1535)	20, 40, 60 µmol/plate for 48 hours (plate incorporation)	Gene mutation (Ames test)	Negative (+/-S9)
Roldán-Arjona et al. (1991)	<i>S. typhimurium</i> (BA13)	0 to 13.12 µmol/plate for 20 minutes pre-incubation	Gene mutation (Ara test)	Negative (+/-S9)
Simmon et al. (1977)	<i>S. typhimurium</i> (TA100)	Up to 5 mg/plate for 8 hours in dessicators	Gene mutation (Ames test)	Negative (+/-S9)
Zeiger et al. (1988)	<i>S. typhimurium</i> (TA97, TA98, TA100, TA1535, TA1537)	0 to 3,333 µg/plate for 20 minutes pre-incubation in capped tubes	Gene mutation (Ames test)	Negative (+/-S9)
Mersch-Sundermann (1989) ^a	<i>S. typhimurium</i> (TA97, TA98, TA100, TA102)	Not reported	Gene mutation (Ames test, spot-test, and preincubation procedure)	Negative (+/-S9)
Demarini and Brooks (1992)	<i>E. coli</i> WP2 _s (λ)	8,438.46 to 540,061.46 µM/plate for 24 hours (in suspension)	λ Prophage induction (microsuspension assay)	Positive (+/-S9)
Fungi				
Bronzetti et al. (1987)	<i>Saccharomyces cerevisiae</i>	Not reported	Mitotic gene conversion	Positive (+/-S9)
Crebelli et al. (1988)	<i>Aspergillus nidulans</i> P1	0 to 0.1 % (v:v) for up to 3 hours in sealed tubes	Chromosome malsegregation	Positive (-S9)
Mammalian cells				
Reddy et al. (1993) ^a	Rat hepatocytes	Not reported	DNA synthesis	Positive (-S9)
Milman et al. (1988)	Rat hepatocytes	Not reported	DNA repair	Positive (-S9)
Milman et al. (1988)	Mouse hepatocytes	Not reported	DNA repair	Negative (-S9)
Williams (1983)	Rat hepatocytes	10 ⁻⁵ to 1% for 18 to 20 hours	DNA repair	Positive (-S9)
Williams (1983)	Mouse hepatocytes	10 ⁻⁶ to 1% for 18 to 20 hours	DNA repair	Negative (-S9)
Milman et al. (1988)	Mouse BALB/c-3T3 cells	Not reported	Cellular transformation	Positive (-S9)
Tu et al. (1985)	Mouse BALB/c-3T3 cells	0 to 50 µg/mL for 3 days	Cellular transformation	Weakly positive (-S9)
Kim et al. (2002)	Chinese hamster lung V79D-MZ	0 to 10 mM for 1.33 times the cell cycle time (cell-	Cell division and chromosome aberrations	Positive

Reference	Test System	Doses and Exposure Conditions	Endpoints	Results
		cycle time estimated to be 12 hours)		
Kim et al. (2002)	MB1 (CYP2E1 +) cells	0 to 10 mM for 1.33 times the cell cycle time (cell-cycle time estimated to be 16 hours)	Cell division and chromosome aberrations	Positive
Human cells				
Doherty et al. (1996)	Human B lymphoblastoid AHH-1 Tk +/- cells	0 to 5 mM for 18 hours (incorporated into media)	Micronuclei	Negative (-S9)
Doherty et al. (1996)	Human B lymphoblastoid MCL-5 cells	0 to 5 mM for 24 hours (incorporated into media)	Micronuclei	Positive (-S9)
Doherty et al. (1996)	Human B lymphoblastoid h2E1 cells	0 to 5 mM for 24 hours (incorporated into media)	Micronuclei	Positive (-S9)
Tafazoli and Kirsch-Volders (1996)	Primary human lymphocytes	0 to 5 mM	Micronuclei	Positive with no dose-response (-S9) Equivocal (+S9)
Tafazoli and Kirsch-Volders (1996)	Primary Human lymphocytes	2.5 mM for 1 or 3 hours	DNA damage	Positive (+/-S9)
Cell-free systems				
Mazzullo et al. (1986)	Calf thymus DNA	2.5 µCi for 90 minutes	DNA binding	Positive (+S9) Negative (-S9)
DiRenzo et al. (1982a)	Calf thymus DNA	1 mM for 60 minutes	DNA adduct formation	Positive (-S9)
DNA = deoxyribonucleic acid ^a As cited in ATSDR (2021) .				

The Sapphire Group report evaluated 1,1,2-trichloroethane cancer potential and concluded that 1,1,2-trichloroethane is genotoxic and stated, “toxicological evidence supporting the use of amount metabolized as the internal dose measure includes genotoxicity studies” ([Sapphire Group, 2004b](#)). Fourteen of the twenty-one genotoxicity studies evaluated in The Sapphire Group report were positive.

2.4.3 Carcinogenic Mode of Action Summary and Conclusions

Summary and Conclusions

1,1,2-Trichloroethane has 22 positive genotoxicity study findings (*in vitro*, *in vivo*, *Drosophila*, mice, rats, etc.), produces multiple reactive metabolites and the liver tumor incidence has a high correlation coefficient for the dose-response ($r = 0.99$ for both male and female mice), so the default linear cancer approach is appropriate. 1,1,2-Trichloroethane does produce immunotoxicity in mice which could contribute to tumorigenesis; however, there is insufficient information to satisfy a Bradford-Hill Criteria analysis to set a threshold NOAEL value with confidence based on this sole mode of action. Based on evidence of genotoxicity and insufficient evidence for a threshold mode of action to set a threshold dose, EPA is applying a linear non-threshold approach, consistent with EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)). While there are positive genotoxicity results, there is no definitive data to

conclusively prove a mutagenic mode of action for 1,1,2-trichloroethane, therefore, an age dependent adjustment factor is not being applied.

Cancer Dose-Response Assessment

The medium-quality NCI cancer study ([NCI, 1978](#)) demonstrated a robust dose-response for liver tumors in both sexes in mice. The cancer slope factors are calculated in the benchmark doses Appendix B. For the inhalation unit risk calculations, the peer-reviewed Sapphire Group PBPK Model produced HEC values that were utilized as inputs for the benchmark dose analysis ([Sapphire Group, 2002](#)).

2.4.4 Selection of Studies and Endpoint Derivation for Carcinogenic Dose-Response Assessment

There is confidence in utilizing the medium-quality NCI 1,1,2-trichloroethane mouse oral cancer study ([NCI, 1978](#)) for the 1,1,2-trichloroethane cancer assessment based on liver tumors, is described below. The dose-response for liver tumors has a high correlation and the study authors reported it as statistically significant ($r = 0.99$, $p < 0.001$). The linear tumor dose-response in both male and female mice supports the linear low dose liver cancer model with a high 77 to 89% tumor incidence in the high-dose group and 33% to 37% tumor incidence in the low-dose group relative to only 0 to 10% liver tumors in the vehicle control groups. The 1,1,2-trichloroethane mouse study has no confounding factors in vehicle control group (male or female), but low levels of pneumonia were reported in the study. There was an average of 2.2% pneumonia across all groups (0.8% males, 3.7% females). Most pneumonia was in the high-dose group and may be due to chemical pneumonia (where an irritating chemical causes pneumonia), and as with oral dosing, 1,1,2-trichloroethane is partially eliminated through expiration via the lungs. For the 1,1,2-trichloroethane cancer study in mice, the incidence of pneumonia in the vehicle control groups was 0% and study had low mortality in test groups, in particular, not due to pneumonia as a confounding factor in male or female mice. The survival of male mice was not affected by treatment. The reduced survival was not dose responsive since survival was reduced just in female mice and only at the low dose, NCI experts concluded it was not a significant factor in study results. The number of test animals increases confidence in the results (45–49 in treated groups for each sex). Shorter-term studies reported liver pathology as well ([Milman et al., 1988](#)).

There were different rooms for mice and rats, so the rat study results would not be affected by any pneumonia concerns and can be independently evaluated. The chemical administration was by gavage dosing, so doses are well quantified and no co-exposure to other chemicals due to volatilization from other dosing types such as from food or water. The 1,1,2-trichloroethane mouse cancer study ([NCI, 1978](#)) is the best available science using target chemical study with no read across uncertainties and time expenditures using analog data. The PBPK model and ADME information indicates that doses did not saturate metabolism which is also supported by the linear tumor dose-response. The body weights of male and female mice were not markedly affected by treatment, supporting the conclusion by the study authors that tested doses did not exceed the maximum tolerated dose. This study also found tumors in the adrenal gland. The mouse cancer study ([NCI, 1978](#)) has a medium systematic review rating and was utilized in multiple authoritative documents, as noted previously in Section 2.4.1.3.1, Cancer Classification and Evidence Integration Conclusions.

2.4.5 Duration, Dosimetric, and Unit Adjustments

An oral cancer study in mice ([NCI, 1978](#)) with 5 day-per-week dosing was utilized for the CSF and IUR calculations. The HED value was calculated from the study based on body weight $^{3/4}$ -scaling and the study doses converted to the full week basis by multiplying the doses by the 5 days/7 days ratio. Other equations are listed in Section 2.3.1.4.1 and POD table notes. The HEC values for the IUR calculations were derived by the Sapphire Group PBPK Model from the oral cancer study data ([Sapphire Group,](#)

2004b). The benchmark dose analysis and models evaluated to calculate the oral cancer slope factors and inhalation unit risk values are listed in Appendix B.

2.4.6 Cancer IUR and CSF for Lifetime Exposures

The cancer CSF and IUR BMD analysis is shown in Appendix B and values are listed in Table 2-25 and Table 2-26. For the oral cancer slope factor, the male BMD value is only 14% higher than the BMDL value and well within the 3-fold range considered to be acceptable. For the inhalation unit risk value, the male BMC value is 2.2-fold higher than the BMCL value and also within the 3-fold range considered to be acceptable. Other factors for model selection are also consider the lowest scaled residuals and the best visual fit.

Table 2-25. Oral and Dermal Cancer Slope Factors

Mouse Tumor	Oral and Dermal Slope Factor	BMD	BMD _L
Female Liver, HED Input	1.88E-02 per mg/kg/day	8.80 mg/kg/day	5.32 mg/kg/day
Male Liver, HED Input	3.48E-02 per mg/kg/day	3.72 mg/kg/day	2.87 mg/kg/day
BMD = benchmark dose; BMDL = lower bound of the benchmark dose			

Table 2-26. Inhalation Unit Risk Cancer Factors

Mouse Tumor	IUR	BMC	BMCL
Female liver, PBPK HEC input in mg/m ³ from oral data	2.38E-06 per ug/m ³	62.40 mg/m ³	42.04 mg/m ³
Female liver, PBPK HEC input in ppm from oral data	0.0130 per ppm	11.47 ppm	7.72 ppm
Male liver, PBPK HEC input in mg/m ³ from oral data	2.98E-06 per ug/m ³	73.30 mg/m ³	33.54 mg/m ³
Male liver, PBPK HEC input in ppm from oral data	0.0163 per ppm	13.48 ppm	6.14 ppm
BMC = benchmark concentration; BMCL = lower bound of the benchmark concentration; HEC = human equivalent concentration; IUR = inhalation unit risk; PBPK = physiologically-based pharmacokinetic			

2.5 Consideration of PESS

2.5.1 PESS Based on Greater Susceptibility

EPA addresses subpopulations expected to be more susceptible to 1,1,2-trichloroethane exposure than other populations. Table 2-27 presents the data sources that were used in the PESS analysis that evaluated susceptible subpopulations and identifies whether and how the subpopulation was addressed quantitatively in the risk evaluation of 1,1,2-trichloroethane.

EPA examined sources of biological susceptibility for each of the susceptibility factors in Table 2-27. The Agency quantitatively incorporated these considerations into hazard values and subsequent risk estimates when possible; however, for many factors, EPA did not identify any reasonably available information to support quantitative adjustment of hazard/risk values. For these other factors, the Agency acknowledges either direct or indirect information suggesting additional susceptibility of certain subpopulations ([Exposure Assessment Tools by Lifestages and Populations - Highly Exposed or Other Susceptible Population Groups](#), accessed January 15, 2026); however, there is insufficient information to calculate quantitative risks for 1,1,2-trichloroethane.

EPA utilized the best available science based on the weight of scientific evidence. EPA refined the UF_A value from 10 to 3 based on interspecies body weight scaling and inhalation dosimetric modeling. EPA used the most sensitive effects from rodent assays for non-cancer dose-response modeling. A $10\times$ intraspecies uncertainty factor (UF_H) factor was applied to account for human toxicokinetic and toxicodynamic variability, which is expected to account for considerations such as genetic polymorphisms and existing disease states. EPA is also using the most sensitive relevant species of rats and mice and the results for the most sensitive sex for deriving PODs to be used in risk estimation. EPA utilized a PBPK model for the oral to inhalation route to route extrapolation.

Infants are a potentially susceptible lifestage because of their higher exposure per body weight, immature metabolic systems, and the potential for chemical toxicants to disrupt sensitive developmental processes. Studies and biomonitoring data demonstrating the presence of 1,1,2-trichloroethane in human or rodent milk have not been identified and currently no animal PBPK models exist for 1,1,2-trichloroethane with lactation as a route of exposure. Although some animal studies indicated developmental toxicity following maternal exposure, no studies have evaluated only lactational exposure from quantified levels of 1,1,2-trichloroethane in milk. In the absence of biomonitoring data and for chemicals with $\log P$ less than 4 such as 1,1,2-trichloroethane ($\log P = 1.89$), milk concentrations are assumed to be driven only by passive transport ([Ebert et al., 2020](#)). There is substantial uncertainty around the assumption of passive transport in the absence of data, but in this scenario, additional modeling based on available data and default assumptions will not provide new information or address data gaps. Additionally, uncertainties arise pertaining to the toxic moiety in infants and whether the model can capture that behavior. 1,1,2-Trichloroethane is lipophilic and distributes preferentially into lipid-rich tissues and would likely partition into breast milk, but the relationship between lipophilicity and milk transfer is not linear. Thus, PBPK modeling was not used to predict breast milk levels as it would likely lead to higher uncertainty.

For cancer, the dose-response model applied to animal tumor data employed low-dose linear extrapolation, and this assumes that 1,1,2-trichloroethane increased exposure is associated with a linear risk of getting cancer. EPA made this assumption in the absence of an established MOA for 1,1,2-trichloroethane and according to guidance from U.S. EPA's *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)).

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Table 2-27. PESS Evidence Crosswalk for Biological Susceptibility Considerations

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to 1,1,2-Trichloroethane		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to 1,1,2-Trichloroethane		Susceptibility Addressed in Risk Evaluation
		Description of Interaction	Key Citation(s)	Description of Interaction	Key Citation(s)	
Lifestage	Embryos/fetuses/infants	An epidemiology study identified associations between maternal exposure to 1,1,2-trichloroethane and other chlorinated solvents (based on proximity to emissions sites) and neural tube defects, spina bifida, septal heart defects, and cleft palate in offspring.	(Brender et al., 2014) mentioned in Section 2.3.1.1.3			The most sensitive effects from rodent assays were used for non-cancer dose-response modeling.
	Pregnancy/lactating status	No direct evidence identified.		Pregnant/lactating women are considered a sensitive lifestage owing to physiological shifts (<i>e.g.</i> , changes in breathing and heart rates, metabolism, blood volume and distribution to the tissues).	(Varshavsky et al., 2020 ; U.S. EPA, 1991)	EPA applied a 10× UF _H .
	Males of reproductive age	Increased testes weight was observed in males following oral short-term or intermediate exposure.	(White et al., 1985)			The most sensitive effects from rodent assays were used for non-cancer dose-response modeling.
	Children	No direct evidence identified.		Childhood is considered a sensitive lifestage due to the continued development of various organ systems.	(U.S. EPA, 1991)	EPA applied a 10× UF _H .
	Elderly	No direct evidence identified.		The elderly are more susceptible to immune and respiratory effects due to age-related reductions in immune response (<i>i.e.</i> , immunosenescence) and lung function, respectively.	(Luoto et al., 2019 ; Fulop et al., 2016)	EPA applied a 10× UF _H .
Pre-existing disease or disorder	Health outcome/target organs	Increased indices of hepatotoxicity (<i>i.e.</i> , serum alanine aminotransferase [ALT] and hepatic triglycerides) were observed	(Hanasono et al., 1975)			EPA applied a 10× UF _H .

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to 1,1,2-Trichloroethane		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to 1,1,2-Trichloroethane		Susceptibility Addressed in Risk Evaluation
		Description of Interaction	Key Citation(s)	Description of Interaction	Key Citation(s)	
Pre-existing disease or disorder		in alloxan-diabetic rodents relative to controls following acute intraperitoneal exposure.				
	Toxicokinetics	No direct evidence identified.		Higher rates of metabolism (<i>e.g.</i> , by cytochrome P450) resulting in increased reactive metabolites or glutathione depletion would increase susceptibility, especially for liver toxicity (a major site of metabolism).	Section 2.2.3; (ATSDR, 2021)	EPA applied a 10× UF _H .
Lifestyle activities	Smoking	No direct evidence identified.		A regular smoking habit or exposure to second-hand tobacco smoke has a clear effect on respiratory function, especially in younger lifestages.	(Chatzimicael et al., 2008 ; Vianna et al., 2008)	No direct evidence available.
	Alcohol consumption	Liver toxicity (measured as serum ALT level) was potentiated in rodents pretreated with ethanol.	(Klaassen and Plaa, 1966) in Section 2.3.1.1.4			Quantitative data for this chemical are not available based on alcohol consumption.
	Physical activity	No direct evidence identified.		Insufficient activity may increase susceptibility to multiple health outcomes. Overly strenuous activity may also increase susceptibility.	(CDC, 2022)	No direct evidence available.
Sociodemo-graphics	Sex	Health effects in rodents observed following oral or inhalation exposures demonstrated differential sensitivity across sexes.	(WIL Research, 2002 ; White et al., 1985)			Based on the best available information and weight of scientific evidence, either the most sensitive sex from rodent assays was used for non-cancer dose-response modeling, or if both sexes were modeled, the most sensitive POD was

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to 1,1,2-Trichloroethane		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to 1,1,2-Trichloroethane		Susceptibility Addressed in Risk Evaluation
		Description of Interaction	Key Citation(s)	Description of Interaction	Key Citation(s)	
						selected for use in risk estimation.
Nutrition	Diet	Tissue:air partition coefficients indicate preferential accumulation in adipose tissue, suggesting that obesity may result in a higher body burden for a given exposure.	(Gargas et al., 1989) in Section 2.2.1			Quantitative data for this chemical are not available based on differing eating habits or obesity.
	Malnutrition	No direct evidence identified.		Micronutrient malnutrition can lead to multiple developmental outcomes that include birth defects, maternal and infant deaths, low birth weight, and poor fetal growth, among others.	(CDC, 2023)	No direct evidence available.
Genetics/ epigenetics	Health outcome/ target organs	No direct evidence identified.		Any polymorphism or mutation impacting biological functions for critical organ systems would impact susceptibility to 1,1,2-trichloroethane.	(Miller et al., 2001)	EPA applied a 10× UF _H .
	Toxicokinetics	No direct evidence identified.		Any genetic or epigenetic changes impacting rates of metabolism and/or the production or detoxification of reactive metabolites (e.g., an inherited aldehyde dehydrogenase-2 [ALDH-2] mutation) would increase susceptibility, especially for liver toxicity (a major site of metabolism).	Section 2.4.1.3 (ATSDR, 2021)	EPA applied a 10× UF _H .

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to 1,1,2-Trichloroethane		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to 1,1,2-Trichloroethane		Susceptibility Addressed in Risk Evaluation
		Description of Interaction	Key Citation(s)	Description of Interaction	Key Citation(s)	
Other chemical and nonchemical stressors	Built environment	No direct evidence identified.		Poor-quality housing is associated with a variety of negative health outcomes.	(ODPHP, 2023a)	No direct evidence available.
	Social environment	No direct evidence identified.		Social isolation and other social determinants (<i>e.g.</i> , decreased social capital, stress) can lead to negative health outcomes.	(ODPHP, 2023b)	No direct evidence available.
	Chemical co-exposures	1,1,2-Trichloroethane-mediated hepatotoxicity (increased serum aspartate aminotransferase [AST] and/or ALT) has been potentiated by pretreatment with acetone, ethanol, isopropyl alcohol, or phenobarbital.	Section 2.3.1.1.4		(MacDonald et al., 1982 ; Traiger and Plaa, 1974 ; Carlson, 1973 ; Klaassen and Plaa, 1966)	Quantitative data for this chemical are not available based on co-exposures.
UF _H = intraspecies uncertainty factor						

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2.6 Human Health Hazard Assessment Conclusions

The 1,1,2-trichloroethane human health toxicology database includes medium- and high-quality literature studies and standard guideline studies that were evaluated by the EPA systematic review process for endpoint selection and POD derivation that provided confidence in these decisions on a weight of scientific evidence basis. Table 2-28 provides a summary of the confidence for the selected PODs for 1,1,2-trichloroethane. The hazards identified for 1,1,2-trichloroethane were neurotoxicity, respiratory tract pathology, immunotoxicity, liver pathology, irritation, genotoxicity, tumors, male reproductive toxicity, body weight changes and mortality. Metabolism of 1,1,2-trichloroethane produces reactive metabolites such as a free radical, a chlorinated aldehyde, an acyl chloride, and hydrochloric acid. Upon evaluating the reasonably available information for the oral, dermal, and inhalation scenarios, dose-response analysis identified human hazard endpoints and PODs that were derived for acute, intermediate, and chronic exposures, as well as derivation of oral, dermal, and inhalation cancer slope values.

The selected endpoints and PODs are presented in Table 2-29, Table 2-30, and Table 2-31. Benchmark dose analysis provided consistent 95% confidence levels for POD derivation utilizing response information at all doses. The PBPK model produced confidence in the oral to inhalation route refinement of the cancer inhalation unit risk calculations. A weight of scientific evidence was the basis of the rationale for selecting these hazard thresholds and confidence levels. EPA considered all information that was reasonably available for 1,1,2-trichloroethane identified through the OPPT systematic review process under the TSCA to characterize human health hazard endpoints and PODs. Overall, there is confidence in the endpoints and PODs selected for the risk evaluation are sensitive and human health protective. The weight of scientific evidence for the POD selection confidence conclusions are listed below.

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Table 2-28. Confidence Summary for Selection of the PODs for 1,1,2-Trichloroethane Human Health Hazard Assessment

Exposure Scenario	Acute			Intermediate			Chronic			Cancer		
	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal
Study and OQD	(WIL Research, 2004), High	(WIL Research, 2001) High	(WIL Research, 2004), High	(Sanders et al., 1985), High	(WIL Research, 2002), High	(Sanders et al., 1985), High	(Sanders et al., 1985), High	(WIL Research, 2002), High	(Sanders et al., 1985), High	(NCL, 1978), Medium	(NCL, 1978), Medium	(NCL, 1978), Medium
POD	NOAEL=55 mg/kg LOAEL=95 mg/kg Neurotoxicity as decreased motor activity in a guideline acute neurotoxicity study	LOAEC = 316 mg/m ³ (58 ppm) Olfactory tissue necrosis	NOAEL=55 mg/kg LOAEL=95 mg/kg Neurotoxicity as decreased motor activity in a guideline acute neurotoxicity study	NOAEL = 3.9 mg/kg LOAEL = 44 mg/kg Immunotoxic as decreased hemagglutination titers	BMCL10 = 22.11 mg/m ³ (4.05 ppm) BMC10 = 31.15 mg/m ³ (5.71 ppm) Model selected provided adequate fit	NOAEL = 3.9 mg/kg LOAEL = 44 mg/kg Immunotoxic as decreased hemagglutination titers	From intermed. duration	From intermed. duration	From intermed. duration	BMDL = 2.87 mg/kg/day BMC = 3.72 mg/kg/day Model selected provided adequate fit	BMCL= 33.54 mg/m ³ BMD = 73.30 mg/m ³ Model selected provided adequate fit	BMDL=2.87 mg/kg/day BMD=3.72 mg/kg/day Model selected provided adequate fit
HED/ HEC/ CSF/ IUR	NOAEL HEDcontinuous = 12.6 mg/kg	LOAECadj HEC = 6.1 mg/m ³ (1.1 ppm)	NOAEL HEDcontinuous = 12.6 mg/kg	NOAEL HEDcontinuous = 0.52 mg/kg/day	BMCL10 HECContinuous = 0.62 mg/m ³ (0.11 ppm)	NOAEL HEDcontinuous = 0.52 mg/kg/day	From intermed. duration	From intermed. duration	From intermed. duration	0.0348 per mg/kg/day	2.98×10 ⁻⁶ per ug/m ³	0.0348 per mg/kg/day
Route-to-route extrapol.	Route- specific data	Route-specific data	From acute oral data	Route-specific data	Route-specific data	From intermediate duration oral	Route-specific data	Rout-e specific data	From intermed. duration oral data	Route-specific data	From oral data using PBPK model refinement	From oral data
Interspecies consideration	Allometric ³ / ₄ BW scaling (PK = 1×, PD = 3×)	Dosimetrically adjusted (PK = 1×, PD = 3×)	Allometric ³ / ₄ BW scaling (PK = 1×, PD = 3×)	Allometric ³ / ₄ BW scaling (PK = 1×, PD = 3×)	Dosimetrically adjusted (PK = 1×, PD = 3×)	Allometric ³ / ₄ BW scaling (PK = 1×, PD = 3×)	Allometric ³ / ₄ BW scaling (PK = 1×, PD = 3×)	Dosimetrically adjusted (PK = 1×, PD = 3×)	Allometric ³ / ₄ BW scaling (PK = 1×, PD = 3×)	N/A	N/A	N/A
Intraspecies consideration	Default 10× factor	Default 10× factor	Default 10× factor	Default 10× factor	Default 10× factor	Default 10× factor	Default 10× factor	Default 10× factor	Default 10× factor	N/A	N/A	N/A
Other UFs	N/A	UFL=3	N/A	N/A	N/A	N/A	UFs = 10	UFs = 10	UFs = 10	N/A	N/A	N/A
Overall confidence comment	Robust confidence in the duration- and route specific POD from a study of high OQD	Robust confidence in the duration- and route-specific POD from a study of high OQD	Moderate-to-robust confidence in the POD from a study of high OQD using a default extrapolation	Robust confidence in the duration- and route specific POD from a study of high OQD	Robust confidence in the duration- and route-specific POD from a study of high OQD	Moderate-to-robust confidence in the POD from a study of high OQD using a default extrapolation	Moderate-to-robust confidence in the POD from a study of high OQD using a default	Moderate- Robust confidence in the POD from a study of high OQD using a default	Moderate confidence in the POD from a study of high OQD using a default extrapolation	Moderate confidence in a duration specific and route specific data from a	Low-to-moderate confidence in the duration-specific POD from a study of	Low-to-moderate confidence in the POD from a duration specific study of

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Exposure Scenario	Acute			Intermediate			Chronic			Cancer		
	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal
		Harmonized with ATSDR	approach and applying route-to route extrapolation. A high quality guideline dermal absorption study on human skin was utilized.	Harmonized with ATSDR and PPRTV	Harmonized with ATSDR and PPRTV	approach and applying route-to route extrapolation. A high quality guideline dermal absorption study on human skin was utilized.	extrapolation approach and applying a duration extrapolation Harmonized with PPRTV	extrapolation approach Harmonized with PPRTV	approach and applying a duration extrapolation	study of medium OQD Harmonized with PPRTV and IRIS	medium OQD using a high quality PBPK model for route to route extrapolation from the oral data. Harmonized with PPRTV and IRIS	medium OQD using a default extrapolation approach and applying route-to route extrapolation from oral data. A high quality guideline dermal absorption study on human skin was utilized. Harmonized with PPRTV and IRIS
ATSDR = Agency for Toxic Substances and Disease Registry; BMC = benchmark concentration; BMCL = lower bound of the benchmark concentration; BMD = benchmark dose; BMDL = lower bound of the benchmark dose; BW = body weight; CSF = cancer slope factor; HEC = human equivalent concentration; HED = human equivalent dose; IRIS = Integrated Risk Information System; IUR = inhalation unit risk; LOAEL = lowest-observed-adverse-effect level; NOAEC = no-observed-adverse-effect level; OQD = overall study quality determination; PB = physiologically-based; PD = pharmacodynamics; PK = pharmacokinetics; POD = point of departure; PPRTV = provisional peer reviewed toxicity values; UF _L = LOAEL-to-NOAEL uncertainty factor; UFs = subchronic-to-chronic duration extrapolation												

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Duration	Effect	Study POD	NOAEL HED	Uncertainty Factors	Total Uncertainty Factors	Reference, Species, Duration, Route	Confidence Conclusion
Acute	Neurotoxicity, Decreased acute motor activity in rats	LOAEL=95 mg/kg NOAEL=55 mg/kg	NOAEL HED = 12.6 mg/kg	UF _A = 3 UF _H = 10	30	(WIL Research, 2004) Sprague-Dawley Rats Acute Oral, Acute Neurotoxicity Guideline Study OECD 424	Oral – Robust
							Dermal – Moderate-to-Robust
Intermediate	Immunotoxicity, Decreased hemagglutination titers in mice	LOAEL=44 mg/kg NOAEL=3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10	30	(Sanders et al., 1985) CD-1 Mice 90 days Oral	Oral – Robust
							Dermal – Moderate-to-Robust
Chronic	Immunotoxicity, Decreased hemagglutination titers in mice	LOAEL=44 mg/kg NOAEL=3.9 mg/kg	NOAEL HED = 0.52 mg/kg/day	UF _A = 3 UF _H = 10 UF _S = 10	300	(Sanders et al., 1985) CD-1 Mice 90 days Oral	Oral – Moderate-to-Robust
							Dermal – Moderate
HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; UF _S = subchronic-to-chronic uncertainty factor							

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2853 **Table 2-30. PODs for Inhalation Scenarios for 1,1,2-Trichloroethane**

Duration	Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Summary
Acute	Olfactory epithelium necrosis	LOAEC = 316 mg/m ³ (58 ppm) in 4 hours	LOAECadj = 52.7 mg/m ³ (9.7 ppm) LOAECadj HEC = 6.1 mg/m ³ (1.1 ppm)	UF _A = 3 UF _H = 10 UF _L = 3	100	(WIL Research, 2001) F-344 Rats 4 hours Inhalation, TSCA 799.9135	Robust
Intermediate	Lesions in the olfactory epithelium	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm) BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm) BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm)	UF _A = 3 UF _H = 10	30	(WIL Research, 2002) F-344 Rats 13 weeks, 6 hours/day, 5 days/week, Whole body Inhalation, TSCA 799.9346	Robust

Duration	Hazard Effect	Study POD	POD	Uncertainty Factors	Total Uncertainty Factor	Reference, Species, Duration, Route	Confidence Summary
Chronic	Lesions in the olfactory epithelium	BMC ₁₀ = 31.15 mg/m ³ (5.71 ppm) BMCL ₁₀ = 22.11 mg/m ³ (4.05 ppm)	BMCL ₁₀ = 3.95 mg/m ³ (0.72 ppm) BMCL ₁₀ HEC = 0.62 mg/m ³ (0.11 ppm)	UF _A = 3 UF _H = 10 UF _S = 10	300	(WIL Research, 2002) F-344 Rats 13 weeks, 6 hours/day, 5 days/week, Whole body Inhalation, TSCA 799.9346	Robust
BMC = benchmark concentration; BMCL = lower bound of the benchmark concentration; HEC = human equivalent concentration; LOAEC = lowest-observed-adverse-effect level; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor Acute Scenario: Inhalation study is 4 hours in one 24-hour day. Continuous is 24 hours in 1 day. POD Continuous = Study POD × (4 hours per day/24 hours per day); POD Continuous HEC = POD Continuous × RGDR; RGDR=0.115 based on study animal weight data Intermediate and Chronic Scenarios: Inhalation study is 6 hours per day and 5 days per week; POD is 168 hours per week; Intermediate and Chronic POD Continuous = Study POD(6 hours per day/24 hours per day) × (5 days per week/7 days per week); POD HEC = POD × RGDR; RGDR = 0.157 based on animal weight data in study							

Table 2-31. Cancer Hazard Values for Risk Estimates of Lifetime Exposure Scenarios

Oral/Dermal Slope Factor	(Inhalation) Unit Risk	Reference	Confidence Summary
3.48E-02 per mg/kg/day	1.63E-02 per ppm (2.98E-06 per µg/m ³)	NCI 1978 Oral Cancer Study in Mice 64554 utilized for both OSF and IUR	Oral – Moderate Dermal and Inhalation – Low-to-Moderate
IUR = inhalation unit risk; OSF = oral slope factor; ppm = parts per million			

3 ENVIRONMENTAL HAZARD ASSESSMENT

3.1 Approach and Methodology

TSCA requires that EPA use data and/or information in a manner consistent with the best available science and that the Agency base decisions on the weight of scientific evidence. To meet the TSCA science standards, the EPA applies a systematic review process to identify data and information across taxonomic groups for both aquatic and terrestrial organisms with a focus on apical endpoints (e.g., those affecting survival, growth, or reproduction). The data collection, data evaluation, and data integration stages of the systematic review process are used to develop the hazard assessment to support the integrative risk characterization. The Agency uses several considerations when weighing scientific evidence to determine confidence in the environmental hazard data. These considerations include the quality of the database, consistency, strength and precision, biological gradient/dose-response, and relevance. During scoping and problem formulation, EPA reviewed potential environmental hazards associated with 1,1,2-trichloroethane. EPA identified sources of environmental hazard data shown in Figure 2-10 of *the Scope of the Risk Evaluation for 1,1,2-Trichloroethane* ([U.S. EPA, 2020](#)). Initial reviews and public comments emphasized the importance of conducting risk evaluations to a high degree of accuracy and developing conclusions of high confidence to develop effective risk mitigation strategies that are specifically tailored to a condition of use. With this goal in mind, EPA sought additional information about the toxicity to aquatic benthic midges (*Chironomus*) following chronic exposures via sediment with a test order under TSCA section 4(a)(2) (*TSCA section 4(a)(2) Order for 1,1,2-Trichloroethane (TCA) on ecotoxicity and occupational exposure*; [EPA-HQ-OPPT-2018-0421-0034](#)). Thus, EPA also considered hazard data received in response to this test order ([Smithers, 2023](#)).

EPA completed the review of environmental hazard data and information sources during risk evaluation using the data quality review evaluation metrics and the rating criteria described in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021a](#)) and *Draft Risk Evaluation for 1,1,2-Trichloroethane – Systematic Review Protocol* ([U.S. EPA, 2026g](#)). Studies were assigned overall quality determinations of high, medium, low, or uninformative. EPA systematically evaluated and integrated all data from studies rated high, medium, or low for this hazard characterization. Hazard data for a number of species were included in Adema ([1981](#)) and were initially assigned low ratings because of cursory descriptions of experimental designs while referring to its complementary document ([TNO, 1980](#)) for full descriptions. EPA subsequently reviewed the experimental designs contained in ([TNO, 1980](#)) and incorporated the resulting hazard data despite the initial low ratings.

EPA considered all available studies to characterize the environmental hazards of 1,1,2-trichloroethane to surrogate species representing ecological receptor groups, including aquatic vertebrates, aquatic invertebrates, amphibians, algae, plants, terrestrial invertebrates, and mammals. Hazard studies with mammalian wildlife exposed to 1,1,2-trichloroethane were not available; therefore, EPA used ecologically relevant endpoints from human health laboratory rat and mouse model organisms to establish a hazard threshold for terrestrial mammals ([U.S. EPA, 2024, 2012b](#)).

EPA uses probabilistic approaches with acute exposures to aquatic species (e.g., species sensitivity distribution, or SSD) when empirical and/or modeled data from at least eight species are available ([Raimondo et al., 2010](#)) and deterministic approaches (e.g., deriving a geometric mean of several comparable values) when limited data are available. For 1,1,2-trichloroethane, an SSD was derived for acute aquatic exposure hazards, and a deterministic approach was used to assess chronic hazards in aquatic and terrestrial exposures.

An SSD analysis was used to derive an acute aquatic hazard threshold. An SSD is a model of the variation in sensitivity of species to a particular chemical stressor and is generated by fitting a statistical distribution to the proportion of species affected as a function of concentration. This hazardous concentration (HC) is represented as an HC_p, where p is the percent of species below this threshold. EPA used an HC₀₅ (a hazardous concentration threshold for 5% of species) to estimate the concentration of 1,1,2-trichloroethane that is protective of 95% of species. To account for uncertainty, the concentration of concern (COC) was derived as the lower bound of the 95th percent confidence interval (CI) of the HC₀₅. Specifically, because the HC₀₅ was estimated from limited available data, the lower bound of the 95% CI accounts for uncertainty such that there is approximately a 5% probability that the true HC₀₅ is a lower concentration. Thus, the lower bound of the 95% confidence interval of the HC₀₅ represents a concentration that protects 95% of species from adverse effects with 95% confidence ([Raimondo et al., 2025](#); [Maltby et al., 2005](#)). Overall, EPA has more confidence in this probabilistic approach compared to a deterministic approach when enough data are available because an HC₀₅ integrates all of the available acute hazard data and is representative of a larger proportion of species in the environment.

EPA used deterministic approaches for all other COCs and hazard thresholds because limited data for each endpoint was available. For the aquatic chronic vertebrate and sediment-dwelling animal deterministic approaches, COCs were derived after selecting the most appropriate endpoint from a set of species for effects on survival, reproduction, and growth endpoints. EPA calculated geometric means of the NOEC and LOEC values resulting in chronic values (ChV) ([U.S. EPA, 2002b](#)). Assessment factors (AF) were used to extrapolate from the appropriate ChV to an environmental concentration that will be protective of most species in a medium. In this assessment, an AF of 10 was used to account for variation in sensitivity among species and uncertainties in extrapolating from laboratory conditions to environmental concentrations and durations ([Zeeman, 1995](#); [Zeeman and Gilford, 1993](#)). For example, studies of chronic effects in laboratory conditions report hazards across concentrations, but at one standard exposure duration (e.g., 7-day, 32-day, etc.). The AF accounts for environmental conditions where similar hazard effects may occur over longer exposure durations but at lower concentrations. Behavioral and mechanistic endpoints were considered as additional lines of evidence where appropriate ([U.S. EPA, 2016](#)). The COCs and hazard thresholds served as screening values that are expected to be protective of most resident organisms under each respective exposure route. These screening values are deliberately protective to minimize the likelihood of false negatives such that concentrations below them are unlikely to cause hazard effects.

For terrestrial species, EPA estimated hazard thresholds with the most appropriate fitness-related endpoints (e.g., survival or reproduction) that ultimately lead to population-level adverse effects. For 1,1,2-trichloroethane a hazard threshold was calculated as the geometric mean of the lowest NOEC and LOEC (or NOAEL and LOAEL) combination for terrestrial mammals, terrestrial invertebrates, and terrestrial plants similar to the standard approach for aquatic organisms ([U.S. EPA, 2002b](#); [Zeeman, 1995](#)). As a matter of policy, AFs are generally not applied by EPA when deriving hazard thresholds for terrestrial organisms. Chapman ([1998](#)) reviewed assessment factor extrapolations in terrestrial environments and concluded that there is no clear or consistent relationship between laboratory-based and field-based hazard effects on mammals and plants as being more or less conservative than the hazard concentration itself. Thus, AFs were not used to derive terrestrial hazard thresholds.

EPA used systematic review processes to search, screen, evaluate, extract, and integrate reasonably available information to make conclusions about relevant adverse health effects from 1,1,2-trichloroethane exposure (Figure 3-1). Following evidence integration, EPA derived hazard values for

use in risk characterization. The Agency evaluated the weight of scientific evidence for each aspect of the assessment and determined overall confidence ratings for each critical hazard outcome.

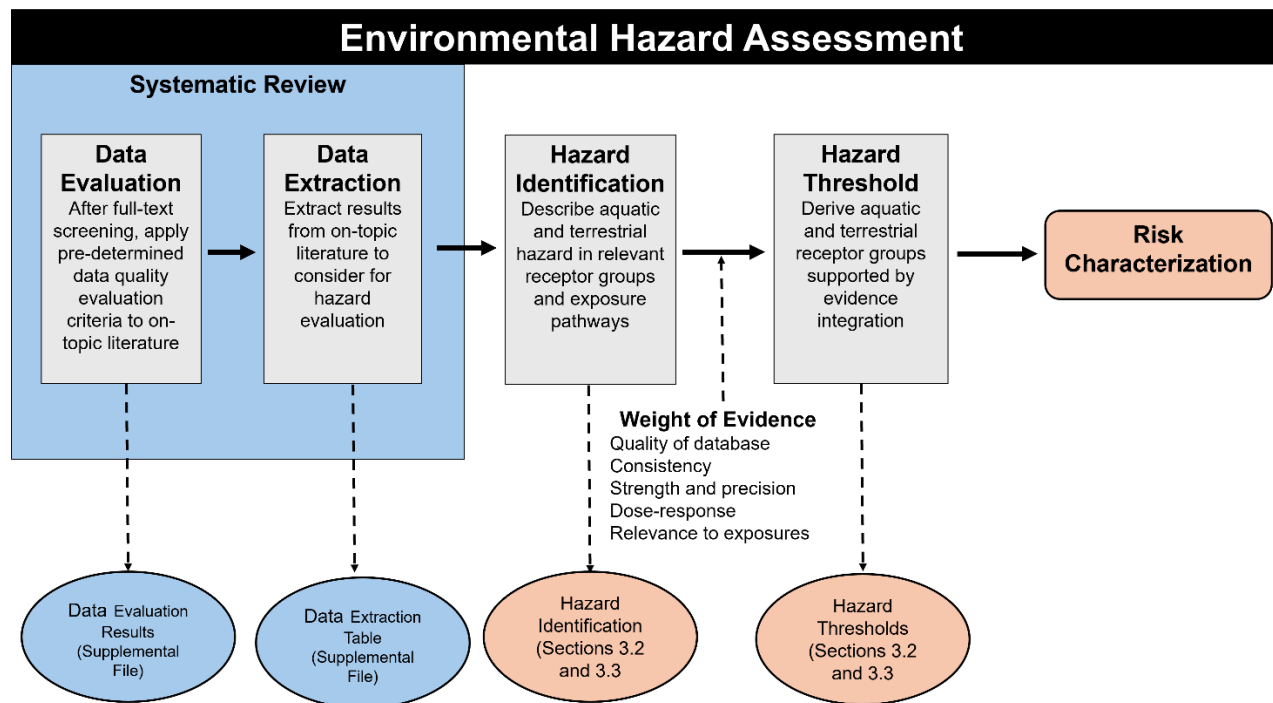


Figure 3-1. EPA Approach to Environmental Hazard Assessment for 1,1,2-Trichloroethane

3.2 Aquatic Species Hazard

EPA reviewed and assigned an overall quality determination of high, medium, or low to 18 studies and uninformative to 5 studies. These studies contained relevant aquatic toxicity data for 19 aquatic species. The Agency identified 29 aquatic hazard endpoints as the most relevant for quantitative assessment (Table 3-1).

3.2.1 Acute Exposure Hazards

Aquatic Vertebrates

EPA reviewed three studies that received overall quality determinations of high or medium for acute toxicity in aquatic vertebrates. Lethal concentrations resulting in 50% mortality (LC50) of fish from acute (96-hour) exposure hazard ranged from 40 mg/L (Buccafusco et al., 1981) to 89.1 mg/L 1,1,2-trichloroethane (Table 3-1). In the American flagfish (*Jordanella floridae*), the 96-hour LC50s for mortality were 89.1 mg/L and 45.1 mg/L in static-renewal and flow through systems, respectively (Smith et al., 1991). In the fathead minnow (*Pimephales promelas*), two studies report the 96-hour LC50 (flow-through) of 81.6 mg/L (Geiger et al., 1985; Walbridge et al., 1983). EPA also reviewed two studies that received overall quality determinations of low for acute toxicity in aquatic vertebrates. In bluegill (*Lepomis macrochirus*), a 96-hour LC50 of 40 mg/L was observed for larval mortality in a study rated low because of unreported sample size (Buccafusco et al., 1981). In the European plaice (*Pleuronectes platessa*) a 96-hour larval mortality LC50 of 55 mg/L was identified in a study initially rated low (Adema and Vink, 1981) because the study design was described in a complementary publication (TNO, 1980). EPA also reviewed one study that received an overall quality determination of low for 7-day exposure mortality in which 7-day LC50s of 70 and 75 mg/L were identified for juvenile and adult guppy (*Poecilia reticulata*) mortality, respectively (Adema and Vink, 1981). Additionally in this study a 7-day mortality LC50 of 27 mg/L was observed in juvenile sand goby (*Pomatoschistus*

minutus) ([Adema and Vink, 1981](#)). All studies reported in Adema ([1981](#)) were initially rated low due to inadequate study design description but incorporated into this assessment after review of additional information in its complementary publication ([TNO, 1980](#)).

Aquatic Invertebrates

EPA reviewed three studies that received overall quality determinations of high or medium for acute toxicity in aquatic invertebrates. In the water flea (*Daphnia magna*), the range of 48-hour LC50s was 18 mg/L to 190 mg/L for mortality ([3M Environmental Lab, 1984](#); [Richter et al., 1983](#); [Leblanc, 1980](#)). EPA also reviewed two studies that received overall quality determinations of low for acute toxicity in aquatic invertebrates. In the water flea, a 48- and 24-hour LC50 of 43 and 23 mg/L, respectively, were identified for neonate immobilization ([Freitag et al., 1994](#); [Adema, 1978](#)). Data from Adema ([1981](#)) was initially rated low due to inadequate study design description but incorporated into this assessment after review of additional information in its complementary publication ([TNO, 1980](#)).

Table 3-1. 1,1,2-Trichloroethane Toxicity to Acute Aquatic Vertebrates and Invertebrates

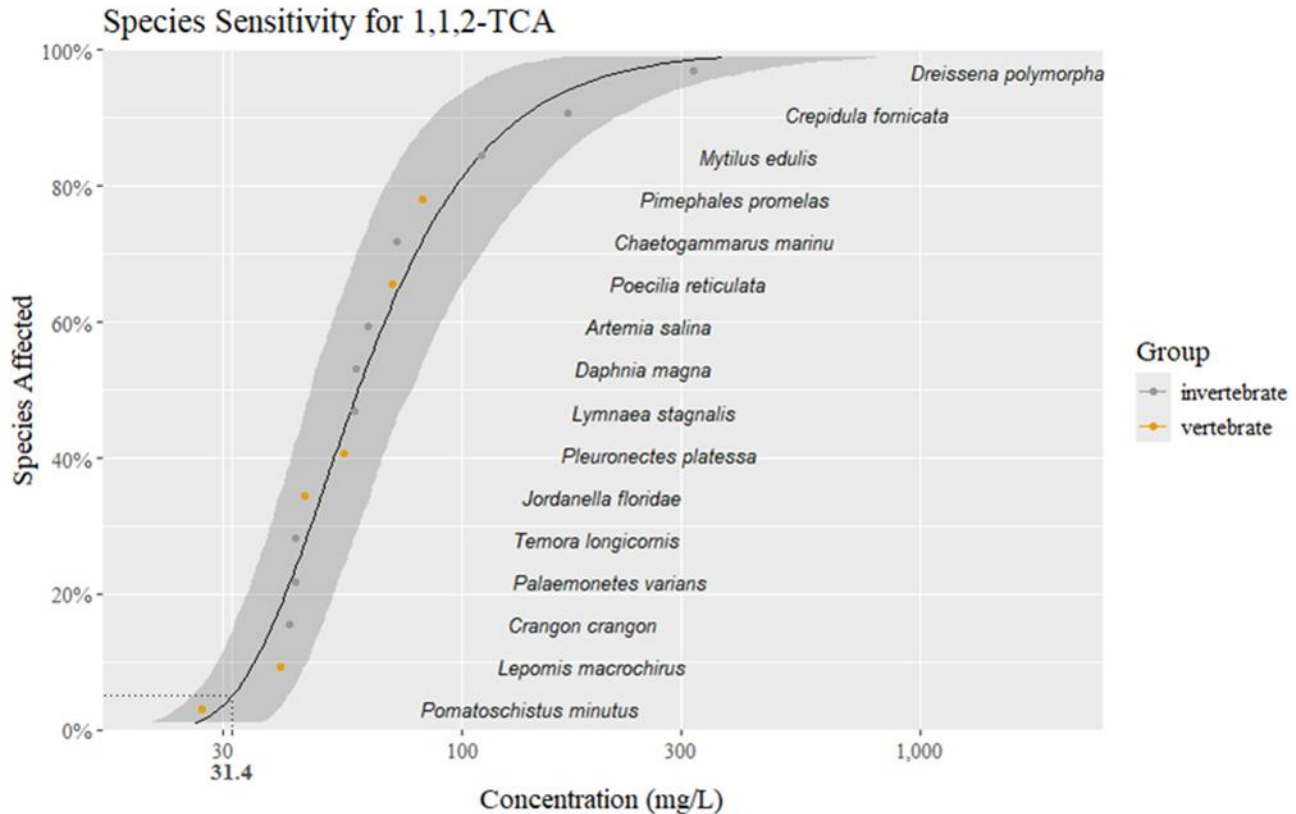
Test Organism	Hazard Value (mg/L)	Endpoint	Effect	Citation (Study Quality)
Vertebrates				
Fathead minnow (<i>Pimephales promelas</i>)	81.6	96-hour LC50 (flow-through)	Larval mortality	(Geiger et al., 1985) (High)
	81.6	96-hour LC50 (flow-through)		(Walbridge et al., 1983) (Medium)
	5E-03	1-hour LOEC	Fingerling Ventilatory Behavior	(Kaiser K et al., 1995) (High)
American flagfish (<i>Jordanella floridae</i>)	89.1	96-hour LC50 (static renewal)	Mortality	(Smith et al., 1991) (High)
	45.1 ^a	96-hour LC50 (flow-through)		
Bluegill (<i>Lepomis macrochirus</i>)	40	96-hour LC50 (closed)	Larval Mortality	(Buccafusco et al., 1981) (Low)
European plaice (<i>Pleuronectes platessa</i>)	27	96-hour LC50		(Adema and Vink, 1981) (Low)
Guppy (<i>Poecilia reticulata</i>)	70 ^b	7-day LC50	Juvenile Mortality	(Adema and Vink, 1981) (Low)
	75	7-day LC50	Mortality	(Adema and Vink, 1981) (Low)
Sand goby (<i>Pomatoschistus minutus</i>)	27	7-day LC50	Juvenile Mortality	(Adema and Vink, 1981) (Low)
Invertebrates				
Water flea (<i>Daphnia magna</i>)	18 ^c	48-hour LC50	Mortality	(Leblanc, 1980) (Medium)
	190	48-hour LC50		(Richter et al., 1983)

Test Organism	Hazard Value (mg/L)	Endpoint	Effect	Citation (Study Quality)
Water flea (<i>Daphnia magna</i>)			Neonate Immobilization	(Medium)
	81	48-hour LC50 (Static)		(3M Environmental Lab, 1984) (High)
	43	48-hour LC50		(Adema, 1978) (Low)
	23	24-hour LC50		(Freitag et al., 1994) (Low)
Brine shrimp (<i>Artemia salina</i>)	62	48-hour LC50	Larval Mortality	(Adema, 1978) (Low)
Amphipod (<i>Chaetogammarus marinus</i>)	72	48-hour LC50		
Marine copepod (<i>Temora longicornis</i>)	43	96-hour LC50	Mortality	
Blue mussel (<i>Mytilus edulis</i>)	110	96-hour LC50		
Zebra mussel (<i>Dreissena polymorpha</i>)	320	96-hour LC50		
Pond snail (<i>Lymnaea stagnalis</i>)	58	7-day LC50		
<i>Palaemonetes varians</i>	43	7-day LC50		
<i>Crangon crangon</i>	42	7-day LC50		
<i>Crepidula fornicata</i>	170	7-day LC50		
LC50 = lethal concentration at which 50% of test organisms die; LOEC = lowest-observed-effect concentration				
^a Hazard value derived from flow-through bioassay included in the SSD.				
^b geometric mean of <i>P. reticulata</i> hazard values (72.5 mg/L) included in the SSD.				
^c geometric mean of <i>D. magna</i> hazard values (48.7 mg/L) included in the SSD.				
Bolded values were included in the Species Sensitivity Distribution (SSD; Section 3.2.1.1).				

3.2.1.1 Acute Aquatic COC

EPA developed an SSD for 1,1,2-trichloroethane as empirical toxicity data for 16 species, six fish species, and 10 invertebrate species was identified in systematic review (Figure 3-2). SSDs were derived using EPA's SSD Toolbox (v1.1) ([Etterson, 2020b](#)) and plotted using R Statistical Software (v4.4.1) ([R Core Team, 2019](#)) using the ssdtools R package (v1.0.6) and the ggplot2 R package (v3.5.1; Appendix E). The Maximum Likelihood method and a Gumbel distribution model were used. The use of the Gumbel distribution was based on an examination of Akaike's Information Criterion corrected for sample size (aicc) for goodness of fit ([Burnham and Anderson, 2002](#)), visual examination of Q-Q plots, and evaluation of the line of best fit near the low-end of the SSD (Appendix E). The HC05 for this distribution was 31.4 mg/L 1,1,2-trichloroethane with a 95% confidence interval of 25.3 to 41.8 mg/L. After taking the lower 95th percent confidence interval of this HC05, the acute aquatic COC for vertebrates and invertebrates was 25.3 mg/L 1,1,2-trichloroethane (Figure 3-2).

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Figure 3-2. Species Sensitivity Distribution (SSD) of Acute Hazard Effects of 1,1,2-Trichloroethane on Aquatic Animals

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The shaded band indicates the 95th percentile confidence interval. The dotted line indicates the 5% hazard concentration (HC05 = 31.4 mg/L).

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3.2.1.2 Weight of Scientific Evidence for Acute Aquatic COC

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The weight of evidence indicates that 1,1,2-trichloroethane may pose acute hazard to aquatic vertebrates and invertebrates at 25.3 mg/L. EPA has robust confidence in this hazard threshold due to the strengths of the probabilistic SSD approach and the range of aquatic organisms included in the analysis. Ten studies with hazard endpoints for 16 species with short duration exposures and resultant LC50 values were used to create the SSD. These studies all were conducted with reasonable dose-response designs and exposed a range of species including vertebrates and invertebrates. These data also include common test species (e.g., *Daphnia magna*) and less common fish and mussel species across three phyla (Chordata, Arthropoda, Mollusca), thereby enhancing EPA's confidence that the COC is protective of a range of species.

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EPA used a probabilistic technique (SSD) to derive the COC that is protective of 95% of the aquatic animals in a community by incorporating hazard values across species and habitats. Limitations of SSDs include reliance on model species that may not exist or interact in the same ecological community and are weighted equally. Another assumption that may limit the scope of SSD inference is whether the number of species used is adequate. The shape of the data distribution that is fitted to the effects data can be subjective with the HC05 dependent on the lower tail of the distribution, making them sensitive to the most sensitive species ([Dhond and Barron, 2022](#)). The 95% confidence interval of the SSD is narrowest at the lower tail of the distribution (Figure 3-2), providing additional confidence in the COC and that it is protective of 95% of species. Notwithstanding the limitations of SSD analyses, this method is widely

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used and accepted in risk assessments ([Belanger and Carr, 2019](#)). Thus, EPA has robust confidence in the quality of the database, consistency, strength and precision, dose-response, and relevance in the acute hazard assessment.

3.2.2 Chronic Exposure Hazards to Vertebrates

EPA reviewed one study that received an overall quality determination of high for chronic toxicity in aquatic vertebrates (Table 3-2). In this study, a 32-day NOEC/LOEC of 14.8/48.3 mg/L was identified in the fathead minnow ([Ahmad et al., 1984](#)).

Table 3-2. Chronic Toxicity of 1,1,2-Trichloroethane Aquatic Vertebrates

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Vertebrates				
Fathead minnow (<i>Pimephales promelas</i>)	14.8/48.3 mg/L	32-day NOEC/LOEC	Mortality	(Ahmad et al., 1984) (High)
LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration				

3.2.2.1 Chronic Aquatic Vertebrate COC

The hazard value chosen to derive a COC for chronic aquatic vertebrates resulted from a single high-quality study on the fathead minnow ([Ahmad et al., 1984](#)). Fish survival and weight were 25% lower after exposure to 48.3 mg/L 1,1,2-trichloroethane when compared to control fish, but fish survival and weights were not different from control fish after 32-day exposures to 14.8 mg/L, resulting in a NOEC/LOEC of 14.8/48.3 mg/L and a ChV of 26.7 mg/L. After applying an AF of 10 ([Zeeman, 1995](#)), the chronic COC for aquatic vertebrates is 2.67 mg/L. The assessment factor was applied according to standard EPA methods and used to account for variation in species sensitivity and uncertainties in extrapolating from laboratory conditions to environmental concentrations and exposure durations (Section 3.1; ([Zeeman, 1995](#); [Zeeman and Gilford, 1993](#))).

3.2.2.2 Weight of Scientific Evidence for Chronic Aquatic Vertebrate COC

The weight of evidence suggests that 1,1,2-trichloroethane may pose chronic hazard to aquatic vertebrates at 2.67 mg/L. EPA has moderate confidence in this hazard threshold. One study was available for the assessment of the chronic effects to aquatic vertebrates. EPA has slight confidence in the quality of the database due to the availability of only one study. This high-rated study was conducted with a reasonable dose-response design and used measured 1,1,2-trichloroethane concentrations, which enables precise estimations of effect concentrations. Therefore, EPA has moderate confidence in the consistency, strength and precision, dose-response, and relevance in the chronic vertebrate hazard assessment.

3.2.3 Chronic Aquatic Invertebrates

Table 3-3 describes the chronic exposure toxicity to aquatic invertebrates from 1,1,2-trichloroethane. EPA reviewed two studies that received overall quality determinations of high or medium for chronic toxicity in aquatic invertebrates (Table 3-3). A 28-day NOEC/LOEC of 13/26 mg/L for development/growth, a 28-day NOEC/LOEC of 26/42 mg/L for reproduction, and a 21-day NOEC/LOEC of 2.4/4.2 mg/L for mortality were identified for the water flea ([3M Environmental Lab, 1984](#); [Richter et al., 1983](#)). Specifically, *Daphnia* produced 93% fewer young after 28-day exposures to

42 mg/L 1,1,2-trichloroethane, but *Daphnia* reproduction was not reduced in concentrations of 26 mg/L or lower ([Richter et al., 1983](#)). EPA also reviewed one study of multiple species that received an overall quality determination of low for chronic toxicity in aquatic invertebrates ([Adema and Vink, 1981](#)). A 7-day mortality LC50 of 43 mg/L was identified for the Atlantic ditch shrimp (*Palaemonetes varians*), 42 mg/L for the brown shrimp (*Crangon crangon*), for the slipper limpet (*Crepidula fornicata*), and 58 mg/L for the great pond snail (*Lymnaea stagnalis*) ([Adema and Vink, 1981](#)). Data from Adema ([1981](#)) was initially rated low due to inadequate study design description but incorporated into this assessment after review of additional information in its complementary publication ([TNO, 1980](#)).

Table 3-3. 1,1,2-Trichloroethane Chronic Exposure Toxicity to Aquatic Invertebrates

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Water flea (<i>Daphnia magna</i>)	13/26 mg/L	28-day NOEC/LOEC	Development/ Growth	(Richter et al., 1983) (High)
	26/42 mg/L	28-day NOEC/LOEC	Reproduction	(Richter et al., 1983) (High)
	42 mg/L	21-day EC50	Mortality	(3M Environmental Lab, 1984) (Medium)
Atlantic ditch shrimp (<i>Palaemonetes variens</i>)	43 mg/L	7-day LC50	Mortality	(Adema and Vink, 1981) (Low)
Brown shrimp (<i>Crangon crangon</i>)	42 mg/L	7-day LC50	Mortality	(Adema and Vink, 1981) (Low)
Slipper limpet (<i>Crepidula fornicata</i>)	170 mg/L	7-day LC50	Mortality	(Adema and Vink, 1981) (Low)
Great pond snail (<i>Lymnaea stagnalis</i>)	58 mg/L	7-day LC50	Mortality	(Adema and Vink, 1981) (Low)
LC50 = lethal concentration at which 50% of test organisms die; LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration Bolded value indicates the hazard effects used for deriving the chronic 1,1,2-trichlorethane concentration of concern.				

3.2.3.1 Chronic Aquatic Invertebrate COC

The species with the appropriate endpoint, which had a clear population-level fitness effect was *Daphnia magna* ([Richter et al., 1983](#)). The hazard value chosen to derive a COC for chronic aquatic invertebrates resulted from a high-quality rated study in which 93% fewer neonates were produced over 28-days in treatments with 42 mg/L 1,1,2-trichloroethane (LOEC) compared to the number produced in 26 mg/L 1,1,2-trichloroethane (NOEC) or other treatments. The study also reported differences in the body length of adults in 26 mg/L exposures (3.9 mm) compared to controls (4.1 mm). However, considerable variation in adult body length occurred, resulting in non-monotonic effects across the

treatments. Also, shorter adult *Daphnia* body length can be the result of a phenotypically plastic trade-off with reproduction, introducing uncertainty in the population level impact of 1,1,2-trichloroethane induced shorter body length. Thus, EPA considered the treatment concentration resulting in 93% fewer offspring on which to derive a hazard threshold. This study also followed standard OECD test guidelines for measuring effects of chemical exposure (OECD, 2010) with a well-established test species that is widely distributed across the United States (Thorp and Covich, 2001). Based on the presence of a clear dose-response relationship and a population-level fitness endpoint, the 28-day reduction in reproduction was selected to derive the COC for chronic 1,1,2-trichloroethane exposure to invertebrates. EPA calculated the ChV as the geometric mean of the NOEC and LOEC for reproduction equal to 33 mg/L. After applying an AF of 10 (Zeeman, 1995), the chronic COC for aquatic invertebrates is 3.3 mg/L 1,1,2-trichloroethane. The assessment factor was applied according to standard EPA methods and used to account for variation in species sensitivity and uncertainties in extrapolating from laboratory conditions to environmental concentrations and exposure durations (Section 3.1; (Zeeman, 1995; Zeeman and Gilford, 1993)).

3.2.3.2 Weight of Scientific Evidence for Chronic Aquatic Invertebrate COC

The weight of evidence suggests that 1,1,2-trichloroethane may pose chronic hazard to aquatic invertebrates at 3.3 mg/L. One high-rated, one-medium rated, and one low-rated study with data for four species were available for the chronic aquatic invertebrate assessment. These studies examined numerous apical endpoints including mortality, reproduction, and development/growth. EPA has moderate confidence in the quality of the database that includes freshwater and marine arthropods and molluscs. Consistent effects were observed among all the studies, which maintained reasonable dose-response designs using measured concentrations. Therefore, EPA has robust confidence that this COC represents a protective concentration for chronic exposures to aquatic invertebrates due to the consistency, strength and precision, dose-response, and relevance of the available data.

3.2.4 Chronic Sediment Dwelling Aquatic Invertebrates

One study of 1,1,2-trichloroethane exposure to aquatic invertebrates in sediment was reasonably available to EPA and received a data quality evaluation of high (Smithers, 2023) (Table 3-4). This study resulted from a test order under TSCA section 4(a)(2) (EPA-HQ-OPPT-2018-0421-0034). The toxicity of 1,1,2-trichloroethane to the midge (*Chironomus riparius*) in sediment was assessed over two generations following the guidelines of OECD 233. Consistent and chronic exposure to 1,1,2-trichloroethane was not observed in this study because measured concentrations fell to less than 20% of nominal very rapidly such that Day 0 treatment concentrations in sediment were 13, 20, 52, 73, and 170 mg/kg dry weight (dw) instead of the nominal 63, 130, 250, 500, and 1,000 mg/kg dw target concentrations. By day 14, all treatment groups except the highest had measured 1,1,2-trichloroethane concentrations less than the level of detection of 1 mg/kg dw. None of the treatment groups had measurable 1,1,2-trichloroethane remaining in the sediment by day 28 of either the parental (P) or second generations (F1). Similar loss rates occurred in sediment pore water and water column concentrations.

1,1,2-Trichloroethane has low log K_{OC} (2.05) and is considered volatile (U.S. EPA, 2026a), giving it low affinity for sediment sorption and low ability to remain in solution in the open-air containers. Thus, the resulting hazard effects to midge larvae were likely due to pulsed or short duration exposures and not chronic exposures. A significant 50% decrease in emergence of the F1 larvae was observed at the highest tested concentration, resulting in a 28-day NOEC/LOEC of 19/44 mg/kg dw. No effects on other definitive endpoints were observed in P or F1 midges. While percent emergence was significantly decreased in first-generation (F0) larvae ($44 \pm 16\%$ compared to $81 \pm 8\%$ emergence in the controls) at the second highest 1,1,2-trichloroethane concentration (10 mg/kg), no significant effect was observed at

the highest (30 mg/kg) and therefore a LOEC for F0 emergence could not be established. Because the exposure concentration was highest at the beginning of the P and F1 generations and rapidly decreased, and effects were observed only in one endpoint in the F1 generation after 56 days, the hazard can be described as being the result of pulse exposure to higher concentrations than indicated by time-weighted averages. Thus, midges were not exposed to consistent, non-lethal concentrations that typically occur in chronic exposure hazard studies.

Table 3-4. 1,1,2-Trichloroethane Toxicity to Chronic Aquatic Sediment-Dwelling Invertebrates

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Sediment-dwelling invertebrates				
Midge (<i>Chironomus riparius</i>)	19/44 mg/kg	56-day NOEC/LOEC	50% lower F1 larval emergence	(Smithers, 2023) (High)
LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration				

3.2.4.1 Chronic Sediment-Dwelling Invertebrate COC

The hazard value chosen to derive a COC for chronic sediment-dwelling invertebrate resulted from one high-quality study in which a NOEC/LOEC of 19/44 mg/kg was observed for 50% fewer F1 larvae than emerged after 56 days ([Smithers, 2023](#)). EPA calculated the ChV as the geometric mean of the NOEC and LOEC equal to 28.9 mg/kg. After applying an AF of 10 ([Zeeman, 1995](#)), the chronic COC for aquatic sediment-dwelling invertebrates was 2.89 mg/kg 1,1,2-trichloroethane. Only one study was available for the sediment-dwelling assessment, thus increasing uncertainty. An assessment factor of 10 was applied according to standard EPA methods and used to account for variation in species sensitivity and uncertainties in extrapolating from laboratory conditions to environmental concentrations and exposure durations (Section 3.1; ([Zeeman, 1995](#); [Zeeman and Gilford, 1993](#))).

3.2.4.2 Weight of Scientific Evidence for Chronic Sediment-Dwelling Invertebrate COC

The weight of evidence suggests that 1,1,2-trichloroethane may pose hazard to sediment-dwelling species at 2.89 mg/kg after repeated acute exposures over 56-days. EPA has slight to moderate confidence that this threshold represents a COC resulting in adverse population-level effects due to chronic exposure for a few reasons. First, only one study was available for the chronic sediment-dwelling assessment. Therefore, EPA has moderate confidence in the quality of the database. Second, while a dose-response was observed in the second-generation (F1), no other definitive population-level effects were observed in either the F1 or parent generations. Third, there was no measurable 1,1,2-trichloroethane in test sediment or solution at the completion of the study likely due to the chemical's low log K_{OC} (2.05) and volatility ([U.S. EPA, 2026a](#)), giving it low affinity for sediment sorption and low ability to remain in solution in open-air containers. Thus, the observed hazard effects to midge larvae were likely due to pulsed or short duration exposures and not consistent with chronic exposures. Finally, the population-level effects of lower emergence rates but not fecundity or development rate in the second generation of pulsed exposures may be minimal due to the dispersal characteristics of flying adults that may continuously immigrate into a local population. Therefore, EPA has (1) slight confidence in the consistency of studies (*i.e.*, only 1 study); (2) slight confidence in the study's relevance in describing chronic effects; and (3) moderate confidence in the dose-response and strength and precision of the available data—resulting in slight-to-moderate overall confidence in this COC.

3.2.5 Algae and Aquatic Plants

EPA reviewed four studies, one that received an overall quality rating of high, one that included five species that received a rating of low, and two that received uninformative ratings for toxicity in algae (Table 3-5). In green algae (*Chlamydomonas reinhardtii*), a 72-hour EC10 of 26.3 mg/L and EC50 of 57 mg/L for population growth inhibition was characterized in a closed system that prevented loss of 1,1,2-trichloroethane due to volatilization (Brack and Rottler, 1994). Additional studies on other species also report adverse effects on algal population growth at comparable but generally higher 1,1,2-trichloroethane concentrations with EC50 values ranging from 60 to 260 mg/L in open experimental systems (Tsai and Chen, 2007; Hsieh et al., 2006; Adema and Vink, 1981). Adema (1981) found a higher 96-hour EC50 (260 mg/L) to a *Chlamydomonas* sp. than the 72-hour EC10 and EC50 from the similar green alga *C. reinhardtii* (Brack and Rottler, 1994). The difference may be attributable to the closed system used by Brack (1994). Nevertheless, the 96-hour EC50 in an open system to *Phaeodactylum tricornutum* was comparable to the hazard EC50 to algae from the closed system in Brack (1994). No aquatic vascular plant studies were available for assessment.

Table 3-5. 1,1,2-Trichloroethane Toxicity to Algae and Aquatic Plants

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Algae				
Green algae (<i>Chlamydomonas reinhardtii</i>)	57 mg/L	72-hour EC50	Population growth inhibition	(Brack and Rottler, 1994) (High)
	26.3 mg/L	72-hour EC10		
Green algae (<i>Chlamydomonas</i> sp.)	260 mg/L	96-hour EC50		(Adema and Vink, 1981) (Low)
Green algae (<i>Raphidocelis subcapitata</i>)	160.4 mg/L	48-hour EC50		(Hsieh et al., 2006) (Uninformative)
	105.4 mg/L	48-hour EC50		(Tsai and Chen, 2007) (Uninformative)
Diatom (<i>Phaeodactylum tricornutum</i>)	60 mg/L	96-hour EC50		(Adema and Vink, 1981) (Low)
Green algae (<i>Dunaliella</i> sp.)	200 mg/L			
Green algae (<i>Chlorella vulgaris</i>)	200 mg/L			
Green algae (<i>Auxenochlorella pyrenoidosa</i>)	170 mg/L			

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
EC50 = concentration at which 50% of test organisms exhibit an effect Bolded value indicates the hazard effects used for deriving the chronic 1,1,2-trichlorethane algae concentration of concern.				

3.2.5.1 Algae COC

The hazard value chosen to derive a COC for aquatic algae resulted from a high-quality study in green algae (*C. reinhardtii*; (Brack and Rottler, 1994)). In this study, a 72-hour EC10 of 26.3 mg/L and EC50 of 57 mg/L for population growth inhibition was characterized in a closed system where exposure concentrations were more precisely controlled for this volatile chemical than in the open systems used by the other available studies (Brack and Rottler, 1994). For algae, low-effect endpoints (e.g., EC10) where the population has a 10% adverse effect on the population represents a more protective COC than the median endpoint (e.g., EC50). EPA did not apply an AF to the EC10 value because it is already at the low end of the distribution of data across a range of freshwater and marine species (Table 3-5). The EC10 is also at the low-end of effect concentrations within Brack (1994). Moreover, the EC50 of this study is comparable to the EC50 of the most sensitive species tested in an open experimental system that is likely more representative of real-world conditions in which 1,1,2-trichloroethane volatilizes from surface water. As a result, the EC10 of 26.3 mg/L to *Chlamydomonas reinhardtii* represents the COC of 1,1,2-trichloroethane to algae.

3.2.5.2 Weight of Scientific Evidence for Algae COC

The weight of evidence indicates that 1,1,2-trichloroethane may pose hazard to algae species at 26.3 mg/L with moderate confidence. EPA has moderate confidence in this hazard threshold for a few reasons. Multiple studies with dose-response designs were available for this assessment, including one study conducted in a closed system and six studies conducted in open systems. While the open testing systems reflect environmental conditions better than closed systems, the COC of 26.3 mg/L from the EC10 from a closed system was considered the most appropriate concentration to be protective across species. This EC10 represents the low end of the hazard effect concentrations within one study (Brack and Rottler, 1994) and the low end of the hazard data across the available studies. Thus, EPA has moderate confidence that this COC is protective. Overall, the Agency has moderate confidence in the quality of the database, and robust confidence in the dose-response and moderate confidence in the relevance to environmental concentrations. EPA has moderate confidence in the consistency and relevance of the algal assessment.

3.3 Terrestrial Species Hazard

EPA identified 10 toxicity studies for terrestrial species comprising 4 studies of oral exposures to human health rodent models, 4 studies of inhalation exposure to human health rodent models, 1 study of terrestrial invertebrates, and 1 study of birds as the most relevant for quantitative assessment.

3.3.1 Terrestrial Vertebrates

No studies of the hazard effects of 1,1,2-trichloroethane on wild mammals or birds were reasonably available to review.

3.3.1.1 Mammals

In lieu of wild mammal hazards, EPA reviewed four studies of human health rodent models with mortality, reproduction, or development hazard endpoints from dietary exposures as surrogate species (Table 3-6). Overall, no effects of orally administered (gavage or drinking water) 1,1,2-trichloroethane were observed in rats or mice up to and including the highest doses in any high- or medium-quality study ([Seidenberg et al., 1986](#); [Sanders et al., 1985](#); [White et al., 1985](#); [Moody et al., 1981](#)). One low-rated study reported mortality effects at 48-hour single dose gavage exposures of 378 mg/kg for male mice and 491 mg/kg for female mice ([White et al., 1985](#)). This study was rated low because 1,1,2-trichloroethane was administered in one gavage bolus and not in drinking water or food. It was used as a range-finding test to determine an upper bounding of concentrations for drinking water exposures.

Three studies of the inhalation hazards of 1,1,2-trichloroethane to human health rodent models intended to inform human health effects were reviewed for potential surrogate inhalation hazard values to mammals (Table 3-6). These studies all report the mortality effects of acute exposure durations (*i.e.*, 2- to 17-hours). WIL Research Laboratories ([2001](#)) reported no mortality effects (NOAEL) at 976 mg/m³ and 7.5% (3/40 female rates) mortality 4,631 mg/m³ after 4-hours of inhalation exposure with a ChV of 2,126 mg/m³. Carlson ([1973](#)) reported hepatotoxicity, one mortality, and two moribund animals 24-hours after inhalation of 9,648 mg/m³ 1,1,2-trichloroethane for 2 hours and phenobarbital pretreatment. A study in mice observed an LD50 of 20,673 mg/m³ based on time to 50% mortality after 17 hours of inhalation exposure ([Gehring, 1968](#)).

Table 3-6. 1,1,2-Trichloroethane Toxicity to Terrestrial Vertebrates

Test Organism	Hazard Value	Endpoint	Effect(s)	Citation (Study Quality)
Dietary exposure to mammals ^a				
Rat (Sprague-Dawley)	No observed effects up to 1,080 mg/kg-bw/day	18-hour Single dose gavage	Mortality/ Reproduction/ Development ^b	(Moody et al., 1981) (High)
Mouse (ICR/SIM)	No observed effects up to 350 mg/kg-bw/day	5-day Gavage	Mortality/ Reproduction/ Development	(Seidenberg et al., 1986) (Medium)
Mouse (CD-1 strain)	378 mg/kg male 491 mg/kg female	48-hour LD50 Single dose gavage	Mortality	(White et al., 1985) (Low)
	No observed effects up to 38 mg/kg-bw/day	14-day Gavage	Reproduction/ Body weight/ Organ weights	(White et al., 1985) (Medium)
	No observed effects up to 38 mg/kg-bw/day		Body weight ^b	(Sanders et al., 1985) (High)
	No observed effects up to 384 mg/kg-bw/day (2,000 mg/L)	90-day Drinking water		(Sanders et al., 1985) (High)
Inhalation exposure to mammals				

Test Organism	Hazard Value	Endpoint	Effect(s)	Citation (Study Quality)
Rat (Fischer 344)	976/4,631 mg/m³ ChV= 2,126 mg/m³	4-hour inhalation study NOAEL/ LOAEL	Mortality	(WIL Research, 2001) (High)
Rat (Albino)	4,128/9,648 mg/m ³ ^c	2-hour inhalation study NOAEL/ LOAEL		(Carlson, 1973) (Medium)
Mouse (Swiss Webster)	One concentration tested of 73,700 mg/m ³	17-hour inhalation		(Gehring, 1968) (Medium)

ChV = chronic value; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

^a Laboratory rodent studies used for human health hazard assessments were used as surrogate hazards because no wild mammal hazard studies were reasonably available.

^b Study focused on immunological endpoints yet found no mortality or reproductive effects at the highest administered doses.

^c Hepatotoxicity estimated after phenobarbital pretreatment. Out of 5 total animals, 1 animal died and 2 were moribund after 24-hours.

Bolded values indicate the hazard effects used for deriving the chronic 1,1,2-Trichloroethane hazard threshold.

3.3.1.1.1 Terrestrial Mammal Hazard Threshold

No hazard threshold for dietary exposure to terrestrial mammals was derived because no effects on reproduction or development were observed up to and including the highest doses of exposure. A single dose gavage of 1,1,2-trichloroethane resulted in mortality as reported in one low-rated study, but the exposure method and concentration were not environmentally relevant ([White et al., 1985](#)).

The hazard value chosen to derive an inhalation hazard threshold resulted from a high rated study of the survival effects from a 4-hour inhalation exposure and subsequent 7.5% lower rat survival ([WIL Research, 2001](#)). Because no data were available on the chronic inhalation effects on mammals, EPA used the hazard value from acute inhalation effects to derive a mammal hazard threshold. The acute hazard threshold for terrestrial vertebrates was calculated as the geometric mean of the NOAEL (976 mg/m³) and LOAEL (4,631 mg/m³) equal to a ChV of 2,126 mg/m³ 1,1,2-trichloroethane.

3.3.1.1.2 Weight of Scientific Evidence for Terrestrial Mammals

The weight of evidence suggests that 1,1,2-trichloroethane may pose no dietary hazard up to the doses reported in Table 3-6. Only one study reported the dietary effects of 1,1,2-trichloroethane and within this study, only one test concentration was used. EPA has slight confidence in the quality of the dietary hazard database, consistency of the data (*i.e.*, only 1 study), and observed dose-response effects. Additionally, there are considerable uncertainties surrounding whether or how this effect in a human health model species may translate into effects on wild mammal fitness and population parameters. Thus, EPA has slight confidence overall that the hazard value from one study represents a hazard threshold for dietary exposure of 1,1,2-trichloroethane to terrestrial mammals.

The weight of evidence suggests that 1,1,2-trichloroethane poses inhalation hazard to terrestrial vertebrates at 2,126 mg/m³ with slight-to-moderate confidence. Three studies reported the inhalation

effects of 1,1,2-trichloroethane to laboratory rodents ([WIL Research, 2001](#); [Carlson, 1973](#); [Gehring, 1968](#)). WIL Research Laboratories (2001) reported 7.5% mortality effects at 4,631 mg/m³ after 4 hours of inhalation exposure using a dose-response design in a high-rated study. EPA has slight-to-moderate confidence that this hazard value represents an inhalation threshold because of the limited but consistent database (*i.e.*, 3 studies), and limited relevance in extrapolating these results from human health model species translate into effects on wild mammal populations.

3.3.1.2 Avian

No studies of the hazard effects of 1,1,2-trichloroethane on wild avians were reasonably available to review. The effects of 1,1,2-trichloroethane on domesticated chicken via egg injection were reported in one study ([Elovaara et al., 1979](#)) (Table 3-7). This 6-day chicken (*Gallus gallus*) egg injection study did not identify hazard up to the highest concentration tested (13 mg/egg) ([Elovaara et al., 1979](#)). Due to the low-quality determination, as well as the lack of a definitive hazard value, this study was not considered for establishing an avian hazard threshold. The study was rated low because the allocation of eggs, measured test concentrations, and replicates were not reported. Also, hazard to developing embryos is not expected because 1,1,2-trichloroethane is not lipophilic ([U.S. EPA, 2026a](#)) and therefore not likely to be transferred from adult females to eggs.

Table 3-7. 1,1,2-Trichloroethane Toxicity to Avian Species

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Avian				
Chicken (<i>Gallus gallus</i>)	>13 mg/egg	6-day egg injection	Mortality	(Elovaara et al., 1979) (Low)

3.3.1.2.1 Avian Hazard Threshold

Only a single low-quality 6-day egg injection study was available ([Elovaara et al., 1979](#)). In this study, no effects were observed on the single dose-concentration used of 13 mg/egg. Therefore, no hazard threshold could be established for the avian assessment.

3.3.1.2.2 Weight of Scientific Evidence for Avian Assessment

EPA could not establish a hazard threshold for the avian assessment. Only one low-rated study was available for the avian assessment. In this study, a single egg injection dose of 13 mg/egg was used resulting in no mortality; therefore, a dose-response was not recorded. Effects on mortality were not observed up to the highest tested concentration and hazard to developing embryos is not expected because 1,1,2-trichloroethane is not lipophilic and therefore not likely to be transferred from adult females to eggs. EPA has slight confidence in the quality of the database, consistency, strength and precision, dose-response, and relevance in the avian assessment. Extrapolation of the mammalian inhalation toxicity data to birds was not conducted due to fundamental differences in bird respiratory physiology and toxicokinetics, which introduce additional uncertainty ([Clewell and Fuchsman, 2024](#)).

3.3.2 Terrestrial Invertebrates

Only one study was available for the assessment of terrestrial invertebrates that was reviewed and received overall quality determinations of high (Table 3-8). A study using 1,1,2-trichloroethane filter paper contact with earthworms (*Eisenia fetida*) resulted in a 48-hour LC50 of 42 µg/cm² ([Neuhauser et](#)

[al., 1985](#)). Using a paper thickness of 0.2 cm, the authors also reported this value in units of mass as 1.05 mg/kg.

Table 3-8. 1,1,2-Trichloroethane Toxicity to Terrestrial Invertebrates

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Invertebrates				
Earthworm (<i>Eisenia fetida</i>)	42 µg/cm ² (1.05 mg/kg)	48-hour LC50	Mortality	(Neuhauser et al., 1985) (High)
LC50 = lethal concentration at which 50% of test organisms die				

3.3.2.1 Terrestrial Invertebrate COC

The hazard value chosen to derive a hazard threshold for terrestrial invertebrates resulted from a high-quality rated study on the earthworm ([Neuhauser et al., 1985](#)). In this study, a 48-hour mortality LC50 of 42 µg/cm² (1.05 mg/kg) was established using 1,1,2-trichloroethane applied to filter paper. The terrestrial invertebrate hazard threshold is 42 µg/cm² (1.05 mg/kg).

3.3.2.2 Weight of Scientific Evidence for Terrestrial Invertebrates

The weight of evidence suggests that 1,1,2-trichloroethane may pose hazard to terrestrial invertebrates at 1.05 mg/kg with moderate confidence. Only one study was available for the assessment of terrestrial invertebrates; however, it had an overall rating of high. Thus, EPA has moderate confidence in the quality of the database, but slight confidence in consistency across studies because there was only one study. Test concentrations were not measured, and test concentrations were applied via filter paper, which introduces uncertainty and lowered confidence in the ecological relevance. EPA has moderate confidence in the precision of results from a dose-response experimental design.

3.3.3 Terrestrial Plants

EPA reviewed one study that received an overall quality determination of medium for toxicity in terrestrial plants (Table 3-9). This 16-day Canadian poplar (*Populus x canadensis*) study using a hydroponic nutrient solution established a 50% reduction in transpiration after 16-days of 253 mg/L and a zero-growth concentration of 306.9 mg/L ([Dietz and Schnoor, 2001](#)).

Table 3-9. 1,1,2-Trichloroethane Toxicity to Terrestrial Plants

Test Organism	Hazard Value	Endpoint	Effect	Citation (Study Quality)
Plants				
Canadian Poplar (<i>Populus x canadensis</i>)	253 mg/L ^a	16-day EC50	Reduced transpiration	(Dietz and Schnoor, 2001) (Medium)
	307 mg/L		Zero growth ^b	
EC50 = concentration at which 50% of test organisms exhibit an effect				
^a Hydroponic nutrient solution.				
^b Zero growth concentration reported by authors as the concentration at which net plant growth was zero over 16-days. Lower-bound metrics were not reported.				

3.3.3.1 Terrestrial Plant COC

The hazard value chosen to derive a hazard threshold for terrestrial plants resulted from a medium-quality rated study on Canadian poplar ([Dietz and Schnoor, 2001](#)). In this study, a 16-day zero-growth concentration of 306.9 mg/L was identified using a hydroponic nutrient solution. The terrestrial plant hazard threshold is 306.9 mg/L.

3.3.3.2 Weight of Scientific Evidence for Terrestrial Plants

The weight of evidence suggests that 1,1,2-trichloroethane may pose hazard to terrestrial plants at 306.9 mg/L. Only a single study was available for the terrestrial plant assessment, therefore EPA has moderate confidence in the quality of the database. Dose-response effects were observed using measured concentrations. EPA has moderate confidence in the quality of the database, strength and precision, and dose-response in the acute hazard assessment. The Agency has slight confidence in the relevance and consistency because only one study was available and the study was hydroponic, which results in environmental relevance uncertainties. EPA has overall moderate confidence in this hazard threshold.

3.4 Weight of Scientific Evidence Conclusions for Environmental Hazard Assessment

Based on the weight of the scientific evidence and uncertainties, a confidence statement was developed that qualitatively ranks (*i.e.*, robust, moderate, slight, or indeterminate) the confidence in the hazard threshold. The evidence considerations and criteria detailed within the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021a](#)) guide the application of strength-of-evidence judgments for environmental hazard effect within a given evidence stream. See Appendix D for more information on the weight of scientific evidence conclusions.

EPA determined the weight of scientific evidence that 1,1,2-trichloroethane poses hazards from acute exposures to aquatic vertebrates and invertebrates (Section 3.2.1.2), and chronic exposures to aquatic vertebrates (Section 3.2.2.2), chronic exposures to aquatic invertebrates (Section 3.2.3.2), exposure to sediment dwelling animals (Section 3.2.4.2), exposure to algae (Section 3.2.5.2), acute inhalation exposure to terrestrial mammals (Section 3.3.1.1.2), chronic soil exposure to terrestrial invertebrates (Section 3.3.2.2), and chronic soil exposure terrestrial plants (Section 3.3.3.2). Due to the weight of evidence, EPA has robust confidence that the 1,1,2-trichloroethane hazard thresholds are concentrations that cause adverse effects to populations of these organisms in the environment.

3.5 Environmental Hazard Thresholds

EPA considered all reasonably available information identified through the systematic review process under TSCA to characterize environmental hazard endpoints for 1,1,2 trichloroethane. The following bullets summarize the hazard values:

Aquatic Species

- EPA developed an SSD for 1,1,2-trichloroethane with acute empirical toxicity data for 6 fish species and 10 invertebrate species. The lower 95 percent confidence value of the HC05 was used as the COC at 25.3 mg/L 1,1,2-trichloroethane.
- The chronic exposure COC for aquatic vertebrates is 2.67 mg/L derived from the most sensitive hazard value from a 32-day fathead minnow study.
- For the chronic exposure aquatic invertebrate assessment, the most sensitive organism with a clear population-level fitness endpoint was *Daphnia magna*. The COC for chronic exposure to aquatic invertebrates is 3.3 mg/L.
- The COC for multiple acute exposures over 56-days to sediment-dwelling invertebrates is 2.89

3376 mg/kg.

- 3377 • For the algal assessment, EPA derived an algal COC of 26.3 mg/L.

3378 ***Terrestrial Species***

- 3379 • Using human health rodent models as a surrogate for wildlife mammalian species, the terrestrial
3380 vertebrate hazard threshold was 4-hour inhalation of 2,126 mg/m³ 1,1,2-trichloroethane. EPA has
3381 slight-to-moderate confidence in this hazard threshold.
- 3382 • The hazard threshold for terrestrial invertebrates was 1.05 mg/kg based on a 48-hour earthworm
3383 exposure study.
- 3384 • The hazard threshold for 16-day exposure to terrestrial plants was 306.9 mg/L.
- 3385

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APPENDICES

Appendix A EVIDENCE INTEGRATION TABLES

This appendix presents evidence integration tables for the human health hazard outcomes associated with 1,1,2-trichloroethane.

Table Apx A-1. Cancer Evidence Integration Profile

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Cancer			
Evidence in studies of exposed humans considered for deriving toxicity values			
Pancreatic cancer			Available data are limited to 2 case-control studies evaluating different tumor types. The only association identified was for death from pancreatic cancer in black men with a high probability of exposure to 1,1,2-trichloroethane; however, the association was based on only 8 cases with high probability of exposure and no association was observed with intensity of exposure in other race/sex groups.
Population-based, case-control study; 63,097 cases of death from pancreatic cancer and 252,386 controls that died from noncancer causes; exposure intensity and probability based on job-exposure matrix (Kernan et al., 1999).	Significant association between high probability of 1,1,2-trichloroethane exposure and death from pancreatic cancer in black men. Large magnitude of effect (OR = 3.0, 95% CI: 1.2–7.6).	Association in black men based on only eight cases with high probability of exposure. No association between intensity of 1,1,2-trichloroethane exposure and pancreatic cancer. No association between low, medium, or high probability of 1,1,2-trichloroethane exposure and death from pancreatic cancer among black women, white women, or white men.	
Kidney cancer			
Population-based, case-control study; 438 cases of renal cell carcinoma and 687 controls; exposure (yes/no) based on job-exposure matrix (Dosemeci et al., 1999).		No association between 1,1,2-trichloroethane exposure and renal cell carcinoma (Dosemeci et al., 1999).	Overall judgement for cancer effects based on human evidence: <i>Indeterminate</i>
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
High-quality, 7-week gavage studies in male rats evaluated the potential for tumor initiation and/or promotion in the liver based on numbers of	Hepatocellular carcinomas		1,1,2-trichloroethane induced liver and adrenal gland tumors in mice in both sexes, but not in rats, exposed by gavage in a medium confidence study. No inhalation cancer bioassays were located. It should be noted that a 78-week cancer study in rats is considerably
	Dose-related trend and significantly increased incidence over untreated and vehicle controls in male and female mice exposed by gavage	Decreased survival only in low-dose female mice unrelated to tumor incidence which was not considered to be significant by NCI cancer experts (NCI, 1978).	

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
γ-glutamyltranspeptidase (GGT)-positive foci (Milman et al., 1988). Medium-quality, 78-week gavage studies in male and female rats and mice (NCI, 1978). Unacceptable subcutaneous injection study of rats exposed for 2 years (Norpoth et al., 1988).	after only 78 weeks of exposure (NCI, 1978). Large magnitude of effect; incidences were 76 and 89% in high-dose male and female mice, respectively ($\leq 12\%$ in controls). Vehicle control in female mice had 0% tumor incidence. High linear correlation between liver tumors and dose in both male and female mice supporting a linear, low dose cancer approach ($R = 0.99$) <i>Medium</i> confidence study. Increased number of GGT-positive liver foci in male rats exposed to 1,1,2-trichloroethane for 7 weeks in the Milman study. Results indicate that 1,1,2-trichloroethane is a complete carcinogen (potent liver tumor promoter and positive for liver tumor initiation).	No cancer bioassays of animals exposed by inhalation were located.	shorter than the standard duration of 104 weeks and that more robust responses in rats may have been observed in a longer study. <i>Overall WOSE judgement for cancer based on animal evidence:</i> Moderate for liver tumors Slight for adrenal gland tumors
	<i>Adrenal gland pheochromocytomas</i>		
	Dose-related trend in male mice exposed by gavage, and dose-related trend and significantly increased incidence over untreated and vehicle controls in high-dose female mice exposed by gavage (NCI, 1978). <i>Medium</i> confidence study.	No significant increase over controls in male mice (NCI, 1978).	
Evidence in Mechanistic Studies and Supplemental Information ^a			
<i>Bioactivation to DNA reactive metabolites</i>			<i>Key findings:</i> Bioactivation is expected to be important to carcinogenicity of 1,1,2-trichloroethane, but there are no metabolism data for humans. There is moderate evidence for genotoxicity related to liver tumors. No
<i>In vivo</i> studies in rats and mice exposed by oral administration.	In rats and mice, 1,1,2-trichloroethane is oxidized at the C position by CYP450s to reactive intermediates (free radicals, chloroacetic acid) that can covalently bind to	Data on metabolism of 1,1,2-trichloroethane in humans were not located.	

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
	macromolecules or lead to lipid peroxidation. Conjugation with glutathione also occurs, resulting in metabolites that are excreted via urine.		mechanistic data pertaining to adrenal gland tumors were located. <i>Overall WOSE judgement for cancer based on mechanistic evidence:</i> Moderate for liver Indeterminate for adrenal gland
<i>Genotoxicity</i>			
<i>In vivo</i> micronucleus and DNA adduct, unscheduled DNA synthesis, and DNA damage assays in mice exposed orally or rats and mice exposed by intraperitoneal injection. Sex-linked recessive mutation and mitotic recombination in fruit flies. <i>In vitro</i> mutagenicity assays in bacteria. <i>In vitro</i> micronucleus assays in human cells. <i>In vitro</i> DNA adduct, damage, synthesis, and repair assays in human lymphocytes and rat and mouse hepatocytes. <i>In vitro</i> cellular transformation assays in mouse BALB/c-3T3 cells. <i>In vitro</i> chromosome malsegregation and mitotic gene conversion assays in fungi.	DNA adducts detected in livers of rats and mice <i>in vivo</i>, with greater number of adducts formed in mice. DNA synthesis (S-phase, replicative) detected in mouse hepatocytes <i>in vivo</i>. Without activation, DNA repair detected in rat hepatocytes, but not in mouse hepatocytes <i>in vitro</i>. Micronuclei detected in several human cell types <i>in vitro</i> without activation. DNA damage in human lymphocytes <i>in vitro</i> with and without activation. DNA synthesis in rat hepatocytes <i>in vitro</i> without activation. In fungi, chromosome malsegregation without activation, and mitotic gene conversion with and without activation.	1,1,2-trichloroethane did not induce DNA damage (unwinding) or unscheduled DNA synthesis in mouse hepatocytes <i>in vivo</i>. 1,1,2-trichloroethane did not produce micronuclei in mouse bone marrow cells <i>in vivo</i>. 1,1,2-trichloroethane was not mutagenic in fruit flies <i>in vivo</i> or in bacterial assays at any dose with or without activation.	
CI = confidence interval; DNA = deoxyribonucleic acid ^a All information obtained from (ATSDR, 2021), unless otherwise noted.			

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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
Respiratory effects			
Evidence in studies of exposed humans considered for deriving toxicity values			
No data. <i>Overall judgement for respiratory effects based on human evidence:</i> Indeterminate			
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
High-quality acute inhalation toxicity tests in rats (WIL Research, 2001). High-quality 90-day repeated inhalation exposure study in rats (WIL Research, 2002). Medium-quality 14-day gavage study in male rats (White et al., 1985). Medium-quality 6-month repeated inhalation exposure study in a single dog (Mellon Institute, 1947). Medium-quality 78-week gavage studies in male and female rats and mice; nasal cavity tissues were not examined for histopathology (NCI, 1978). High-quality 90-day drinking water study in mice (high-dose male data considered uninformative due to markedly reduced drinking water consumption) (White et al., 1985).	Exposure-related increased incidence and/or severity of nasal lesions in male and female rats exposed to 1,1,2-trichloroethane at ≥ 58 ppm for 4 hours and ≥ 15 ppm for 90 days (WIL Research, 2002, 2001). Lesions in larynx of male and female rats exposed to 1,1,2-trichloroethane at ≥ 58 and 1,527 ppm, respectively, for 4 hours (WIL Research, 2001). Increased total protein in bronchoalveolar lavage fluid of male and female rats exposed to 1,1,2-trichloroethane at 1,474 and 840 ppm, respectively, for 4 hours (WIL Research, 2001). <i>High-quality studies.</i>	No larynx lesions in rats exposed to 1,1,2-trichloroethane at ≤ 100 ppm for 90 days (WIL Research, 2002).	1,1,2-trichloroethane consistently induced nasal lesions in rats exposed via inhalation for 4 hours or 90 days in 2 high-quality guideline studies. Lesions of the larynx were also observed after 4-hour exposures but not after 90-day exposures. <i>Overall WOSE judgement for respiratory effects based on animal evidence:</i> Moderate to high for nasal lesions Slight for larynx lesions
Evidence in mechanistic studies and supplemental information			
No data. <i>Overall judgement for respiratory effects based on mechanistic evidence:</i> Indeterminate			

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Table Apx A-3. 1,1,2-Trichloroethane Immunological and Hematological Toxicity 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
Immunological and hematological effects			
Evidence in studies of exposed humans considered for deriving toxicity values			
No data. Overall judgement for immunological/hematological effects based on human evidence: Indeterminate			
Evidence from in vivo mammalian animal studies considered for deriving toxicity values			
High-quality 13-week inhalation study in male and female rats (WIL Research, 2002). High-quality 90-day drinking water study in male and female mice (high-dose male data considered uninformative due to markedly reduced drinking water consumption) (Sanders et al., 1985; White et al., 1985). Medium-quality 6-month inhalation study in a male dog (Mellon Institute, 1947). Medium- to high quality 14-day gavage study in male mice (Sanders et al., 1985; White et al., 1985). Medium-quality 78-week gavage studies in male and female rats and mice (NCI, 1978). Unacceptable or Uninformative for dose-response two-generation drinking water study in rats (DuPont, 2006).	Immunological effects		In a high-quality 90-day drinking water study, 1,1,2-trichloroethane exposure potentially suppressed humoral immune responses in male and female mice but did not affect cell-mediated immune responses. Inhalation exposure decreased white blood cell counts in dogs in an uninformative study. In a high quality study, hemoglobin, hematocrit and platelet counts were decreased in female mice. Overall WOSE judgement for immunological/hematological effects based on animal evidence: Moderate for immunological effects Low for hematological effects
	1,1,2-Trichloroethane potently suppressed humoral immune responses in female mice exposed to ≥44 mg/kg-day and male mice exposed to ≥46 mg/kg-day via drinking water for 90 days in a high-quality study (Sanders et al., 1985).		
	Hematological effects		
	In a 90-day drinking water study (high quality), hematological changes were noted in female mice, including decreased prothrombin time at ≥44 mg/kg-day; decreased hemoglobin, hematocrit, and platelet counts, and increased leukocyte count at 384 mg/kg-day; and nonmonotonic increases in fibrinogen at ≥4.4 mg/kg-day (White et al., 1985).	No effects on hematological parameters in male mice exposed to doses up to 305 mg/kg-day via drinking water for 90 days (White et al., 1985); data at the highest dose were considered uninformative due to markedly decreased water consumption.	
Evidence in mechanistic studies and supplemental information			
No data. Overall judgement for immunological and hematological effects based on mechanistic evidence: Indeterminate			

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Table Apx A-4. 1,1,2-Trichloroethane Neurological and Behavioral 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
Neurological and behavioral effects			
Evidence in studies of exposed humans considered for deriving toxicity values			
No data. <i>Overall judgement for neurological and behavioral effects based on human evidence:</i> Indeterminate			
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
High-quality 1-hour, 4-hour, and 13-week inhalation exposure tests in male and female rats (WIL Research, 2002, 2001; Niklasson et al., 1993). High-quality 90-day drinking water study in male and female mice (high-dose male data considered uninformative due to markedly reduced drinking water consumption) (White et al., 1985). Low-quality 1-day ($\leq 1,000$ minutes) inhalation exposure in female mice (Gehring, 1968). High-quality single-dose oral toxicity test in male and female rats (WIL Research, 2004). Medium-quality 14-day gavage study in male mice (White et al., 1985). Medium-quality 78-week gavage studies in male and female rats and mice (NCI, 1978). Low-quality single-dose oral toxicity test in male and female mice (White et al., 1985). Unacceptable 90-day and 2-generation drinking water studies in male and female rats (DuPont, 2006; Dow Chemical, 2005).	Clinical signs of central nervous system (CNS) depression at lethal exposure levels in male and female rats exposed to 1,527 ppm via inhalation for 4 hours in a high-quality study (WIL Research, 2001) and female mice exposed to 3,750 ppm via inhalation for $\leq 1,000$ minutes in a low-quality study (Gehring, 1968). Decreased mean body temperatures and hypoactivity/disruption of habituation in functional observational battery (FOB) in male and female rats after a single gavage dose of ≥ 95 mg/kg in a high-quality study (WIL Research, 2004). Altered vestibular and optokinetic function in male and female rats exposed to ≥ 350 ppm via inhalation for approximately 1 hour in a high-quality study (Niklasson et al., 1993). Increased brain weight in male mice administered gavage doses of 38 mg/kg-day for 14 days in a medium-quality study (White et al., 1985). Sedation and/or loss of righting reflex in male and female mice administered a single lethal gavage	No effects on nervous system histopathology in rats after acute inhalation or oral exposure (WIL Research, 2004, 2001), in rats after subchronic inhalation or oral exposure (Dow Chemical, 2005; WIL Research, 2002), or in rats or mice after chronic oral exposure (DuPont, 2006; NCI, 1978).	1,1,2-Trichloroethane induced CNS depression at high acute inhalation and oral exposure levels, sometimes associated with lethality; evidence was from high-quality studies in rats showed neurotoxicity at 95 mg/kg gavage dosing (NOAEL=55 mg/kg) with support from low-quality studies in mice. One high-quality acute inhalation study in rats provides additional evidence for CNS impairments at sub-lethal concentrations (altered vestibular optokinetic function). Altered FOB parameters were identified in rats following single sublethal gavage doses in a high-quality study. Increased brain weight was detected in mice after a 14-day oral exposure in a medium-quality study. <i>Overall WOSE judgement for neurological and behavioral effects based on animal evidence:</i> Moderate

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
	dose of ≥ 450 mg/kg in a low-quality study (White et al., 1985).		
Evidence in mechanistic studies and supplemental information			
No data. <i>Overall judgement for neurological and behavioral effects based on mechanistic evidence:</i> Indeterminate			

Table Apx A-5. 1,1,2-Trichloroethane Liver/Hepatic Toxicity 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
Liver/hepatic effects			
Evidence in studies of exposed humans considered for deriving toxicity values			
No data. <i>Overall judgement for hepatic effects based on human evidence:</i> Indeterminate			
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
High-quality inhalation studies in male and female rats exposed for 4 hours (WIL Research, 2001) or 13 weeks (WIL Research, 2002). Medium-quality inhalation studies in male rats exposed for 2 hours (Carlson, 1973) and female mice exposed for up to 1,000 minutes (Gehring, 1968). High-quality 90-day drinking water study in male and female mice (high-dose male data considered uninformative due to markedly reduced drinking water consumption) (White et al., 1985). Medium-quality gavage studies in female rats exposed for 1 day (Xia and Yu, 1992), male mice exposed for 14 days (White et al., 1985), and male and female rats and mice exposed for 78 weeks (NCI, 1978).	Hepatic lesions in rats exposed to ≥ 181 ppm for 4 hours (necrosis) or ≥ 15 ppm for 13 weeks (hepatocellular vacuolation) in high-quality inhalation studies (WIL Research, 2002, 2001); incidences and/or severity increased with dose. Increased serum alanine aminotransferase (ALT) after inhalation exposure to 2,080 ppm for 2 hours in rats or 3,750 ppm for up to 1,000 minutes in mice in medium-quality studies (Carlson, 1973 ; Gehring, 1968). Hepatic lesions (vacuolar degeneration, scattered necrosis) with increased serum enzymes in rats after a single gavage dose of 667 mg/kg in a medium-quality study (Xia and Yu, 1992). Increased liver weights in female mice in a 90-day drinking water exposure		1,1,2-Trichloroethane induced hepatic lesions in rats exposed via inhalation for 4 hours or 13 weeks days in high-quality studies; findings were dose-responsive. Hepatic lesions were also observed in rats following a single gavage exposure to a high dose and mice exposed via s.c. injection in medium-quality studies. Supporting evidence includes altered serum liver enzymes and liver triglyceride levels in rats and mice following acute inhalation, gavage, or injection exposure. <i>Overall WOSE judgement for hepatic effects based on animal evidence:</i> Moderate

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Medium-quality subcutaneous (s.c.) injection study in male mice (Plaa et al., 1958) and intraperitoneal (i.p.) injection studies in male or female rats (Charbonneau et al., 1991; Lundberg et al., 1986; Harms et al., 1976; Klaassen and Plaa, 1969). Unacceptable two-generation drinking water study in rats (DuPont, 2006).	to 384 mg/kg-day in a high-quality study (White et al., 1985). Hepatic lesions (vacuolation, necrosis) in mice after a single s.c. injection of ≥ 1.2 mmol/kg in a medium-quality study (Plaa et al., 1958). Increased serum sorbitol dehydrogenase (SDH) in rats after a single i.p. injection of 50.6 mg/kg and increased liver triglycerides in rats after a single i.p. injection of ~700 mg/kg in medium-quality studies (Lundberg et al., 1986; Klaassen and Plaa, 1969).		
Evidence in mechanistic studies and supplemental information			
Assays testing whether CYP450 inducers (acetone, ethanol, or phenobarbital) potentiate 1,1,2-trichloroethane-induced hepatotoxicity in rats and mice (Carlson, 1973; Klaassen and Plaa, 1966; Macdonald et al., 1982; Traiger and Plaa, 1974 as cited in ATSDR, 2021). Assay of free radicals in livers of rats exposed by gavage (Xia and Yu, 1992). Assays of 1,1,2-trichloroethane covalent binding to proteins and lipids in hepatic microsomes from rats of different ages (DiRenzo et al., 1982b).	Serum aspartate aminotransferase (AST) and/or ALT levels were increased in animals pretreated with CYP450 inducers compared with those exposed only to 1,1,2-trichloroethane (Carlson, 1973; Klaassen and Plaa, 1966; Macdonald et al., 1982; Traiger and Plaa, 1974; as cited in ATSDR, 2021). Hepatic free radical concentrations increased following gavage dosing of rats with 1,1,2-trichloroethane (Xia and Yu, 1992). Lower covalent binding of 1,1,2-trichloroethane to proteins and lipids was observed in microsomes from aged rats compared with those from younger rats (DiRenzo et al., 1982b).	Data on metabolism of 1,1,2-trichloroethane in humans or human tissues were not located.	<i>Key findings:</i> Bioactivation and oxidative stress may play roles in the hepatotoxicity of 1,1,2-trichloroethane, but data are very limited. An <i>in vitro</i> study suggested the possibility that age may alter susceptibility to 1,1,2-trichloroethane hepatotoxicity. <i>Overall WOSE judgement for hepatotoxicity based on mechanistic evidence:</i> Slight to moderate

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Table Apx A-6. 1,1,2-Trichloroethane Reproductive/Developmental Toxicity 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
Reproductive/developmental effects			
Evidence in studies of exposed humans considered for deriving toxicity values			
High-quality case-control study examined the association between proximity to point sources of chlorinated solvents and birth defects such as spina bifida and other neural tube 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).	When comparing mothers with exposure risk to 1,1,2-trichloroethane greater than zero to those mothers with no exposure risk, a high-quality case-control study found increased odds of neural tube defects (OR = 1.56, 95% CI 1.11, 2.18), spina bifida (OR = 1.94, 95% CI 1.32, 2.84), and septal heart defects (OR = 1.12, 95% CI 1.01, 1.24) (Brender et al., 2014). This study found increased odds of spina bifida in offspring with mothers in the “low” intensity of exposure risk group compared with no intensity of exposure risk (OR = 3.01, 95% CI 1.77, 5.10), and also found increased odds of cleft lip without cleft palate in the “high” intensity of exposure group compared with no intensity of exposure risk (OR = 1.99, 95% CI 1.05, 3.76) (Brender et al., 2014). This study also found increased odds of septal heart defects in offspring in the “medium” intensity of exposure group compared with no intensity of exposure risk (OR = 1.25, 95% CI 1.06, 1.47) (Brender et al., 2014).	Although a high-quality case-control study found increased odds of spina bifida in offspring with mothers in the “low” intensity of exposure risk group compared with no intensity of exposure risk, this result was not consistent in the “medium” or “high” intensity of exposure risk groups when compared with the no intensity of exposure risk group (Brender et al., 2014). Additionally, this study found increased odds of septal heart defects in offspring in the “medium” intensity of exposure group compared with no intensity of exposure, but this result was not consistent in the “high” intensity of exposure group when compared with the no intensity of exposure risk group (Brender et al., 2014). There were also potential co-exposures to other chlorinated solvents that were not adjusted for in the analysis, which could have biased effect estimates (Brender et al., 2014).	A single high-quality case-control study found increased odds of spina bifida, neural tube defects, and septal heart defects when comparing mothers with exposure risk greater than zero to those mothers with no exposure. The study also found increased odds of cleft lip without cleft palate in the “high” intensity of exposure risk group compared with the no intensity of exposure risk group. This same study found that the “low” intensity of exposure risk group of mothers had increased odds of spina bifida when compared with the no intensity of exposure risk group, but this result did not follow a logical dose-response gradient as the “medium” and “high” risk of exposure groups did not show this same effect. Similarly, the study found increased odds of septal hear defects in offspring in the “medium” intensity of exposure group when compared with the no intensity of exposure risk group, but this result also did not follow a logical dose-response gradient as the “high” risk of exposure group did not show this same effect. <i>Overall WOSE judgement for reproductive and developmental effects based on human evidence: Indeterminate</i>
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
No data. <i>Overall judgement for reproductive/developmental effects based on animal evidence: Indeterminate</i>			
Evidence in mechanistic studies and supplemental information			
No data. <i>Overall judgement for reproductive/developmental effects based on mechanistic evidence: Indeterminate</i>			

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Appendix B BENCHMARK DOSE MODELING RESULTS FOR CRITICAL ENDPOINTS

B.1 1,1,2-Trichloroethane Cancer Study BMD Modeling Results to Derive Oral Slope Factors (OSF) and Inhalation Unit Risk (IUR) Values

The National Cancer Institute ([NCI, 1978](#)) conducted a 2-year cancer bioassay in Osborne-Mendel rats and B6C3F1 mice (20/sex/species in control groups, 50/sex/species in treatment groups) exposed by gavage 5 days/week. The control groups consisted of untreated controls (not intubated) and vehicle controls (intubated with corn oil). Treated rats were given 1,1,2-trichloroethane at doses of 30 or 70 mg/kg-day for 20 weeks. As these doses were well tolerated, the doses were increased to 50 and 100 mg/kg-day, respectively, for the remaining 58 weeks. Treated mice were initially dosed with 1,1,2-trichloroethane at 150 or 300 mg/kg-day for 8 weeks. Based on the tolerance of these doses, the doses were increased to 200 and 400 mg/kg-day, respectively, for the next 70 weeks. After a 78-week exposure period, the animals were maintained without treatment for an additional 34 to 35 weeks (rats) or 12 to 13 weeks (mice). The time-weighted average doses calculated by the study authors were 0, 46, and 92 mg/kg-day for rats and 0, 195, and 390 mg/kg-day for mice. These were converted into human equivalent doses (HED) for BMD modeling. Utilizing a PBPK model, the oral doses were converted into corresponding human equivalent concentration (HEC) inhalation exposures of 0, 146, and 251 mg/m³ (0, 26.8, and 46.2 ppm) for mice. Histopathology of a comprehensive set of organs was evaluated and the liver tumors in mice had an excellent dose-response for BMD cancer modeling to derive oral slope factors (OSF) and inhalation unit risk (IUR) values. The summary for oral-slope factors for male and female mice is provided in Table_Apx B-1.

Table_Apx B-1. Summary of BMD Cancer Oral Slope Factors for Liver Tumors in Mice

Mouse Tumor	Oral Slope Factor	BMD	BMDL
Female Liver, HED	1.88E-02 per mg/kg/day	8.80 mg/kg/day	5.32 mg/kg/day
Male Liver, HED	3.48E-02 per mg/kg/day	3.72 mg/kg/day	2.87 mg/kg/day
BMD = benchmark dose; BMDL = lower bound of the benchmark dose; HED = human equivalent dose			

Table_Apx B-2. Oral Data in Male Mice Liver Tumors: HED Input

BMD Model	BMD _L mg/kg/day	BMD mg/kg/day	BMD _U mg/kg/day	P-Value	AIC	Scaled Residual in Control	Scaled Residual Low Dose	Scaled Residual High Dose
Multistage Model 1	2.87	3.72	5.13	0.086	139.018	0.330	-1.319	1.050
Multistage Model 2	3.71	9.60	12.85	Failed -9999	137.994	1.540	-1.503	2.266
BMD = benchmark dose; BMDL = benchmark dose limit; HED = human equivalent dose								

The data set in Table_Apx B-2 is based on the HED values calculated from the empirical body weights of male mice and liver tumor incidences in the 1,1,2-trichloroethane NCI cancer study ([NCI, 1978](#)). The liver tumor incidences had the best dose-response and the 1,1,2-Trichloroethane PBPK Model is based on liver metabolism to represent the internal dose. The liver is a target organ based on liver hazards identified in the Milman study ([Milman et al., 1988](#)) and Tyson study ([Tyson et al., 1983](#)). Based on a

weight of scientific evidence ([Haber et al., 2018](#)), the Multistage Model 1 was selected to best represent the liver tumor BMD and BMDL values in male mice. The Multistage Model 1 provided the smallest scaled residual in the control group, it provided the smallest scaled residual in the low dose group, it provided the smallest scaled residual in the high-dose group and had the largest p-value test; thus, this model provides overall confidence in the BMD and BMDL values. Conversely, the Multistage Model 2 had the largest scaled residuals in the control, low-dose, and high-dose groups, but failed the p-value test—thus decreasing confidence in this model. 1,1,2-Trichloroethane produces multiple reactive metabolites in the liver and the Sapphire Group PBPK Model indicates that suicide inhibition of metabolism occurs in female mice; therefore, the male cancer slope factor is recommended to protect both sexes. The oral slope factor is 0.10/BMDL. For male mice, the oral slope factor is 0.10/2.87 or 0.0348 per mg/kg/day.

Table_Apx B-3. Oral Data in Female Mice Liver Tumors: HED Input

BMD Model	BMD _L mg/kg/day	BMD mg/kg/day	BMD _U mg/kg/day	P-Value	AIC	Scaled Residual in Control	Scaled Residual Low Dose	Scaled Residual High Dose
Multistage Model 1	2.27	2.85	3.63	0.007 Low	105.355	−0.0006	−2.3487	2.1043
Multistage Model 2	5.32	8.80	9.98	0.642	95.419	−0.0006	−0.7349	0.5873

Based on a weight of scientific evidence, the Multistage Model 2 in Table_Apx B-3 was selected to best represent the liver tumor BMD and BMDL values in female mice. It provided the smallest scaled residual in the low- and high-dose groups, the smallest scaled residual in the high-dose group, and the highest p-value; thus, the Multistage Model 2 provides overall confidence in the BMD and BMDL values. Conversely, the Multistage Model 1 had the largest scaled residuals at the mid- and high-doses and failed the p-value test. 1,1,2-Trichloroethane produces multiple reactive metabolites in the liver, and the Sapphire Group PBPK Model indicates that suicide inhibition of metabolism occurs in female mice; therefore, the female cancer slope factor is not recommended to protect both sexes.

Table_Apx B-4. PBPK Inhalation Data in Male Mice Liver Tumors: HEC Input

BMD Model	BMCL μg/m ³	BMC μg/m ³	BMC _U μg/m ³	P-Value	AIC	Scaled Residual in Control	Scaled Residual Low Dose	Scaled Residual High Dose
Multistage Model 1	20,448	26,458	36.605	0.0289 Low	140.908	0.3292	−1.6566	1.3860
Multistage Model 2	33,542	73,305	86.821	0.8392	134.347	0.1831	−0.4635	0.3199

Based on a weight of scientific evidence, the Multistage Model 2 in Table_Apx B-4 was selected to best represent the liver tumor BMC and BMCL values in male mice. It provided the smallest scaled residual in the control group, it provided the smallest scaled residual in the low- and high-dose groups and had the highest p-value test; thus, the Multistage Model 2 provides overall confidence in the BMC and BMCL values. Conversely, the Multistage Model 1 had the largest scaled residuals at all doses and had a low p-value test. 1,1,2-Trichloroethane produces multiple reactive metabolites in the liver and the Sapphire Group PBPK Model indicates that suicide inhibition of metabolism occurs in female mice; thus, the male cancer slope factor is recommended to protect both sexes.

4049 **Table_Apx B-5. PBPK Inhalation Data in Female Mice Liver Tumors: HEC Input**

PBPK Inhalation Data in Female Mice Liver Tumors: HEC Input								
BMD Model	BMC _L µg/m ³	BMC µg/m ³	BMC _U µg/m ³	P-Value	AIC	Scaled Residual in Control	Scaled Residual Low Dose	Scaled Residual High Dose
Multistage Model 1	16,401	20,550	26,114	0.0013 Low	109.128	-0.0006	-2.6867	2.4760
Multistage Model 2	42,039	62,400	70,582	0.3005	96.410	-0.0006	-1.4656	1.2299

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4051 Based on a weight of scientific evidence, the Multistage Model 2 in Table_Apx B-5 was selected to best
4052 represent the liver tumor BMC and BMCL values in female mice. It provided the smallest scaled
4053 residual in the low- and high-dose groups and had the highest p-value test; thus, this model provides
4054 overall confidence in the BMC and BMCL values. Conversely, the Multistage Model 1 had the largest
4055 scaled residuals in the low dose group, the largest scaled residuals in the high dose group and had a low
4056 p-value test. 1,1,2-Trichloroethane produces multiple reactive metabolites in the liver and the Sapphire
4057 Group PBPK Model indicates that suicide inhibition of metabolism occurs in female mice; therefore, the
4058 male cancer slope factor is recommended to protect both sexes.

4060 Appendices B.2 through B.9 present all BMD model inputs and outputs for cancer and non-cancer
4061 hazards for 1,1,2-trichloroethane.

4062 **B.2 1,1,2-Trichloroethane Oral Liver Cancer in Male Mice HED Input**

4063 **B.2.1 HED Doses**

4064 **Report Generated:** 2025-Nov-05 19:11 UTC

4065 **Analysis URL:** [View](#)

4066 **BMDS Online Version:** 25.1 (pybmds 25.1; bmdscore 25.1)

4067 **B.2.2 Modeling Summary**

4069 **B.2.3 Datasets**

4071 **B.2.3.1 Name: Dataset #1**

Dose (mg/kg/day)	0	18.9	37.9
Affected / Total (%) (Incidence)	2.0/20.0 (10.0%)	18.0/49.0 (36.7%)	37.0/49.0 (75.5%)

4073 **B.2.3.2 Settings**

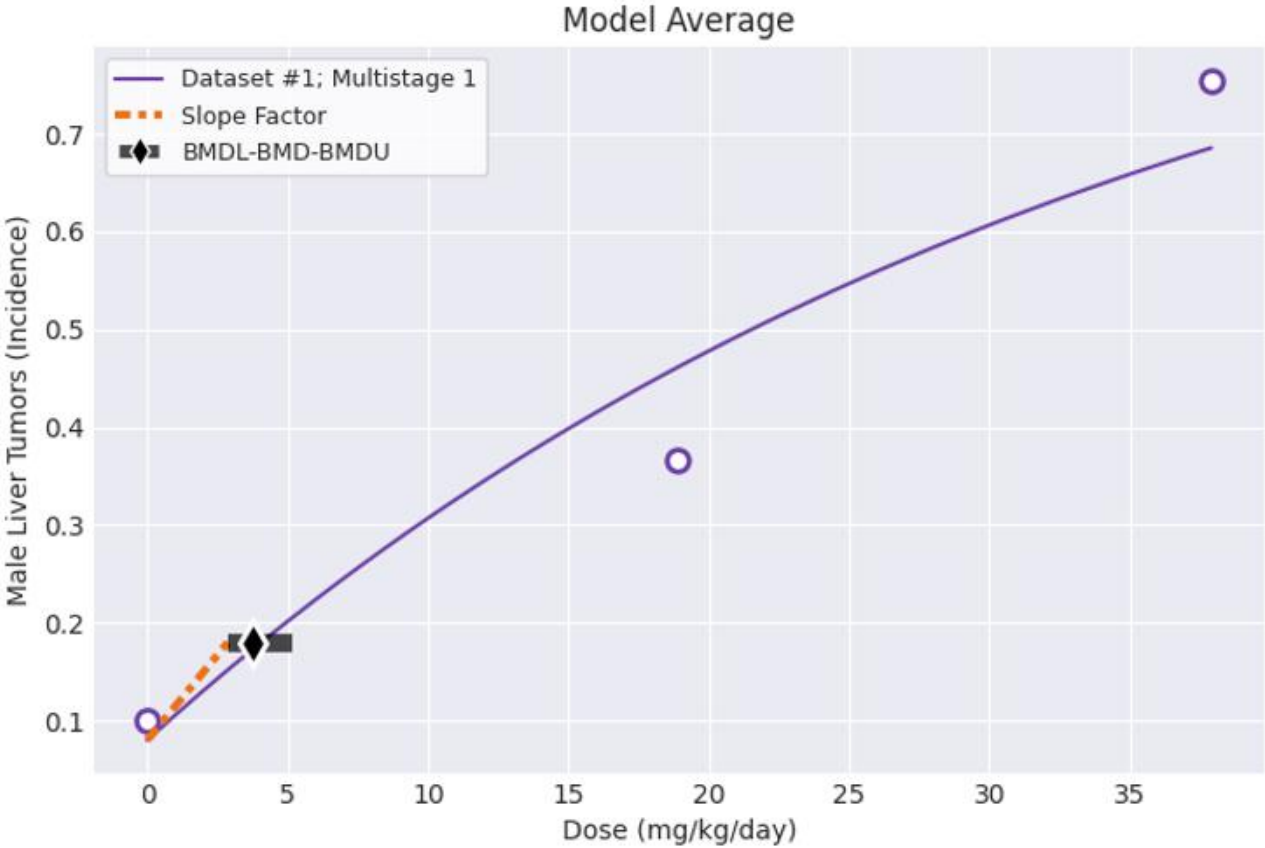
Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Degree	2

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B.2.3.3 Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Dataset #1: Multistage 1	2.873	3.72	5.139	0.035	0.086	139.018	0.33	0.33

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Figure_Apx B-1. BMD Model Average for Oral Cancer Data in Male Mice

Multitumor MS Combo Model

Version: pybmds 25.1 (bmdscore 25.1)

BMD	3.72038
BMDL	2.87275
BMDU	5.13925
Slope Factor	0.0348098
Combined Log-likelihood	-67.5089
Combined Log-likelihood Constant	-60.573

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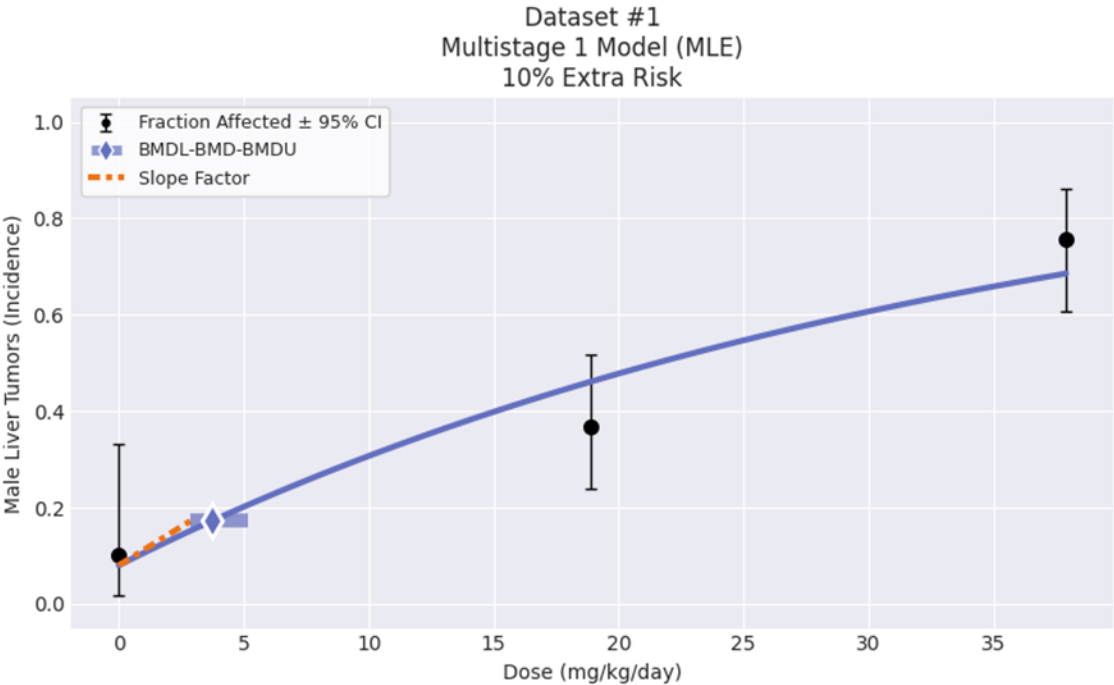
B.2.4 Individual Model Results

B.2.4.1 Dataset #1

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B.2.4.2 Multistage 1



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Figure_Apx B-2. Multistage BMD Model for Oral Cancer Data in Male Mice

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000

Modeling Summary:

BMD	3.72038
BMDL	2.8728
BMDU	5.13941
Slope Factor	0.0348093
AIC	139.018
Log-Likelihood	-67.5089
P-Value	0.0857953
Overall d.f.	1
Chi ²	2.95155

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0799888	no	0.0453105
b1	0.0283199	no	0.176041

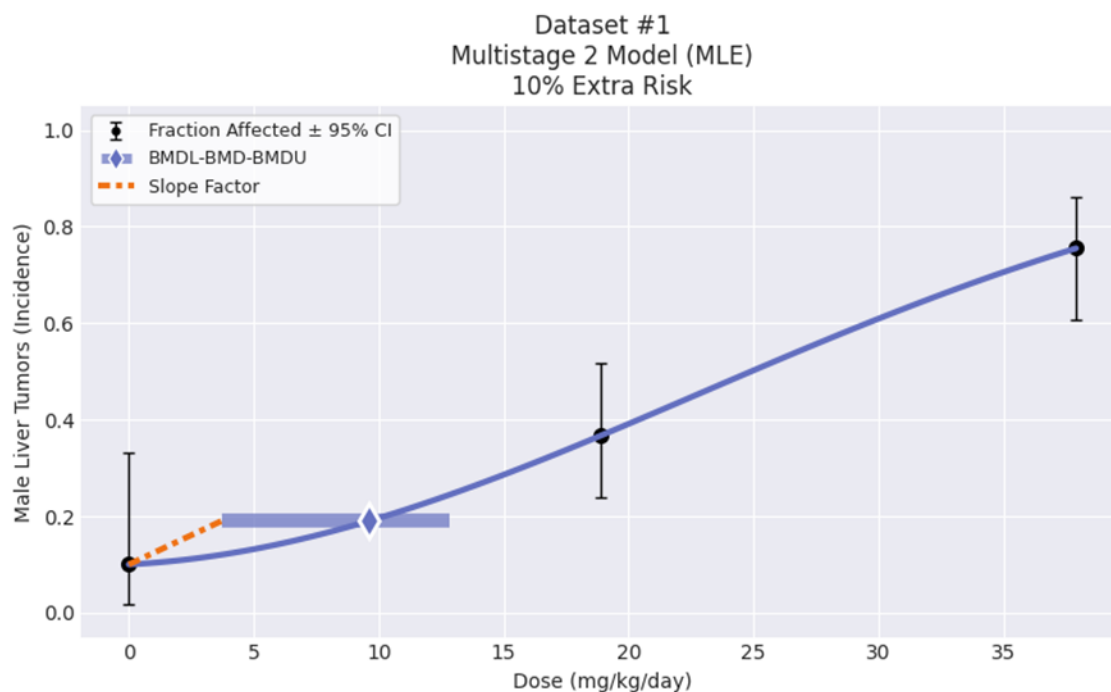
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.59978	0.0799888	0.329896
18.9	49	18	22.6042	0.46131	-1.31944
37.9	49	37	33.5883	0.685475	1.04967

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-65.9969	3	-	-	-
Fitted model	-67.5089	2	3.02394	1	0.0820441
Reduced model	-81.7236	1	31.4533	2	1.47912e-07

B.2.4.3 Multistage 2



Figure_Apx B-3. Multistage Model 2 for Oral Cancer Data in Male Mice

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	2

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000
b2	0.1	0	10000

Modeling Summary:

BMD	9.60342
BMDL	3.70728
BMDU	12.8521
Slope Factor	0.026974
AIC	137.994
Log-Likelihood	-65.9969
P-Value	-9999
Overall d.f.	0
Chi ²	9.76728e-16

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.1	no	0.0462533
b1	0.00303951	no	0.535078
b2	0.000825917	no	0.672664

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2	0.1	1.54013e-08
18.9	49	18	18	0.367347	-1.50344e-08
37.9	49	37	37	0.755102	2.26604e-08

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-65.9969	3	-	-	-
Fitted model	-65.9969	3	0	0	1
Reduced model	-81.7236	1	31.4533	2	1.47912e-07

U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmbs 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed November 05, 2025.

B.3 1,1,2-Trichloroethane Oral Liver Cancer in Female Mice HED Input

B.3.1 HED Doses

Report Generated: 2025-Nov-05 20:11 UTC

Analysis URL: [View](#) / [Update](#)

BMDS Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

B.3.2 Modeling Summary

B.3.2.1 Datasets

Name: Dataset #1

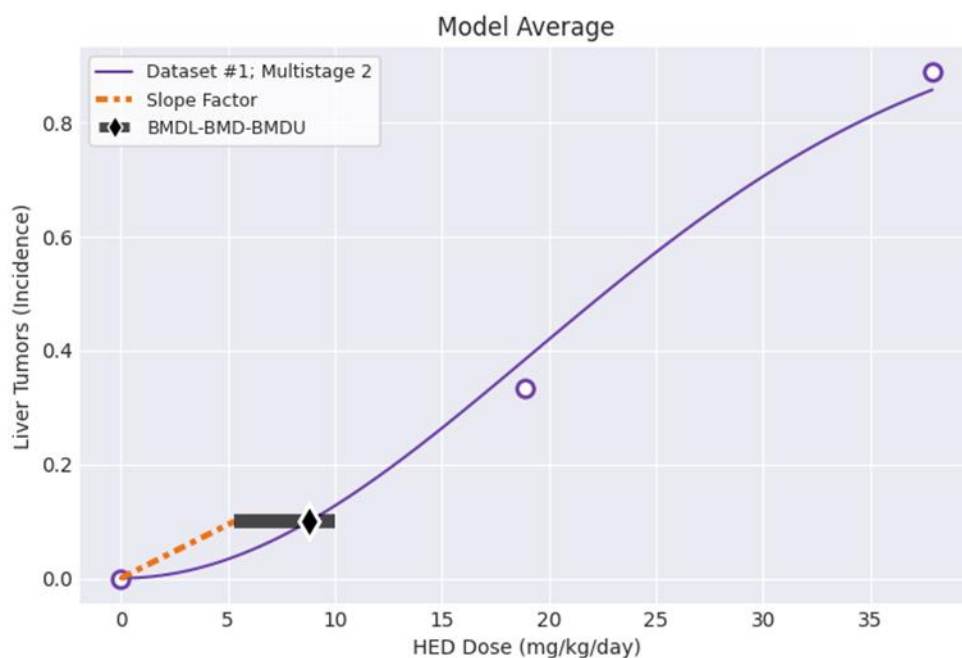
Dose (mg/kg/day)	0	18.9	37.9
Affected / Total (%) (Incidence)	0.0/20.0 (0.0%)	16.0/48.0 (33.3%)	40.0/45.0 (88.9%)

B.3.2.2 Settings

Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Degree	2

B.3.2.3 Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Dataset #1: Multistage 2	5.318	8.8	9.977	0.019	0.642	95.419	-0.001	-0.001



Figure_Apx B-4. BMD Model Average for Oral Cancer Data in Female Mice

Multitumor MS Combo Model

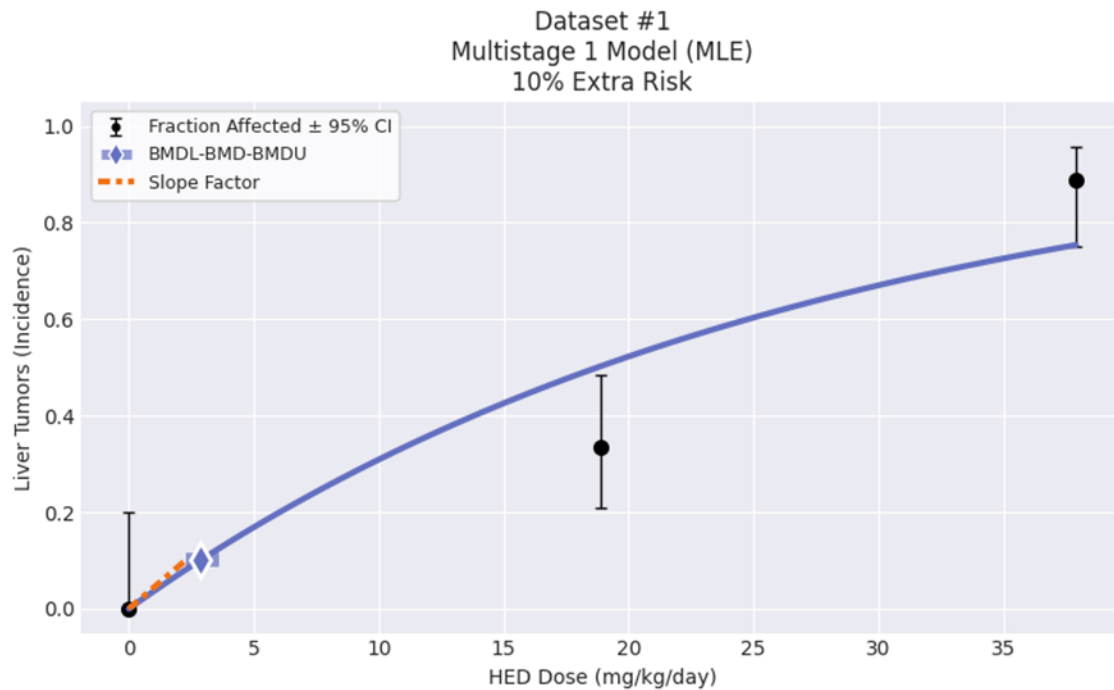
Version: pybmds 25.1 (bmdscore 25.1)

BMD	8.7996
BMDL	5.31813
BMDU	9.97789
Slope Factor	0.0188036
Combined Log-likelihood	-46.7095
Combined Log-likelihood Constant	-42.4599

B.3.3 Individual Model Results

B.3.3.1 Dataset #1

B.3.3.2 Multistage 1



Figure_Apx B-5. BMD Multistage 1 Model for Oral Cancer Data in Female Mice

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000

Modeling Summary:

BMD	2.84949
BMDL	2.26986
BMDU	3.62704
Slope Factor	0.0440556
AIC	105.355
Log-Likelihood	-51.6777
P-Value	0.00692695
Overall d.f.	2
Chi ²	9.94467

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
b1	0.0369752	no	0.199349

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

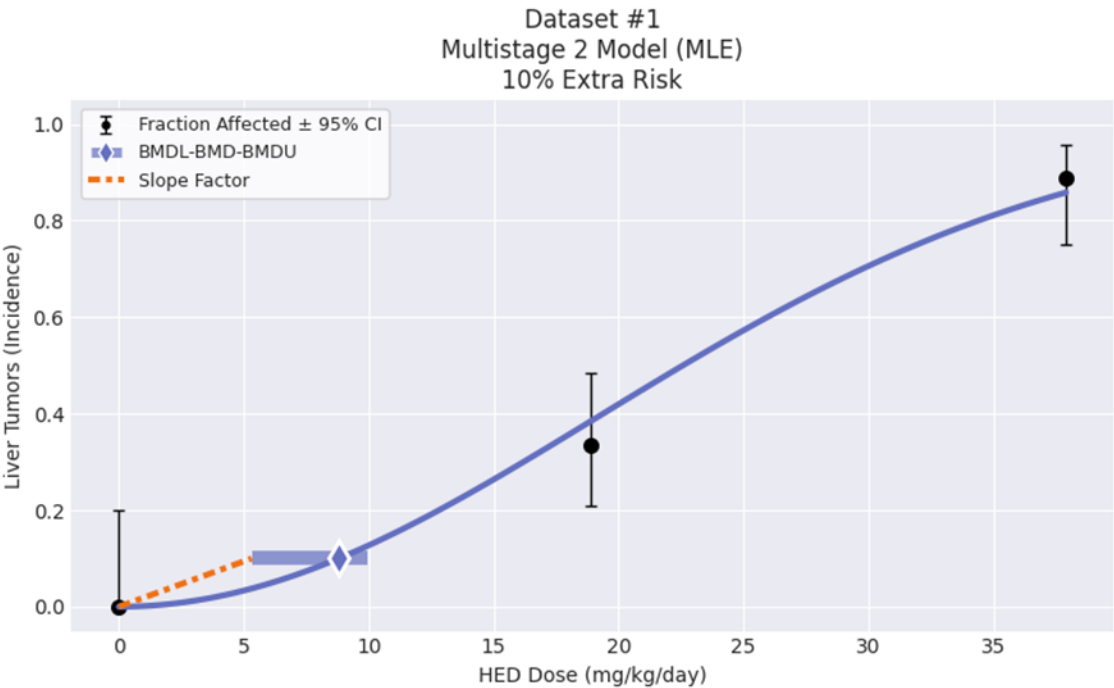
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	0	3.046e-07	1.523e-08	-0.000551905
18.9	48	16	24.136	0.502834	-2.34871
37.9	45	40	33.9182	0.753738	2.10434

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-46.2501	3	-	-	-
Fitted model	-51.6777	1	10.8552	2	0.00439359
Reduced model	-78.3212	1	64.1422	2	1.17684e-14

B.3.3.3 Multistage 2



Figure_Apx B-6. BMD Multistage Model 2 for Oral Cancer Data in Female Mice

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	2

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000
b2	0.1	0	10000

Modeling Summary:

BMD	8.7996
BMDL	5.31785
BMDU	9.97721
Slope Factor	0.0188046
AIC	95.4189
Log-Likelihood	-46.7095
P-Value	0.642434
Overall d.f.	2
Chi ²	0.884984

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
b1	1.27993e-18	yes	Not Reported
b2	0.00136067	no	0.291152

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	0	3.046e-07	1.523e-08	-0.000551905
18.9	48	16	18.4774	0.384945	-0.734874
37.9	45	40	38.6263	0.858361	0.587319

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-46.2501	3	-	-	-
Fitted model	-46.7095	1	0.918671	2	0.631703
Reduced model	-78.3212	1	64.1422	2	1.17684e-14

U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmds 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed November 05, 2025.

B.4 1,1,2-Trichloroethane RfC Liver Cancer IUR in Male Mice PBPK (µg/m³) Input

B.4.1 PBPK HEC Exposures

Report Generated: 2025-Nov-03 23:11 UTC

Analysis URL: [View](#)

BMDS Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

B.4.2 Modeling Summary

B.4.2.1 Datasets

Name: Dataset #1

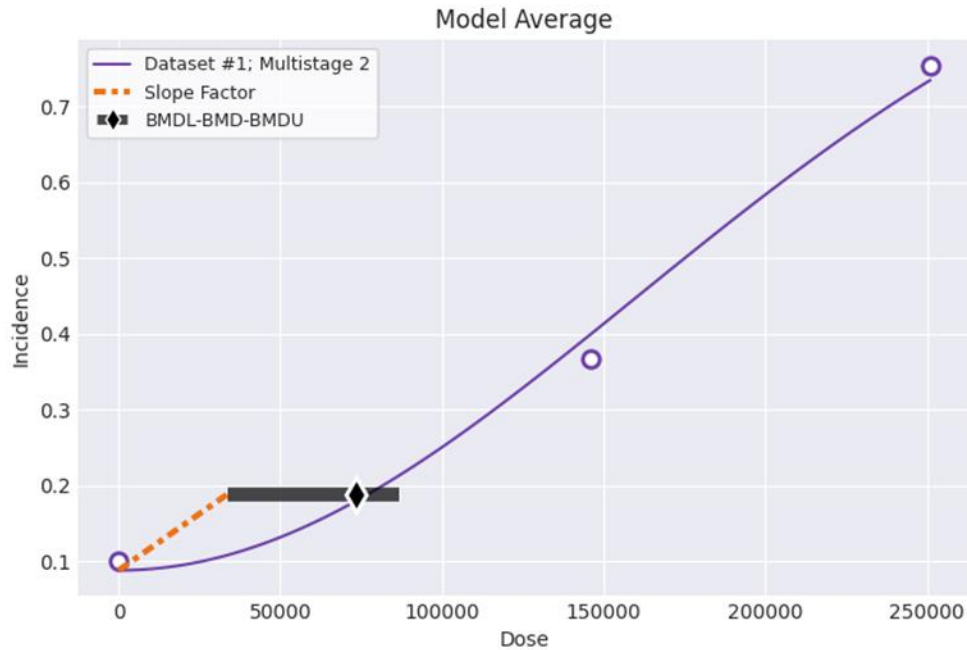
PBPK HEC	0	146000	251000
Affected / Total (%)	2.0/20.0 (10.0%)	18.0/49.0 (36.7%)	37.0/49.0 (75.5%)

B.4.2.2 Settings

Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Degree	2

B.4.2.3 Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Dataset #1:	33542.94	73305.95	86821	<0.001	0.839	134.347	0.183	-0.463
Multistage 2	5							



Figure_Apx B-7. BMD Model Average for Liver Cancer in Male Mice with Inhalation PBPK HEC Input in µg/m

Multitumor MS Combo Model

Version: pybmds 25.1 (bmdscore 25.1)

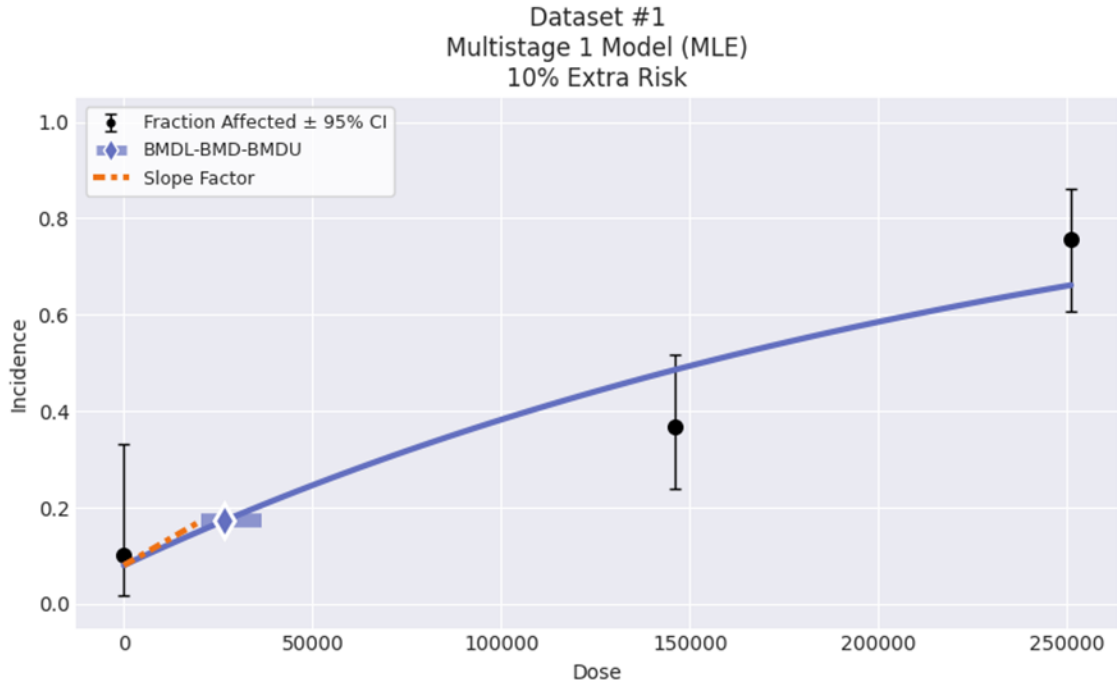
BMD	73306
BMDL	33543.7
BMDU	86827.6
Slope Factor	2.98119e-06
Combined Log-likelihood	-66.1736
Combined Log-likelihood Constant	-60.573

B.4.3 Individual Model Results

B.4.3.1 Dataset #1

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B.4.3.2 Multistage 1



Figure_Apx B-8. BMD Multistage 1 Model for Liver Cancer in Male Mice with Inhalation PBPK HEC Input in $\mu\text{g}/\text{m}^3$

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000

Modeling Summary:

BMD	26458
BMDL	20447.9
BMDU	36605.4
Slope Factor	4.89049e-06
AIC	140.908
Log-Likelihood	-68.4538
P-Value	0.0288958
Overall d.f.	1
Chi ²	4.77381

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.080024	no	0.0455565
b1	3.98218e-06	no	0.170339

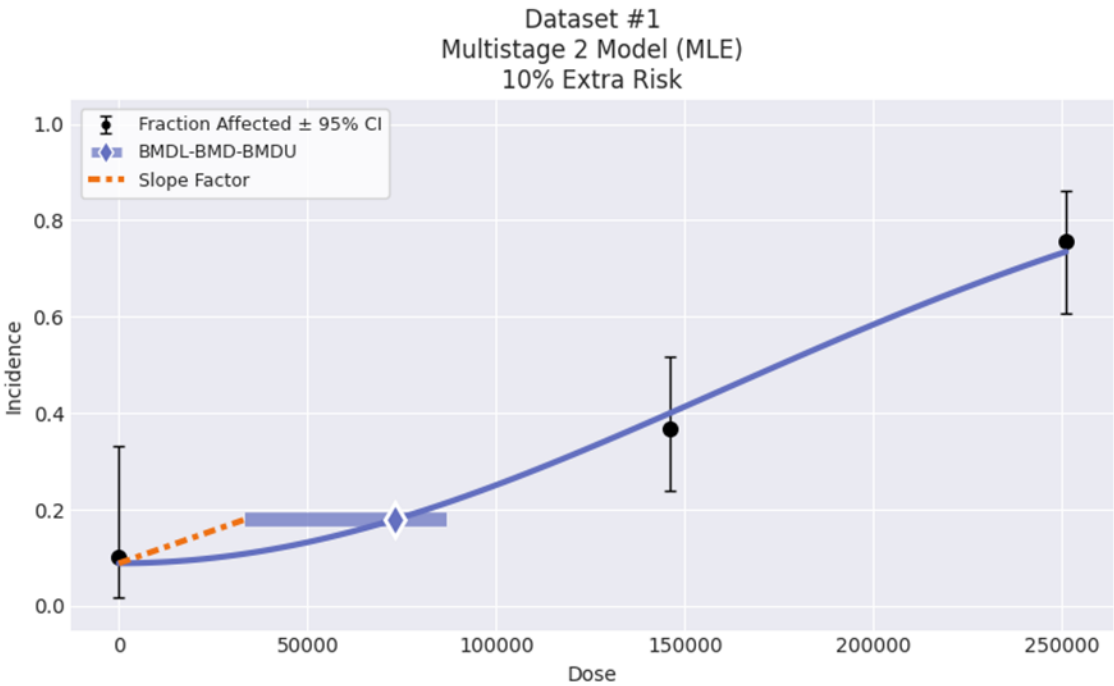
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.60048	0.080024	0.32925
146000	49	18	23.7957	0.485627	-1.6566
251000	49	37	32.4086	0.6614	1.38603

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-65.9969	3	-	-	-
Fitted model	-68.4538	2	4.9137	1	0.0266446
Reduced model	-81.7236	1	31.4533	2	1.47912e-07

B.4.3.3 Multistage 2



Figure_Apx B-9. BMD Multistage Model 2 for Liver Cancer in Male Mice with Inhalation PBPK HEC Input in $\mu\text{g}/\text{m}^3$

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	2

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000
b2	0.1	0	10000

Modeling Summary:

BMD	73305.9
BMDL	33542.9
BMDU	86821
Slope Factor	2.98125e-06
AIC	134.347
Log-Likelihood	-66.1736
P-Value	0.839158
Overall d.f.	2
Chi ²	0.350713

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0883771	no	0.0441796
b1	9.01822e-21	yes	Not Reported
b2	1.96065e-11	yes	Not Reported

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.76754	0.0883771	0.183127
146000	49	18	19.5893	0.399781	-0.46348
251000	49	37	36.0115	0.734929	0.319944

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-65.9969	3	-	-	-
Fitted model	-66.1736	1	0.353336	2	0.838058
Reduced model	-81.7236	1	31.4533	2	1.47912e-07

B.4.3.4 Citation

U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmds 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed November 03, 2025.

B.5 1,1,2-Trichloroethane Liver Cancer IUR in Male Mice PBPK HEC Input in ppm

B.5.1 PBPK HEC Values in ppm from Oral Data

Report Generated: 2025-Dec-12 16:12 UTC

Analysis URL: [View](#)

BMDs Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

B.5.2 Modeling Summary

B.5.2.1 Datasets

Name: Dataset #1

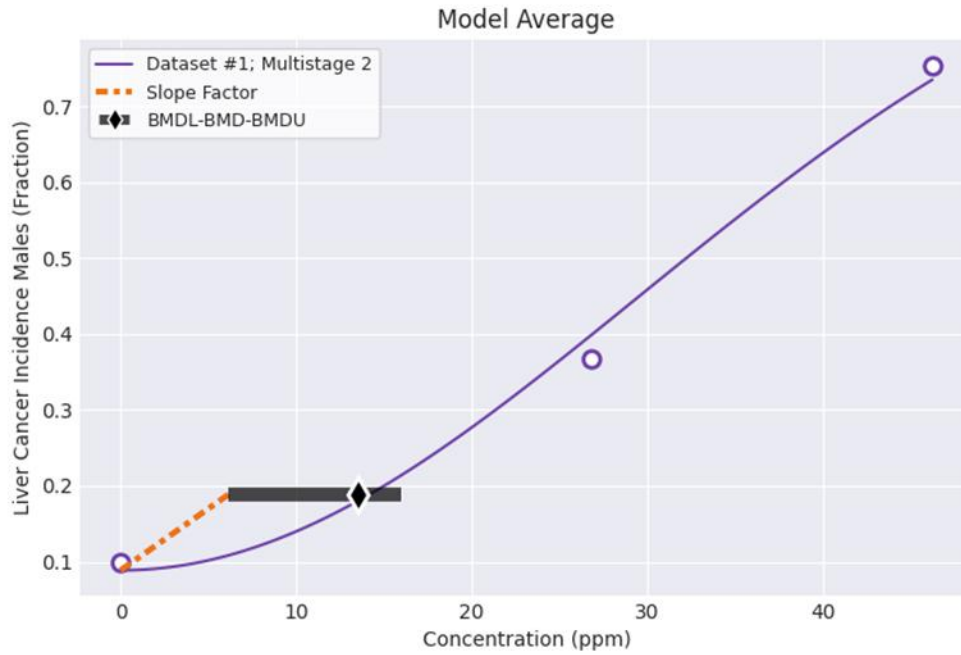
Dose (ppm)	0	26.8	46.2
Affected / Total (%) (Fraction)	2.0/20.0 (10.0%)	18.0/49.0 (36.7%)	37.0/49.0 (75.5%)

B.5.2.2 Settings

Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Degree	2

B.5.2.3 Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Dataset #1: Multistage 2	6.145	13.482	15.971	0.016	0.564	136.329	0.18	-0.452



Figure_Apx B-10. BMD Model Average for Liver Cancer in Male Mice with Inhalation PBPK HEC Input in ppm

Multitumor MS Combo Model

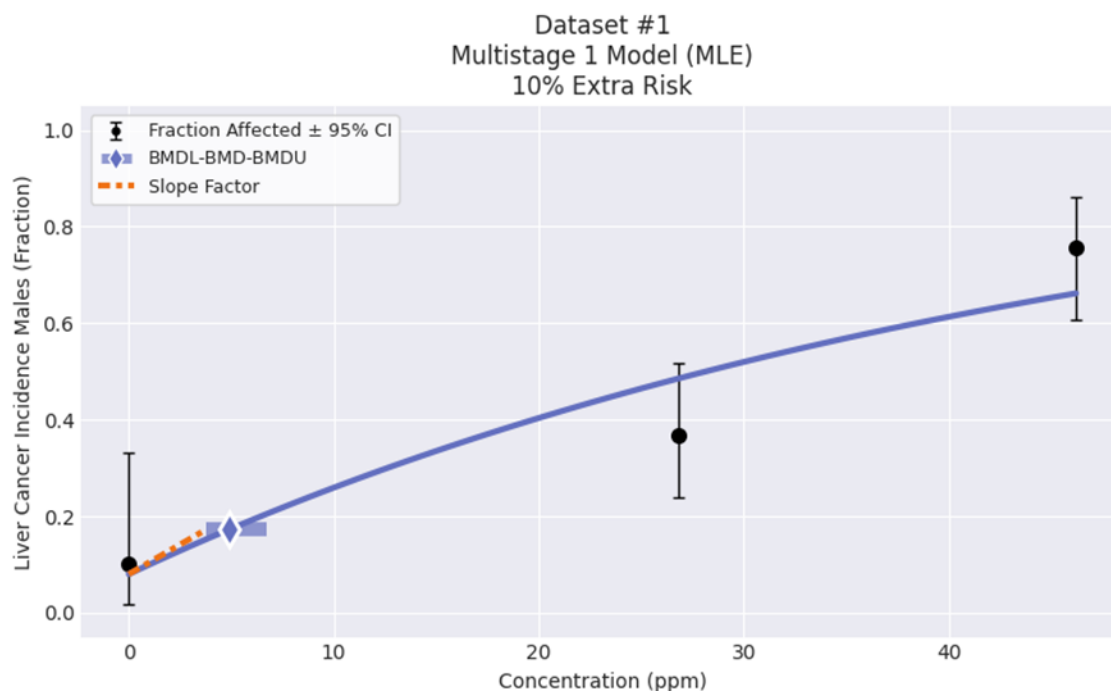
Version: pybmds 25.1 (bmdscore 25.1)

BMD	13.4825
BMDL	6.14495
BMDU	15.9726
Slope Factor	0.0162735
Combined Log-likelihood	-66.1646
Combined Log-likelihood Constant	-60.573

B.5.3 Individual Model Results

B.5.3.1 Dataset #1

B.5.3.2 Multistage



Figure_Apx B-11. Multistage Model 1 for Liver Cancer in Male Mice with Inhalation PBPK HEC Input in ppm

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000

Modeling Summary:

BMD	4.86344
BMDL	3.75868
BMDU	6.72808
Slope Factor	0.0266051
AIC	140.87
Log-Likelihood	-68.4348
P-Value	0.0295141
Overall d.f.	1
Chi ²	4.73738

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0800071	no	0.0455523
b1	0.0216638	no	0.164507

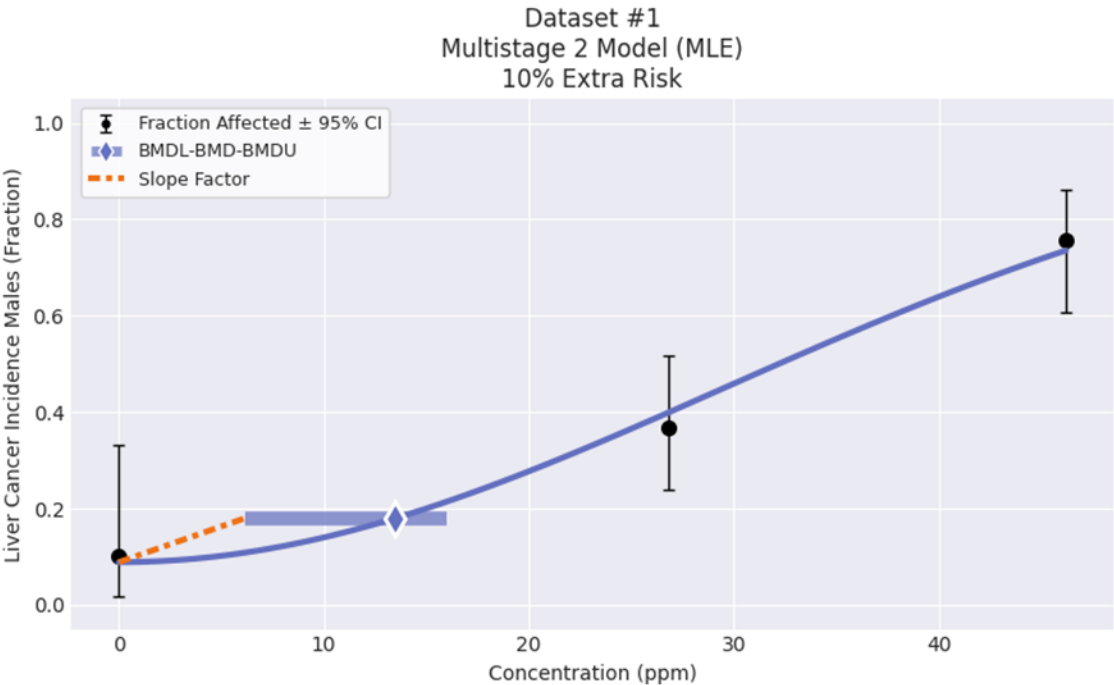
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.60014	0.0800071	0.329561
26.8	49	18	23.7748	0.485201	-1.65068
46.2	49	37	32.4305	0.661847	1.37986

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-65.9969	3	-	-	-
Fitted model	-68.4348	2	4.87587	1	0.0272348
Reduced model	-81.7236	1	31.4533	2	1.47912e-07

B.5.3.3 Multistage 2



Figure_Apx B-12. BMD Multistage Model 2 for Liver Cancer in Male Mice with Inhalation PBPK HEC Input in ppm

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	2

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000
b2	0.1	0	10000

Modeling Summary:

BMD	13.4825
BMDL	6.14515
BMDU	15.9714
Slope Factor	0.016273
AIC	136.329
Log-Likelihood	-66.1646
P-Value	0.563885
Overall d.f.	1
Chi ²	0.333022

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0885937	no	0.0441554
b1	8.96365e-19	yes	Not Reported
b2	0.000579612	no	0.220619

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.77187	0.0885937	0.179515
26.8	49	18	19.5483	0.398944	-0.45168
46.2	49	37	36.0395	0.7355	0.311098

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-65.9969	3	-	-	-
Fitted model	-66.1646	2	0.335433	1	0.562477
Reduced model	-81.7236	1	31.4533	2	1.47912e-07

U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmbs 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed December 12, 2025.

B.6 B.51,1,2-Trichloroethane Inhalation Liver Cancer IUR in Female Mice HEC Input in $\mu\text{g}/\text{m}^3$

B.6.1 HEC Doses

Report Generated: 2025-Nov-11 19:11 UTC

Analysis URL: [View](#)

BMDS Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

B.6.2 Modeling Summary

B.6.2.1 Datasets

Name: Dataset #1

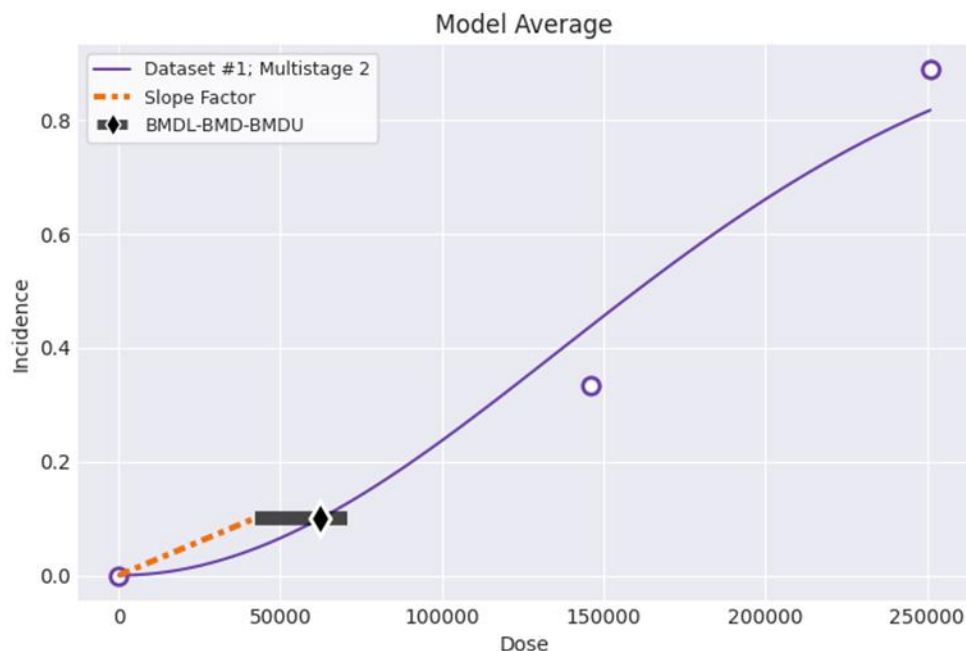
Dose	0	146000	251000
Affected / Total (%)	0.0/20.0 (0.0%)	16.0/48.0 (33.3%)	40.0/45.0 (88.9%)

B.6.2.2 Settings

Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Degree	2

B.6.2.3 Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Dataset #1: Multistage 2	42039	62400	70581	<0.001	0.301	96.411	-0.001	-0.001



Figure_Apx B-13. BMD Average Model for Liver Cancer in Female Mice with Inhalation PBPK HEC Input in $\mu\text{g}/\text{m}^3$

Multitumor MS Combo Model

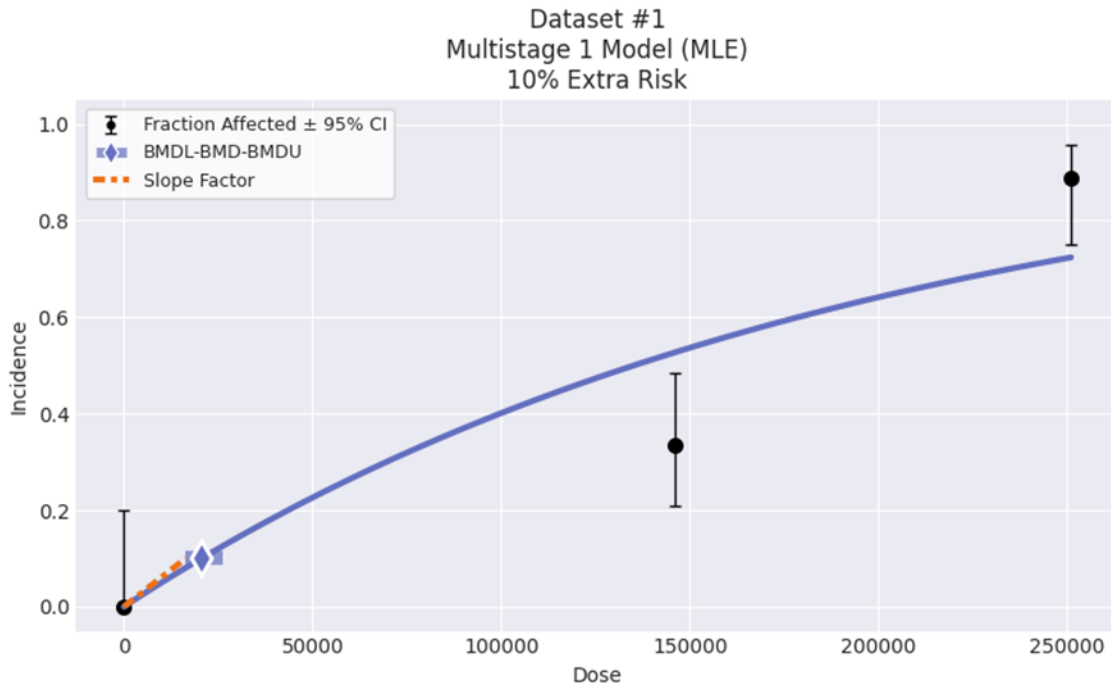
Version: pybmds 25.1 (bmdscore 25.1)

BMD	62400.3
BMDL	42038.8
BMDU	70579.7
Slope Factor	2.37875e-06
Combined Log-likelihood	-48.2054
Combined Log-likelihood Constant	-42.4599

B.6.3 Individual Model Results

B.6.3.1 Dataset #1

B.6.3.2 Multistage 1



Figure_Apx B-14. BMD Multistage 2 Model for Liver Cancer in Female Mice with Inhalation PBPK HEC Input in $\mu\text{g}/\text{m}^3$

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000

Modeling Summary:

BMD	20550.1
BMDL	16401.6
BMDU	26114.5
Slope Factor	6.09697e-06
AIC	109.128
Log-Likelihood	-53.5641
P-Value	0.00126278
Overall d.f.	2
Chi ²	13.3489

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
b1	5.12702e-06	no	0.18166

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

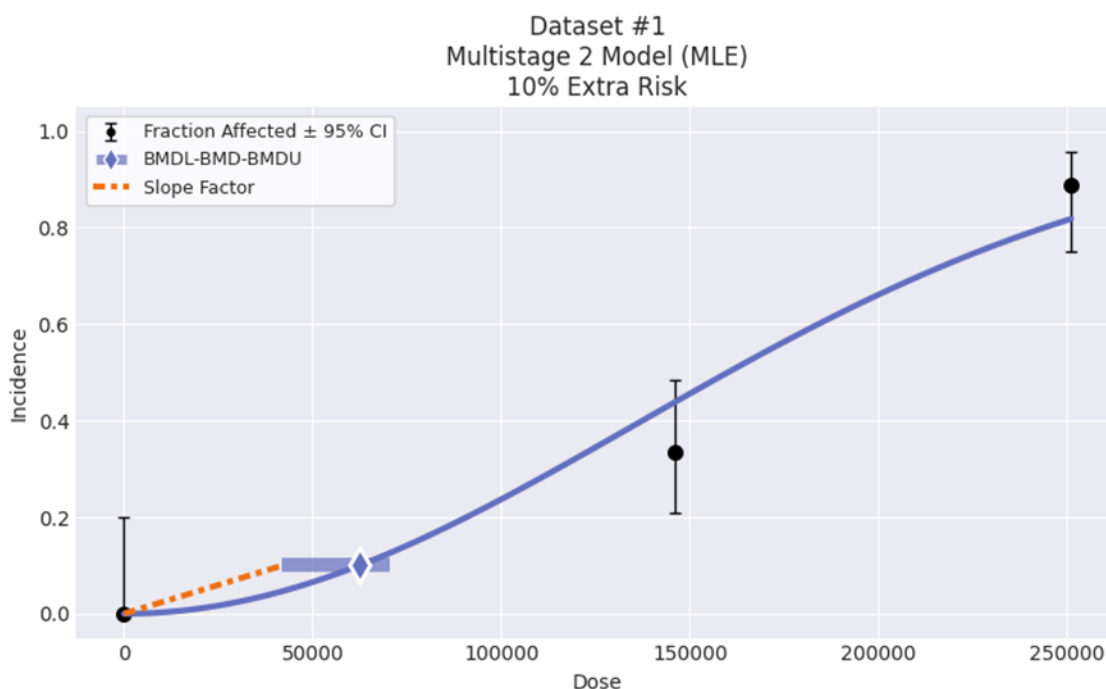
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	0	3.046e-07	1.523e-08	-0.000551905
146000	48	16	25.2934	0.526945	-2.68667
251000	45	40	32.5741	0.723869	2.47602

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-46.2501	3	-	-	-
Fitted model	-53.5641	1	14.628	2	0.000666139
Reduced model	-78.3212	1	64.1422	2	1.17684e-14

B.6.3.3 Multistage 2



Figure_Apx B-15. BMD Multistage 2 Model for Liver Cancer in Female Mice with Inhalation PBPK HEC Input in $\mu\text{g}/\text{m}^3$

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	2

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000
b2	0.1	0	10000

Modeling Summary:

BMD	62400.3
BMDL	42039
BMDU	70581.7
Slope Factor	2.37874e-06
AIC	96.4109
Log-Likelihood	-48.2054
P-Value	0.300527
Overall d.f.	3
Chi ²	3.66056

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
b1	3.95041e-22	yes	Not Reported
b2	2.70585e-11	yes	Not Reported

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	0	3.046e-07	1.523e-08	-0.000551905
146000	48	16	21.0382	0.438296	-1.4656
251000	45	40	36.8179	0.818176	1.22986

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-46.2501	3	-	-	-
Fitted model	-48.2054	0	3.91062	3	0.271279
Reduced model	-78.3212	1	64.1422	2	1.17684e-14

U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmds 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov> (accessed November 11, 2025).

B.7 1,1,2-Trichloroethane Liver Cancer IUR in Female Mice PBPK HEC in ppm

B.7.1 PBPK Model HEC in ppm

Report Generated: 2025-Dec-12 17:12 UTC
Analysis URL: [View](#)
BMDs Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

B.7.1.1 Modeling Summary

B.7.1.2 Datasets

Name: Dataset #1

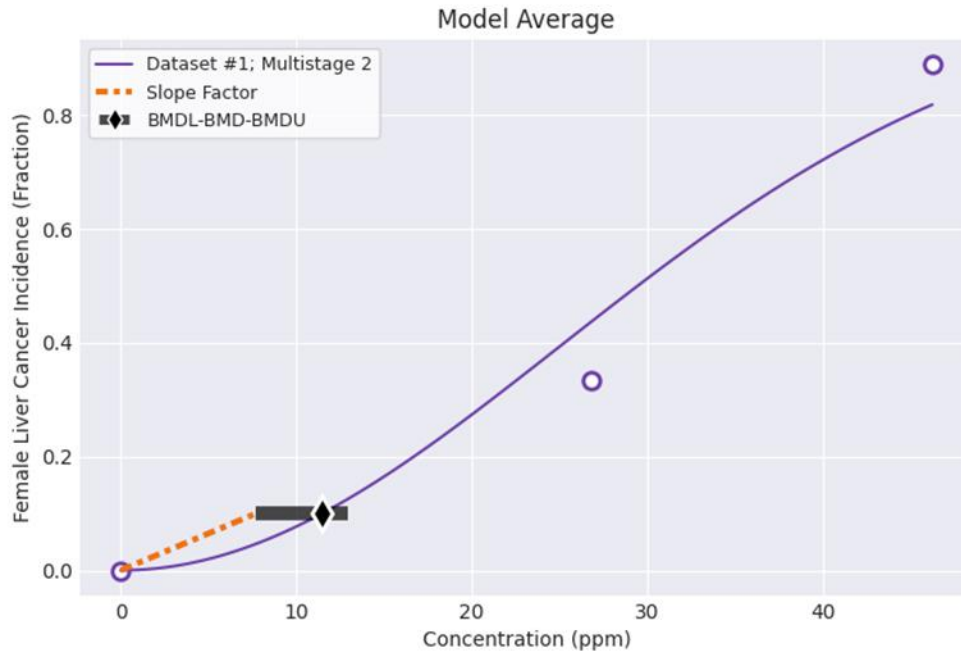
Dose (ppm)	0	26.8	46.2
Affected / Total (%) (Fraction)	0.0/20.0 (0.0%)	16.0/48.0 (33.3%)	40.0/45.0 (88.9%)

B.7.1.3 Settings

Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Degree	2

B.7.1.4 Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Dataset #1: Multistage 2	7.72	11.471	12.975	0.013	0.166	98.339	-0.001	-0.001



Figure_Apx B-16. BMD Model Average for Liver Cancer in Female Mice with Inhalation PBPK HEC Input in ppm

Multitumor MS Combo Model

Version: pybmds 25.1 (bmdscore 25.1)

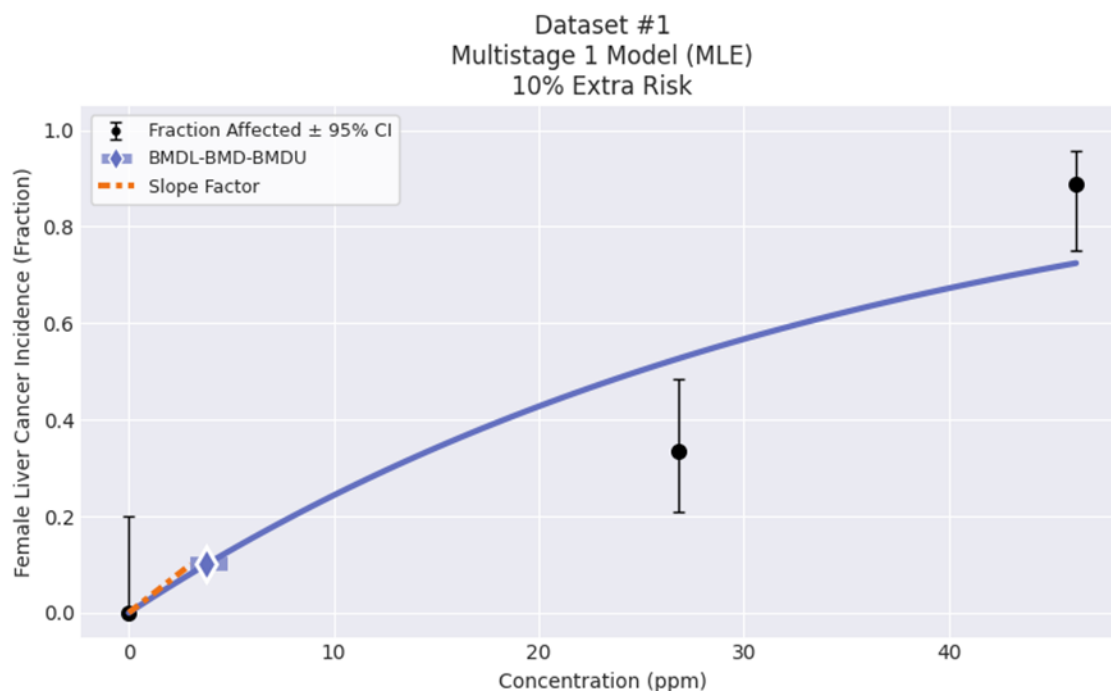
BMD	11.4709
BMDL	7.72005
BMDU	12.975
Slope Factor	0.0129533
Combined Log-likelihood	-48.1694
Combined Log-likelihood Constant	-42.4599

B.7.2 Individual Model Results

B.7.2.1 Dataset #1

B.7.2.2 Multistage 1

Multistage 1 Model



Figure_Apx B-17. BMD Multistage 1 Model for Liver Cancer in Female Mice with Inhalation PBPK HEC Input in ppm

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000

Modeling Summary:

BMD	3.77666
BMDL	3.01415
BMDU	4.79938
Slope Factor	0.0331768
AIC	109.056
Log-Likelihood	-53.5281
P-Value	0.00130457
Overall d.f.	2
Chi²	13.2838

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.57656e-08	yes	Not Reported
b1	0.0278978	no	14.2763

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

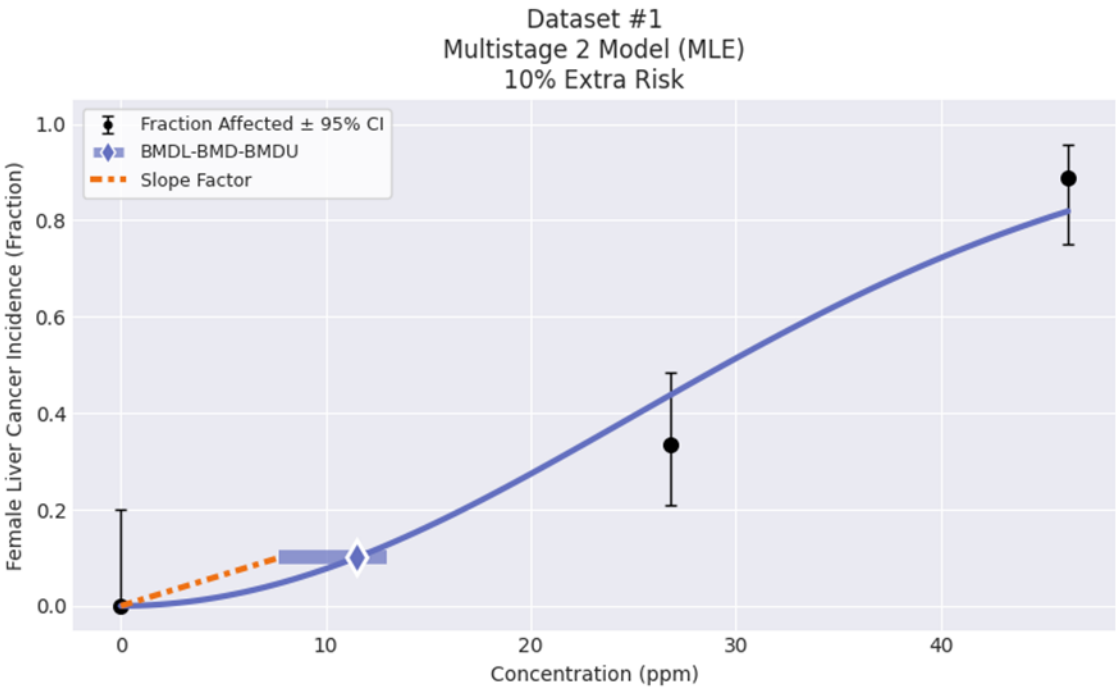
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	0	3.15311e-07	1.57656e-08	-0.000561526
26.8	48	16	25.2733	0.526527	-2.68074
46.2	45	40	32.5989	0.72442	2.46928

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-46.2501	3	-	-	-
Fitted model	-53.5281	1	14.556	2	0.000690568
Reduced model	-78.3212	1	64.1422	2	1.17684e-14

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B.7.2.3 Multistage 2



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Figure_Apx B-18 . BMD Multistage 2 Model for Liver Cancer in Female Mice with Inhalation PBPK HEC Input in ppm

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	2

Parameter Settings:

Parameter	Initial	Min	Max
g	-17	-18	18
b1	0.1	0	10000
b2	0.1	0	10000

Modeling Summary:

BMD	11.4709
BMDL	7.72005
BMDU	12.9754
Slope Factor	0.0129533
AIC	98.3388
Log-Likelihood	-48.1694
P-Value	0.165746
Overall d.f.	2
Chi ²	3.59459

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
b1	7.29618e-19	yes	Not Reported
b2	0.000800726	no	0.249025

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	0	3.046e-07	1.523e-08	-0.000551905
26.8	48	16	20.9932	0.437359	-1.45287
46.2	45	40	36.8537	0.818972	1.2181

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-46.2501	3	-	-	-
Fitted model	-48.1694	1	3.83853	2	0.146715
Reduced model	-78.3212	1	64.1422	2	1.17684e-14

U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmbs 25.1; bmdscore 25.1) [Software]. Available from [Benchmark Dose Tools \(BMDS\) Online](#) (accessed December 12, 2025).

B.8 1,1,2-Trichloroethane Non-Cancer Subchronic Inhalation Study BMD Modeling Results

In a 90-day inhalation exposure study in rats exposed to 1,1,2-trichloroethane, treatment-related lesions were observed in the olfactory epithelium of the nasal turbinates (WIL Research, 2002) with 10 rats per sex. The specific histopathological changes and their incidences are presented below. Vacuolization and cysts in the olfactory epithelium were observed at all exposure levels in both males and females that were test article related at concentrations of 15 ppm and higher. The incidence of nasal olfactory epithelium atrophy was significantly increased at greater than or equal to 40 ppm and was not observed in any animals at 15 ppm. Metaplasia was observed at increased incidence at the highest concentration (100 ppm) in both males and females; the increase was statistically significant only in females (WIL Research, 2002). The fitting routine for POD derivation was the Multistage 1 Model in bold font in the table below. It was selected because it had the highest p-value for data fitting, the smallest residuals near the BMC value, good visual fit near the BMC value, a BMC to BMCL ratio of only 1.4-fold and a small confidence interval, all of which provides confidence that the model well represents the empirical data.

Based on the values shown in the table below, the study BMC₁₀ is 31.2 mg/m³ for vacuolation/microcysts, with values for the study BMCL₁₀, continuous BMCL₁₀, and continuous BMCL₁₀ HEC as 22.11, 3.95, and 0.62 mg/m³, respectively. The dosimetric adjustments were made to convert the study BMDL₁₀ value for rodents to a human equivalent concentration (HEC) given that 1,1,2-trichloroethane induced portal-of-entry nasal lesions (U.S. EPA, 1994). A Regional Gas Deposition Ratio (RGDR) of 0.157 was calculated as follows (see Equation 4-18 and default variables from U.S. EPA, 1994b):

$$RGDR_{ET} = \frac{(V_E/SA_{ET})_{rat}}{(V_E/SA_{ET})_{human}}$$

The calculates regional gas deposition ratio, which equal to total dividend minute volume rats divided by the surface area of the extrathoracic region in rats ratioed to the minute volume in humans divided by the human extrathoracic surface area, where: VE = Minute volume (L/min) = 0.162 L/min for F344 rats (based on the study body weight of 221 g in the subchronic-duration study) and 13.8 L/min for humans, SAET = Surface area of the extrathoracic region (cm²) = 15 cm² for rats and 200 cm² for humans

The BMCL_{HEC} of 0.62 mg/m³ was subsequently derived as

$$BMCL_{10HEC} = RGDR_{ET} \times BMDL_{10} = 0.157 \times 3.95 = 0.62 \text{ mg/m}^3$$

Table_Apx B-6. Intermediate and Chronic Inhalation PODs

Duration	Study BMC ₁₀ (mg/m ³)	Study BMCL ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)	BMCL ₁₀ HEC (mg/m ³)	UF
Intermediate	31.15	22.11	3.95	0.62	30
Chronic	31.15	22.11	3.95	0.62	300

B.9 1,1,2-Trichloroethane Subchronic Inhalation Study Male + Female Olfactory Vacuolization/Cysts

B.9.1 Study Doses

Report Generated: 2025-Nov-07 19:11 UTC

5175 Analysis URL: [View](#)
5176 BMDS Online Version: 25.1 (pybmds 25.1; bmdscore 25.1)

5177 **B.9.2 Session for Dataset #1**
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5179 **B.9.2.1 Dataset**
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Name: Dataset #1

Dose (ppm; mg/m3)	N	Total Incidence
0; 0	20	2
15; 81.75	20	6
40; 218	20	10
100; 545	20	18

5182 **B.9.2.2 Settings**

Setting	Value
BMRR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Multistage Degree	1

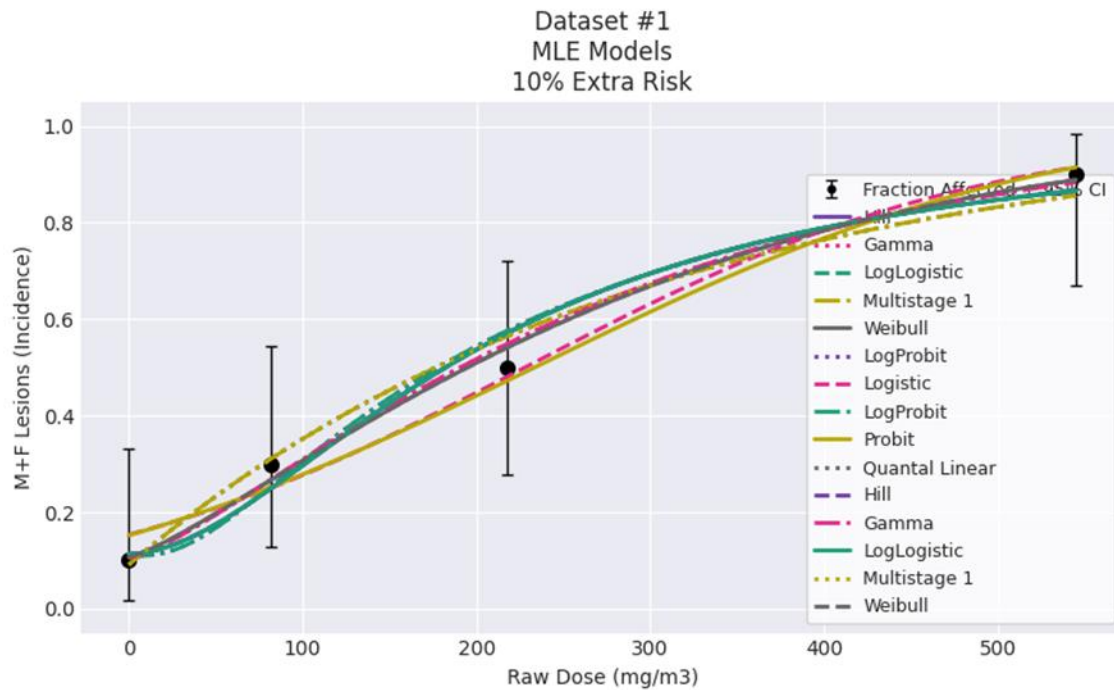
5183 **B.9.2.3 Maximum Likelihood Approach**
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Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Hill	17.176	62.42	170.147	0.336	85.096	-0.188	0.524	Viable lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
Gamma	22.599	50.042	150.55	0.546	84.53	-0.078	0.33	Viable lowest dose/BMDL ratio > 3.0
LogLogistic	17.176	62.42	170.147	0.336	85.096	-0.188	0.524	Viable lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
Multistage 1	22.111	31.151	47.158	0.709	82.883	0.139	0.139	Viable lowest dose/BMDL ratio > 3.0
Weibull	22.71	49.322	141.388	0.591	84.453	-0.095	0.338	Viable lowest dose/BMDL ratio > 3.0
LogProbit	39.271	62.248	171.634	0.339	85.08	-0.139	0.481	Viable
Logistic	53.675	72.729	98.492	0.675	82.99	-0.662	0.511	Viable
LogProbit	19.041	62.248	171.634	0.339	85.08	-0.139	0.481	Viable lowest dose/BMDL

								ratio > 3.0 BMD/BMDL ratio > 3.0
Probit	53.951	70.711	93.23	0.677	82.983	-0.648	0.493	Viable
Quantal Linear	22.111	31.151	47.159	0.709	82.883	0.139	0.139	Viable lowest dose/BMDL ratio > 3.0
Hill	17.043	62.42	170.147	0.336	85.096	-0.188	0.524	Viable lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
Gamma	7.524	50.042	150.552	0.546	84.53	-0.078	0.33	Questionable lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 BMD/BMDL ratio > 3.0
LogLogistic	17.043	62.42	170.147	0.336	85.096	-0.188	0.524	Viable lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
Multistage 1	22.111	31.151	47.159	0.709	82.883	0.139	0.139	Viable lowest dose/BMDL ratio > 3.0
Weibull ^a	10.918	49.322	141.388	0.591	84.453	-0.095	0.338	Recommended - Lowest BMDL lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0

^a BMDS recommended best fitting model

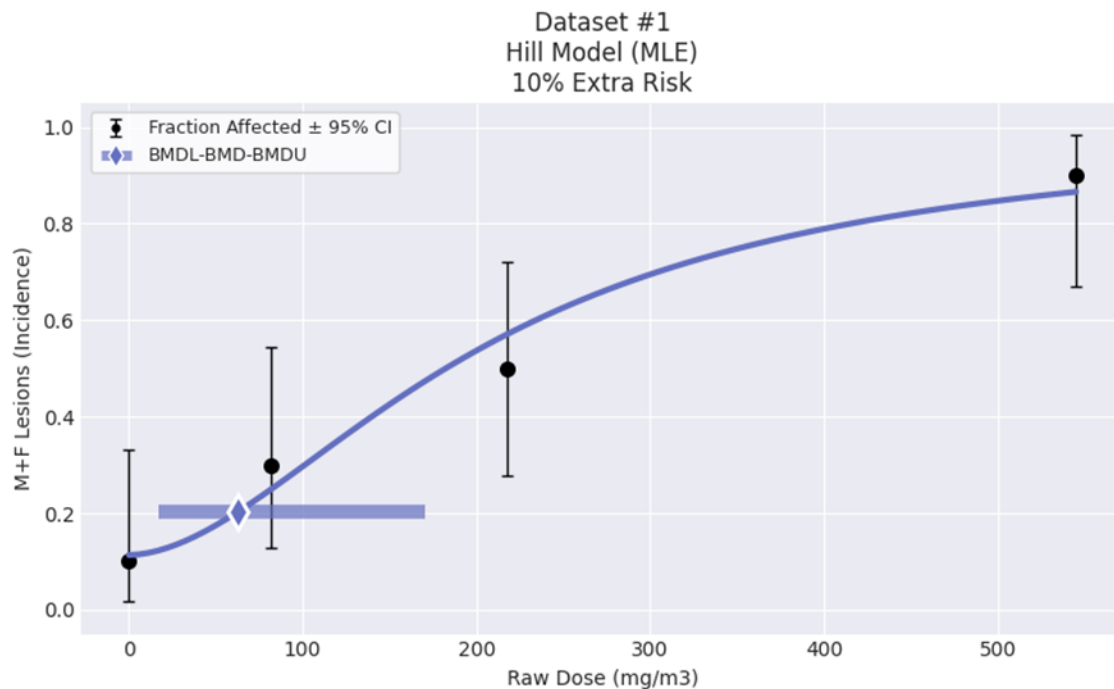
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Figure_Apx B-19. BMD Models Summary for Subchronic Inhalation Study in Rats

B.9.3 Individual Model Results

B.9.3.1 Hill Model



Figure_Apx B-20. BMD Hill Model for Subchronic Inhalation Study in Rats

Hill Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
v	0	-18	18
a	0	-18	18
b	1	1	18

Modeling Summary:

BMD	62.4201
BMDL	17.1757
BMDU	170.147
AIC	85.0964
Log-Likelihood	-39.5482
P-Value	0.335664
Overall d.f.	1
Chi²	0.926921

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.113352	no	0.0480738
v	1	yes	Not Reported
a	-9.68023	no	3.8458
b	1.81016	no	0.673552

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

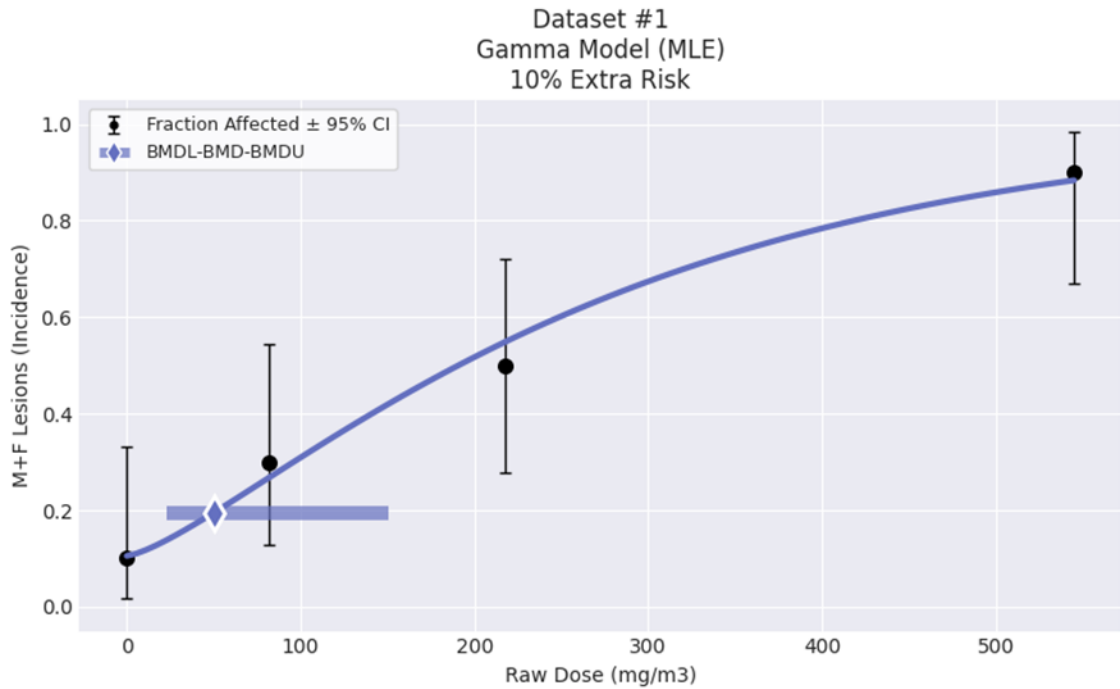
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.26703	0.113352	-0.188348
81.75	20	6	4.98565	0.249283	0.524309
218	20	10	11.4286	0.571428	-0.645492
545	20	18	17.3188	0.865938	0.447087

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.5482	3	0.929326	1	0.335038
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.2 Gamma Model



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Figure_Apx B-21. BMD Gamma Model for Subchronic Inhalation Study in Rats

Gamma Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	1.1	1	18
b	0	0	100

Modeling Summary:

BMD	50.0417
BMDL	22.5986
BMDU	150.55
AIC	84.5296
Log-Likelihood	-39.2648
P-Value	0.546439
Overall d.f.	1
Chi²	0.363735

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.105389	no	0.0467164
a	1.38371	no	0.760519
b	0.00485653	no	0.00297091

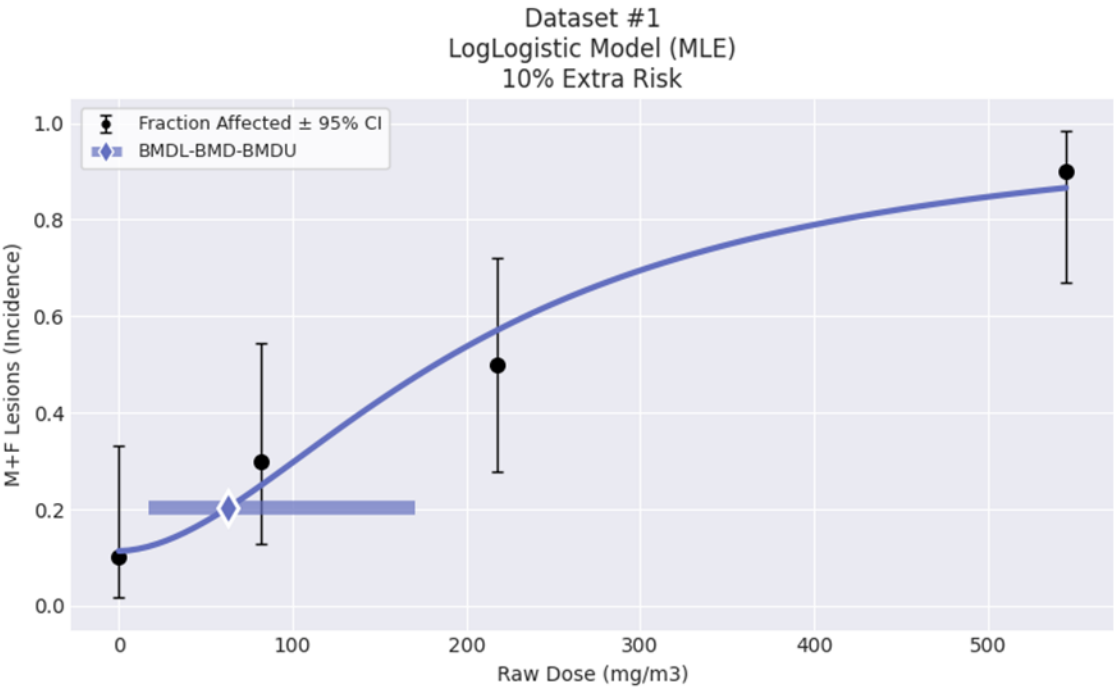
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.10777	0.105389	-0.0784828
81.75	20	6	5.34628	0.267314	0.3303
218	20	10	10.9855	0.549276	-0.442893
545	20	18	17.6719	0.883596	0.228744

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.2648	3	0.362548	1	0.547095
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

B.9.3.3 Log-Logistic Model



Figure_Apx B-22. BMD Log Logistic Model for Subchronic Inhalation Study in Rats

LogLogistic Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	0	-18	18
b	1	1	18

Modeling Summary:

BMD	62.4201
BMDL	17.1757
BMDU	170.147
AIC	85.0964
Log-Likelihood	-39.5482
P-Value	0.335664
Overall d.f.	1
Chi ²	0.926921

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.113352	no	0.0480767
a	-9.68023	no	3.8462
b	1.81016	no	0.673622

Goodness of Fit:

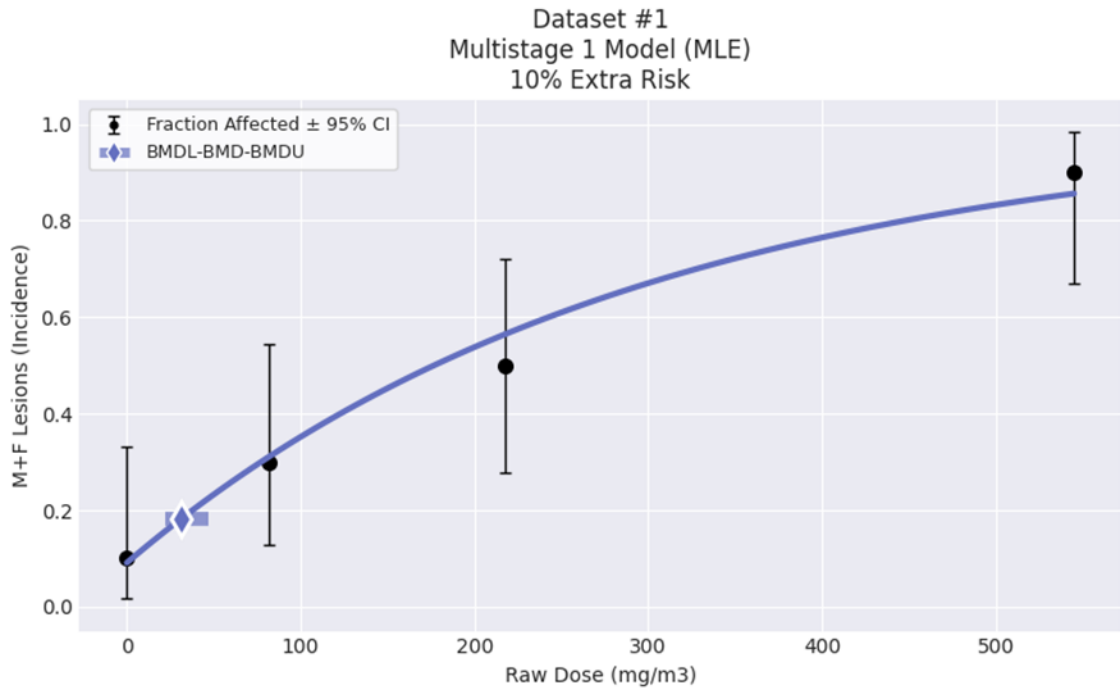
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.26703	0.113352	-0.188348
81.75	20	6	4.98565	0.249283	0.524309
218	20	10	11.4286	0.571428	-0.645492
545	20	18	17.3188	0.865938	0.447087

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.5482	3	0.929326	1	0.335038
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.4 Multistage 1 Model



Figure_Apx B-23. BMD Multistage 1 Model for Subchronic Inhalation Study in Rats

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
b1	0	0	10000

Modeling Summary:

BMD	31.1512
BMDL	22.1113
BMDU	47.1579
AIC	82.8833
Log-Likelihood	-39.4417
P-Value	0.708889
Overall d.f.	2
Chi²	0.688113

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0910537	no	0.0437849
b1	0.00338223	no	0.413841

Goodness of Fit:

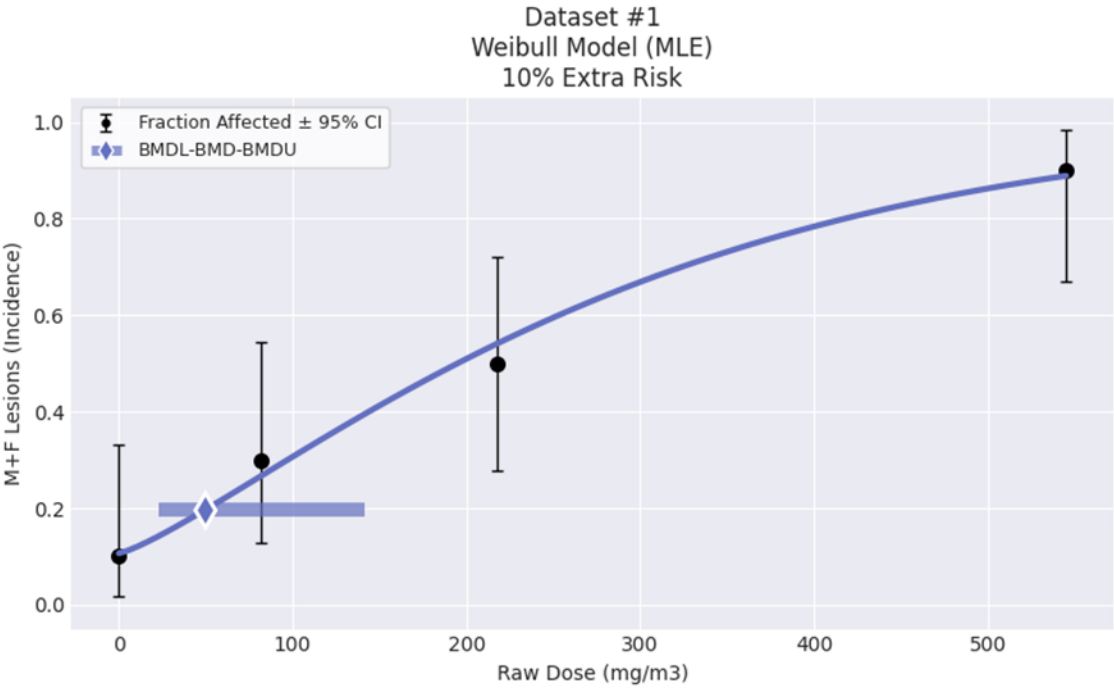
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.82107	0.0910537	0.139073
81.75	20	6	6.21246	0.310623	-0.102662
218	20	10	11.3034	0.565168	-0.587896
545	20	18	17.1224	0.856121	0.559116

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.4417	2	0.716248	2	0.698986
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.5 Weibull Model



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Figure_Apx B-24. BMD Weibull Model for Subchronic Inhalation Study in Rats

Weibull Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	1	1	18
b	1e-06	1e-06	100

Modeling Summary:

BMD	49.3216
BMDL	22.7104
BMDU	141.388
AIC	84.4534
Log-Likelihood	-39.2267
P-Value	0.591101
Overall d.f.	1
Chi ²	0.288628

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.106537	no	0.0463309
a	1.24211	no	0.403595
b	0.000831253	no	0.612475

Goodness of Fit:

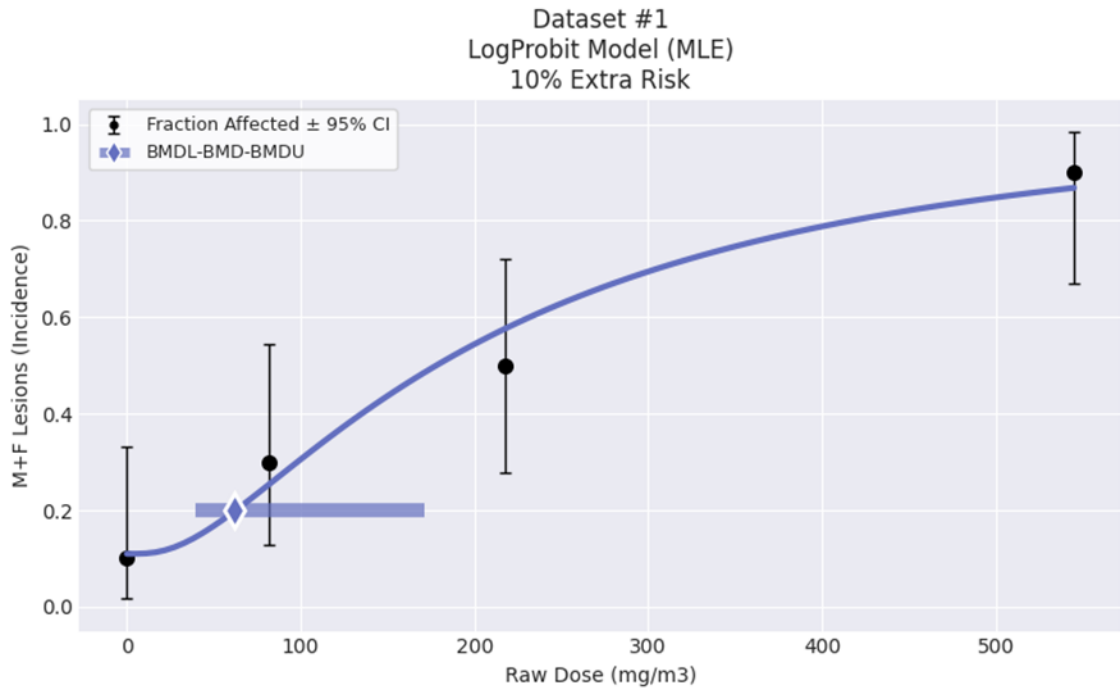
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.13074	0.106537	-0.0947573
81.75	20	6	5.33122	0.266561	0.33821
218	20	10	10.832	0.5416	-0.373377
545	20	18	17.7738	0.888692	0.160789

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.2267	3	0.28629	1	0.592608
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.6 LogProbit Model



Figure_Apx B-25. BMD LogProbit Model for Subchronic Inhalation Study in Rats

LogProbit Model

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Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_restricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	0	-18	18
b	1	1	18

Modeling Summary:

BMD	62.2479
BMDL	39.2706
BMDU	171.634
AIC	85.0799
Log-Likelihood	-39.5399
P-Value	0.339487
Overall d.f.	1
Chi ²	0.912366

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.109711	no	0.0476567
a	-5.7088	no	1.99233
b	1.07168	no	0.350157

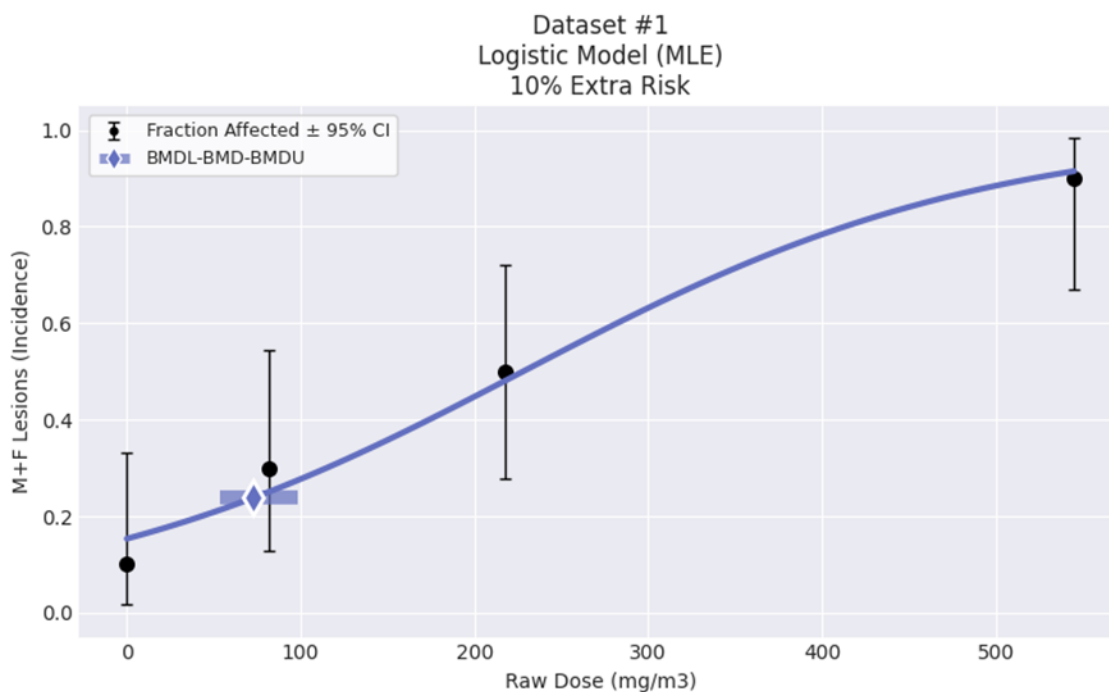
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.19422	0.109711	-0.138963
81.75	20	6	5.0648	0.25324	0.480878
218	20	10	11.5349	0.576743	-0.69464
545	20	18	17.3589	0.867946	0.423422

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.5399	3	0.912778	1	0.339379
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

B.9.3.7 Logistic Model



Figure_Apx B-26. BMD Logistic Model for Subchronic Inhalation Study in Rats

Logistic Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
a	0	-18	18
b	0	0	100

Modeling Summary:

BMD	72.7288
BMDL	53.6747
BMDU	98.4919
AIC	82.9902
Log-Likelihood	-39.4951
P-Value	0.675384
Overall d.f.	2
Chi ²	0.784947

Model Parameters:

Variable	Estimate	On Bound	Std Error
a	-1.70864	no	0.409809
b	0.00749356	no	0.001729

Goodness of Fit:

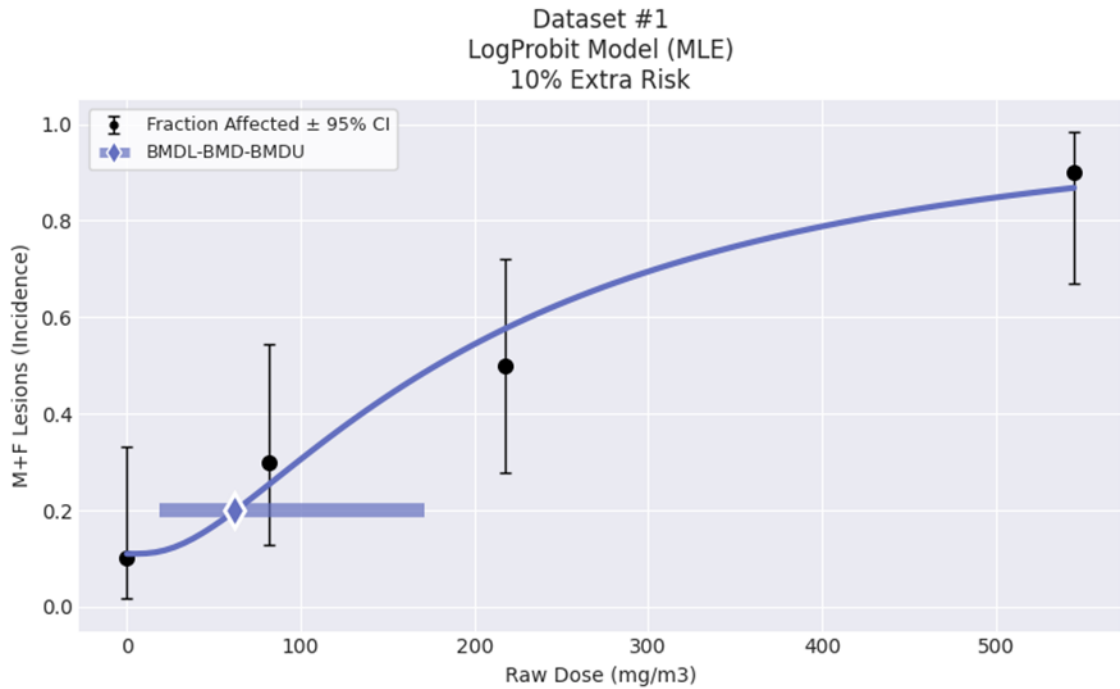
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	3.06681	0.153341	-0.662049
81.75	20	6	5.00966	0.250483	0.511082
218	20	10	9.62497	0.481248	0.167838
545	20	18	18.2986	0.914928	-0.239297

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.4951	2	0.823055	2	0.662637
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.8 LogProbit Model



Figure_Apx B-27. BMD LogProbit Model for Subchronic Inhalation Study in Rats

LogProbit Model

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Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	0	-18	18
b	0.0001	0.0001	18

Modeling Summary:

BMD	62.2479
BMDL	19.0409
BMDU	171.634
AIC	85.0799
Log-Likelihood	-39.5399
P-Value	0.339487
Overall d.f.	1
Chi²	0.912366

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.109711	no	0.0476518
a	-5.7088	no	1.99216
b	1.07168	no	0.350125

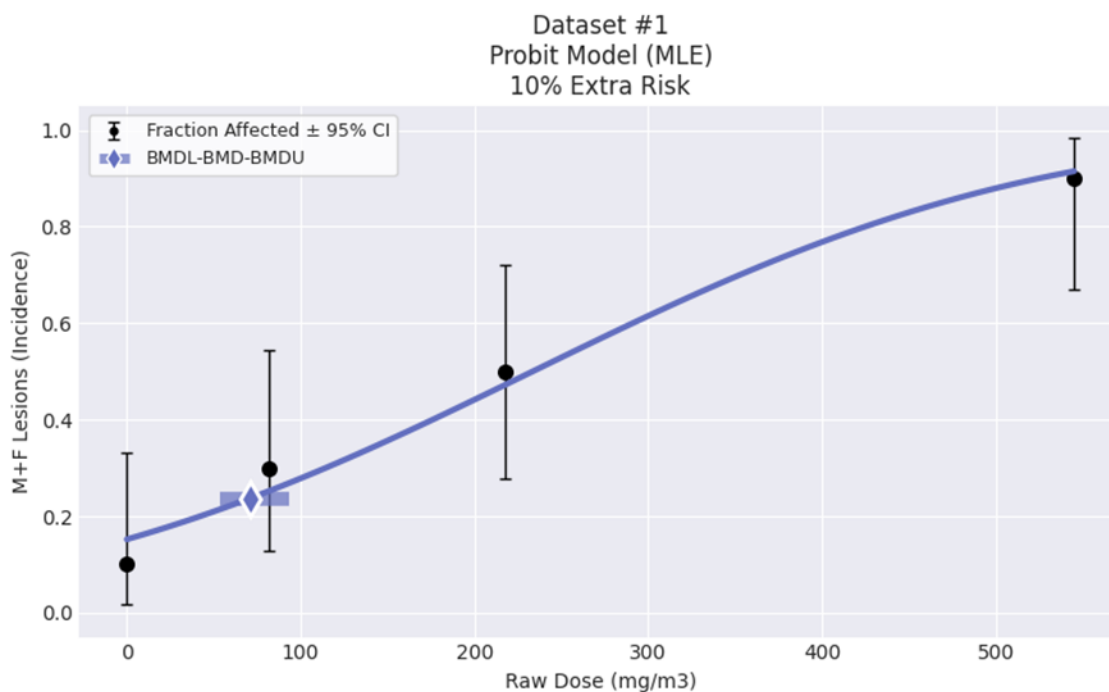
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.19423	0.109711	-0.138963
81.75	20	6	5.06479	0.25324	0.480879
218	20	10	11.5349	0.576743	-0.69464
545	20	18	17.3589	0.867946	0.423422

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.5399	3	0.912778	1	0.339379
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

B.9.3.9 Probit Model



Figure_Apx B-28. BMD Probit Model for Subchronic Inhalation Study in Rats

Probit Model

Version: pybmds 25.1 (bmddscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
a	0	-18	18
b	0	0	18

Modeling Summary:

BMD	70.7111
BMDL	53.9514
BMDU	93.2305
AIC	82.9825
Log-Likelihood	-39.4913
P-Value	0.67734
Overall d.f.	2
Chi ²	0.779163

Model Parameters:

Variable	Estimate	On Bound	Std Error
a	-1.02764	no	0.232994
b	0.00440073	no	0.000897919

Goodness of Fit:

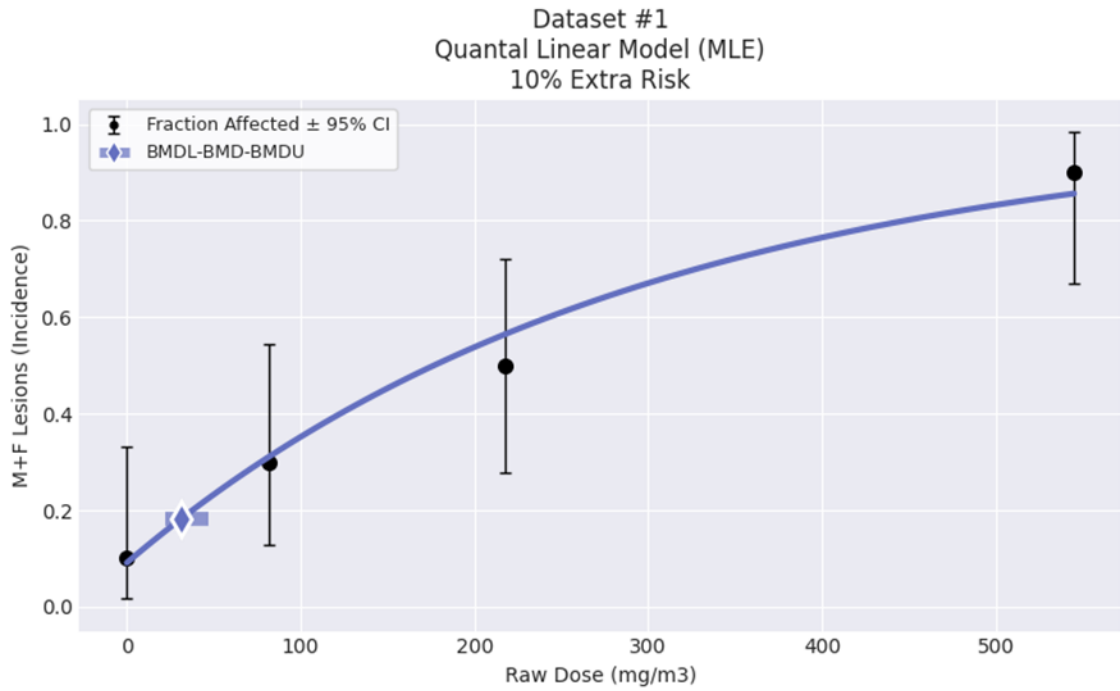
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	3.04119	0.152059	-0.648371
81.75	20	6	5.04209	0.252105	0.493286
218	20	10	9.45561	0.47278	0.243821
545	20	18	18.2955	0.914774	-0.236638

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.4913	2	0.815424	2	0.66517
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.10 Quantal Linear Model



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Figure_Apx B-29. BMD Quantal Linear Model for Subchronic Inhalation Study in Rats-

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Quantal Linear Model

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Version: pybmds 25.1 (bmdscore 25.1)

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Input Summary:

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BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

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Parameter Settings:

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Parameter	Initial	Min	Max
g	0	-18	18
b	0	0	100

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Modeling Summary:

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BMD	31.1512
BMDL	22.1113
BMDU	47.1588
AIC	82.8833
Log-Likelihood	-39.4417
P-Value	0.708889
Overall d.f.	2
Chi ²	0.688113

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0910537	no	0.0437863
b	0.00338223	no	0.00076018

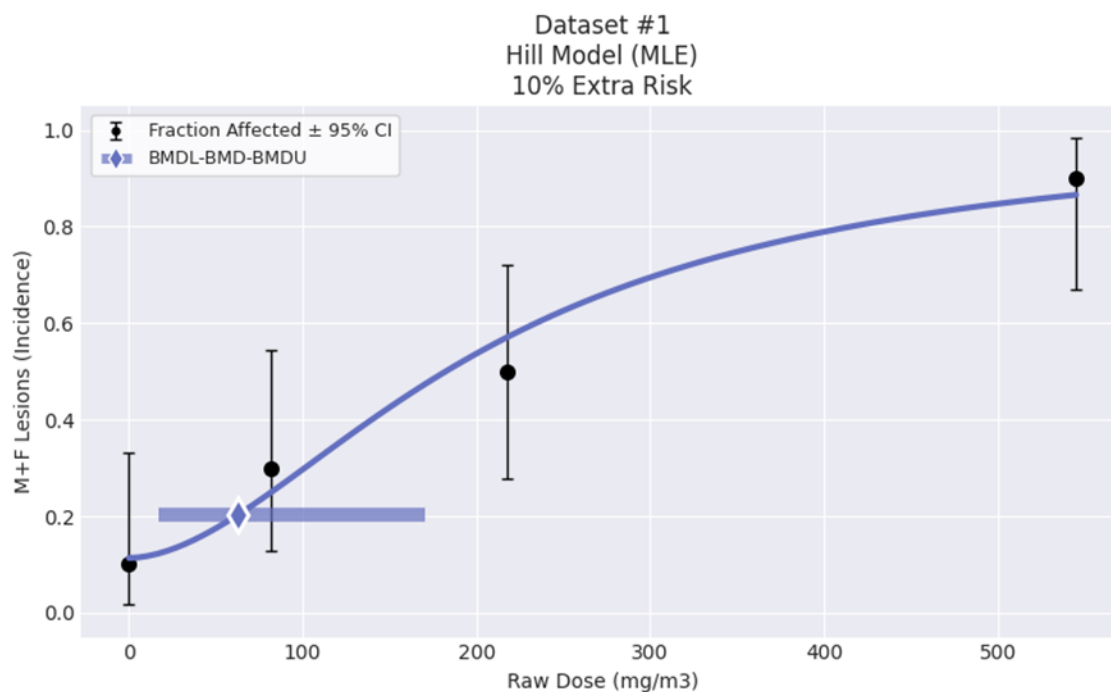
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.82107	0.0910537	0.139073
81.75	20	6	6.21246	0.310623	-0.102662
218	20	10	11.3034	0.565168	-0.587896
545	20	18	17.1224	0.856121	0.559116

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.4417	2	0.716248	2	0.698986
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

B.9.3.11 Hill Model



Figure_Apx B-30. BMD Hill Model for Subchronic Inhalation Study in Rats

Hill Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
v	0	-18	18
a	0	-18	18
b	1e-08	1e-08	18

Modeling Summary:

BMD	62.4201
BMDL	17.0431
BMDU	170.147
AIC	85.0964
Log-Likelihood	-39.5482
P-Value	0.335664
Overall d.f.	1
Chi ²	0.926921

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.113352	no	0.0480746
v	1	yes	Not Reported
a	-9.68023	no	3.84615
b	1.81016	no	0.673617

Standard errors estimates are not generated for parameters estimated on corresponding bounds, although sampling error is present for all parameters, as a rule. Standard error estimates may not be reliable as a basis for confidence intervals or tests when one or more parameters are on bounds.

Goodness of Fit:

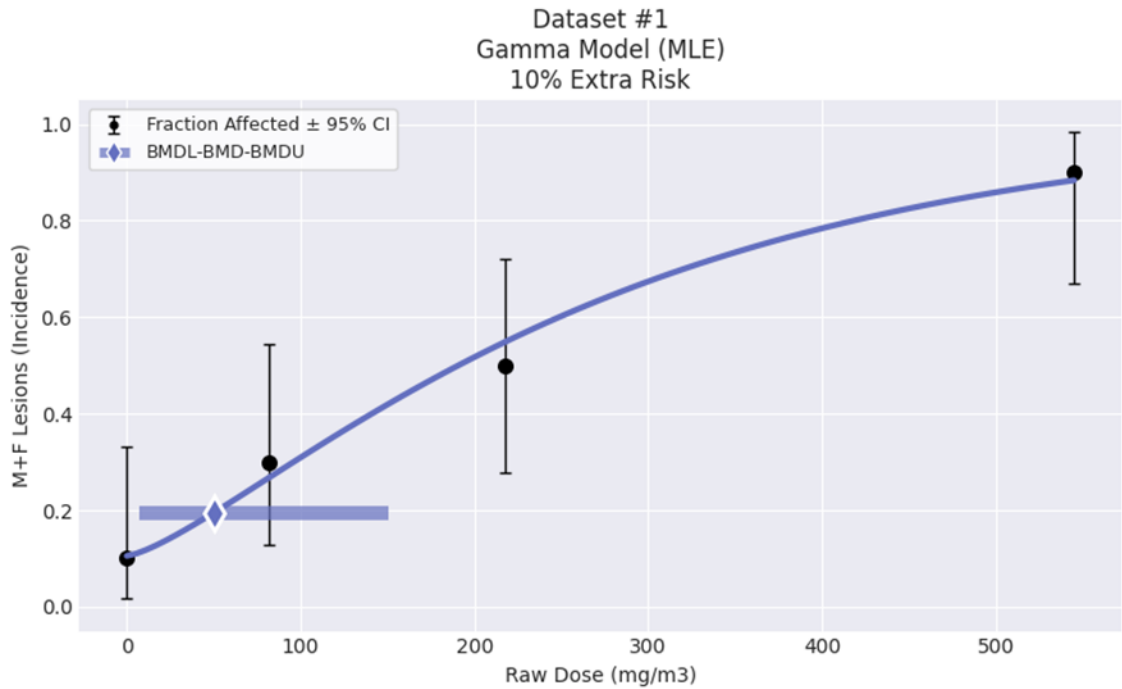
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.26703	0.113352	-0.188348
81.75	20	6	4.98565	0.249283	0.524309
218	20	10	11.4286	0.571428	-0.645492
545	20	18	17.3188	0.865938	0.447087

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.5482	3	0.929326	1	0.335038
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.12 Gamma Model



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Figure_Apx B-31. BMD Gamma Model for Subchronic Inhalation Study in Rats

Gamma Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	0.2	0.2	18
b	0	0	100

Modeling Summary:

BMD	50.0416
BMDL	7.52356
BMDU	150.552
AIC	84.5296
Log-Likelihood	-39.2648
P-Value	0.546439
Overall d.f.	1
Chi²	0.363735

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.105389	no	0.0467196
a	1.38371	no	0.760774
b	0.00485653	no	0.0029719

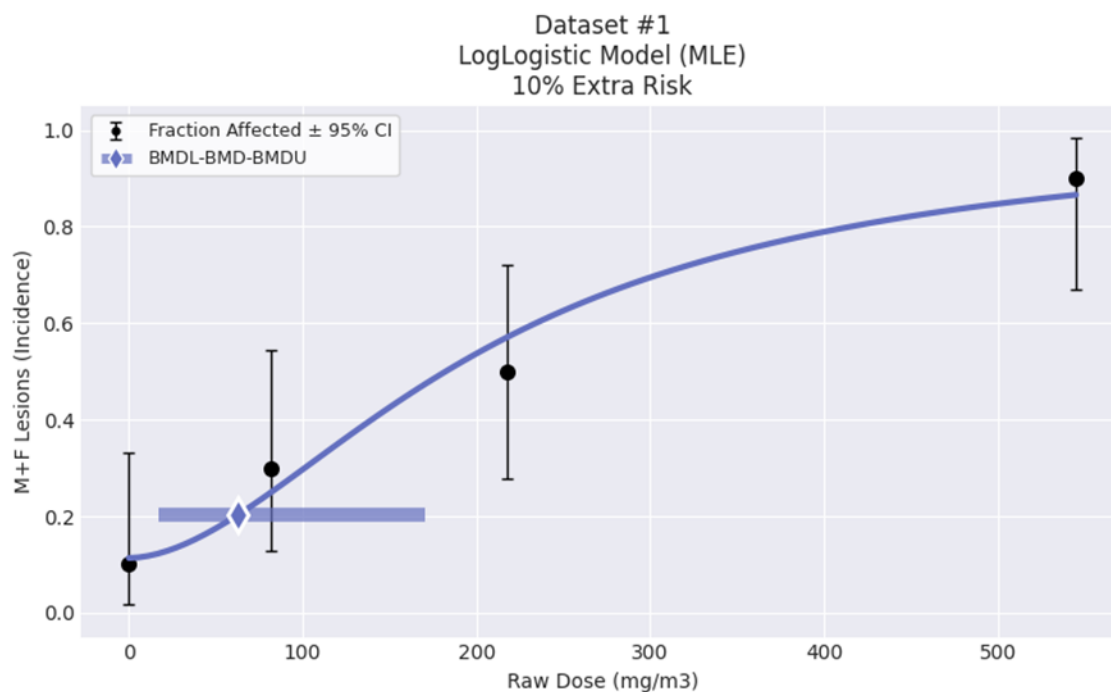
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.10777	0.105389	-0.0784822
81.75	20	6	5.34628	0.267314	0.330299
218	20	10	10.9855	0.549276	-0.442893
545	20	18	17.6719	0.883596	0.228745

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.2648	3	0.362548	1	0.547095
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

B.9.3.13 LogLogistic Model



Figure_Apx B-32. BMD LogLogistic Model for Subchronic Inhalation Study in Rats

LogLogistic Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	0	-18	18
b	0.0001	0.0001	18

Modeling Summary:

BMD	62.4201
BMDL	17.0431
BMDU	170.147
AIC	85.0964
Log-Likelihood	-39.5482
P-Value	0.335664
Overall d.f.	1
Chi ²	0.926921

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.113352	no	0.048074
a	-9.68023	no	3.84617
b	1.81016	no	0.673621

Goodness of Fit:

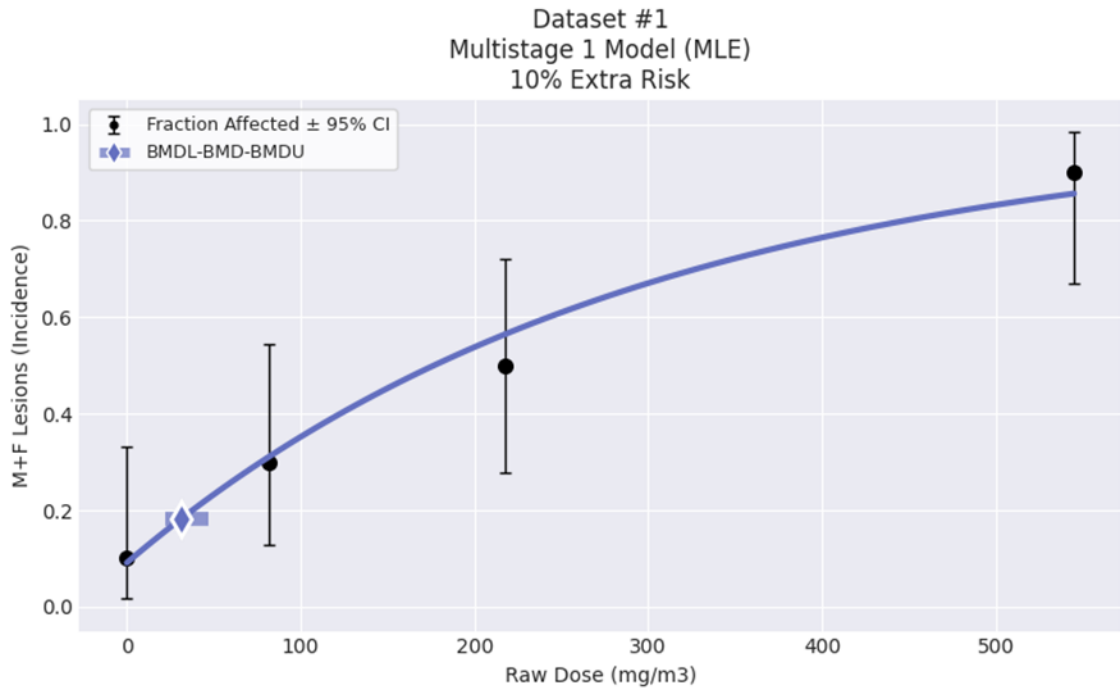
Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.26703	0.113352	-0.188348
81.75	20	6	4.98565	0.249283	0.524309
218	20	10	11.4286	0.571428	-0.645492
545	20	18	17.3188	0.865938	0.447087

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.5482	3	0.929326	1	0.335038
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

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B.9.3.14 Multistage 1 Model



Figure_Apx B-33. BMD Multistage 1 Model for Subchronic Inhalation Study in Rats

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted
Degree	1

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
b1	0	-18	10000

Modeling Summary:

BMD	31.1512
BMDL	22.1113
BMDU	47.1588
AIC	82.8833
Log-Likelihood	-39.4417
P-Value	0.708889
Overall d.f.	2
Chi²	0.688113

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Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0910537	no	0.0437865
b1	0.00338223	no	0.413848

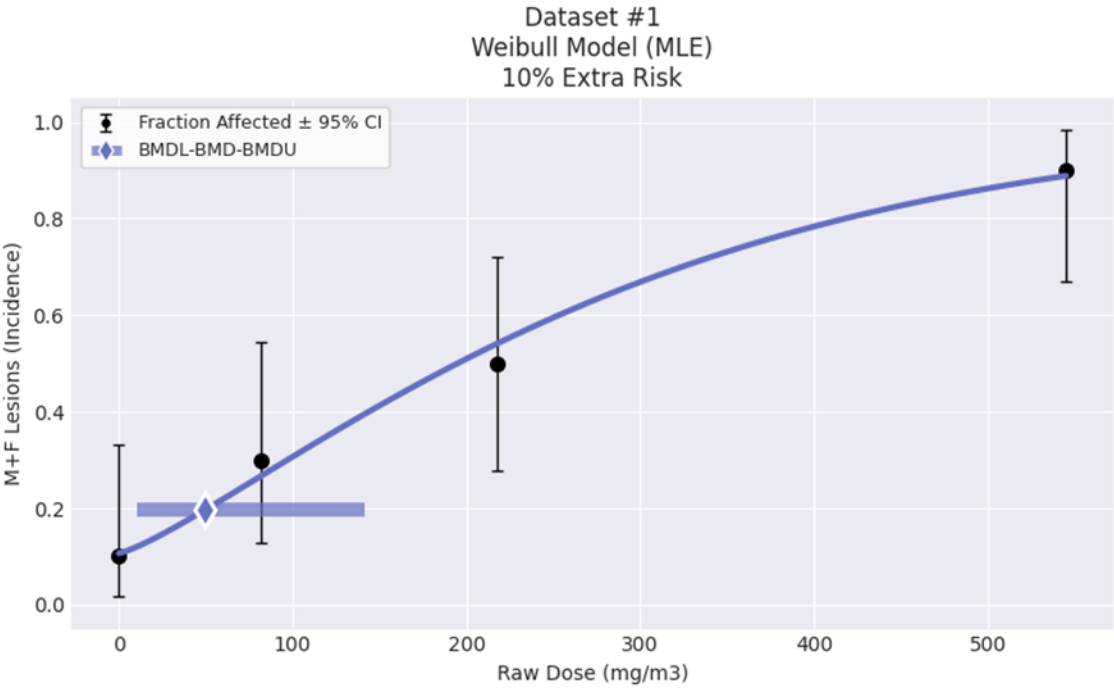
Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	1.82107	0.0910537	0.139072
81.75	20	6	6.21246	0.310623	-0.102662
218	20	10	11.3034	0.565168	-0.587896
545	20	18	17.1224	0.856121	0.559116

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.4417	2	0.716248	2	0.698986
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

B.9.3.15 Weibull Model



Figure_Apx B-34. BMD Weibull Model for Subchronic Inhalation Study in Rats

Weibull Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Modeling approach	frequentist_unrestricted

Parameter Settings:

Parameter	Initial	Min	Max
g	0	-18	18
a	1e-06	1e-06	18
b	1e-06	1e-06	100

Modeling Summary:

BMD	49.3216
BMDL	10.9178
BMDU	141.388
AIC	84.4534
Log-Likelihood	-39.2267
P-Value	0.591101
Overall d.f.	1
Chi ²	0.288628

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.106537	no	0.0463328
a	1.24211	no	0.403598
b	0.000831252	no	0.612466

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	20	2	2.13074	0.106537	-0.0947575
81.75	20	6	5.33122	0.266561	0.33821
218	20	10	10.832	0.5416	-0.373376
545	20	18	17.7738	0.888692	0.160788

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-39.0835	4	-	-	-
Fitted model	-39.2267	3	0.28629	1	0.592608
Reduced model	-55.0511	1	31.9351	3	5.40087e-07

Appendix C HUMAN HEALTH HAZARD CONFIDENCE AND WEIGHT OF SCIENTIFIC EVIDENCE SUMMARY

The toxicology database for human health contains medium and high-quality literature studies as well as reliable OECD and TSCA 799 guideline studies for hazard characterization, endpoint selection and POD derivation for cancer and non-cancer evaluations. The studies used for dose-response analysis had high or medium systematic review ratings.

Non-Cancer Evaluations

The acute oral and dermal scenarios POD was derived from an OECD 424 acute neurotoxicity guideline study ([WIL Research, 2004](#)) which had a high-quality rating by the OPPT systematic review process. It provides the best available science based on the weight of scientific evidence. The study provided a reliable and health protective POD for the risk evaluation based on neurotoxicity which is a common hazard for solvents (NOAEL = 55 mg/kg; LOAEL = 95 mg/kg ([WIL Research, 2004](#))). Thus, there is robust confidence in the study, endpoint and POD, therefore it is the best available science for evaluating the acute oral scenarios for the general population for 1,1,2-trichloroethane using a route-specific study. This study has moderate-to-robust confidence for the acute dermal scenario due the uncertainty in the oral-to-dermal route extrapolation.

The acute inhalation scenarios POD was derived from an OPPT 799 guideline acute inhalation study, which had a high-quality rating by the OPPT systematic review process. The HAP Task Force study ([WIL Research, 2002](#)) provided a reliable and health-protective POD for the risk evaluation based on histopathology in the nasal olfactory epithelium which is a common hazard for solvents (LOAEC = 316 mg/m³ or 58 ppm). This study was also utilized for the acute inhalation scenario assessment by ATSDR ([2021](#)). Thus, there is robust confidence in the study, endpoint and POD; therefore, it is the best available science based on the weight of scientific evidence using a route specific study for evaluating the acute inhalation scenarios for the general population for 1,1,2-trichloroethane.

The intermediate and chronic oral and dermal scenarios POD was derived from a reliable literature study which had a high-quality rating by the OPPT systematic review process. The Sanders study ([Sanders et al., 1985](#)) provided a reliable and sensitive POD for the risk evaluation based on immunotoxicity, which is a common hazard for solvents (NOAEL = 3.9 mg/kg; LOAEL = 44 mg/kg). The endpoint was the TDAR endpoint based on 40 to 47% decreased hemagglutination titer method, which was supported by the TDAR endpoint based on the 31% decrease in the antibody forming cells method at the 38 mg/kg/day dose. This study was also utilized for the intermediate oral and dermal assessment by ATSDR ([2021](#)) and U.S. EPA PPRTV ([U.S. EPA, 2011a](#)). Thus, because there is robust confidence in the study, endpoint, and POD, it is the best available science based on the weight of scientific evidence for evaluating the intermediate oral scenarios utilizing a route-specific study for the general population for 1,1,2-trichloroethane. There is moderate-to-robust confidence in this study for the intermediate dermal scenario due to the uncertainty in the oral to dermal route extrapolation. There is also moderate-to-robust confidence in this study for the chronic oral scenario due to the uncertainty in extrapolating from a subchronic study to the chronic duration. There is moderate confidence in this study for the chronic dermal scenario due to the uncertainty in applying a subchronic study to the chronic duration.

The intermediate and chronic inhalation scenarios POD was derived from a reliable OPPT 799 guideline subchronic inhalation study with a high systematic review rating. The HAP Task Force study ([WIL Research, 2002](#)) provided a reliable and sensitive POD for the risk evaluation based on lesions in the nasal olfactory epithelium, which is a common hazard for solvents (BMC₁₀ = 31.15 mg/m³, BMCL₁₀ = 22.11 mg/m³) and a hazard also identified at a higher concentration in the acute inhalation study for

1,1,2-trichloroethane (LOAEC = 316 mg/m³). There is robust confidence in the study, endpoint and POD, therefore it is the best available science based on the weight of scientific evidence for evaluating the intermediate inhalation scenarios utilizing a route specific study for the general population exposed to 1,1,2-trichloroethane. There is moderate-to-robust confidence in this study for the chronic scenario due to the uncertainty in the use of a subchronic study for chronic durations.

Cancer Evaluations

The chronic oral, dermal and inhalation scenarios cancer slope factors were derived from a reliable chronic oral gavage cancer study in mice performed by the National Cancer Institute ([NCI, 1978](#)), with a medium OPPT systematic review rating. The oral, dermal, and inhalation cancer slope factors are based on an excellent tumor dose-response in the liver of both male and female mice. This study was also the basis of the cancer evaluations reported by U.S. EPA IRIS ([U.S. EPA, 1987](#)), U.S. EPA PPRTV ([U.S. EPA, 2011a](#)) and OEHHA ([OEHHA, 2006](#)). The inhalation unit risk value was refined by the HEC values calculated by the reliable Sapphire Group PBPK Model via oral to inhalation route extrapolation. Thus, there is moderate confidence in the cancer study, endpoint, and POD, and is the best available science for evaluating cancer risks for the chronic oral exposure scenarios for the general population for 1,1,2-trichloroethane. For the dermal route the study has low-to-moderate confidence due to the uncertainty in the route extrapolation from oral data. For the inhalation route the study has moderate confidence due to the application of the robust PBPK model. The factors considered in this decision are listed below.

The 1,1,2-trichloroethane mouse cancer study ([NCI, 1978](#)) systematic review by OPPT concluded that it has no confounding factors in control groups (male or female). The incidence of pneumonia in the vehicle control groups was 0%, so there are no concerns regarding the animal health. Furthermore, there was an average of only 2.2% pneumonia across all groups (0.8% males, 3.7% females), which is essentially random. Most of the pneumonia incidences were in the high-dose group, which may be exacerbated by the chemical irritation properties of 1,1,2-trichloroethane since it has significant lung elimination even via oral dosing. The 1,1,2-trichloroethane study has much less loss of life in test groups (in particular not due to pneumonia as a confounding factor) in male or female mice as compared to other solvents. Because survival was reduced just in female mice and only at the low dose, NCI experts concluded it was not a significant factor in the study results. Importantly, the survival of male mice was not affected by treatment, which is relevant since the oral cancer slope factor and the inhalation unit risk value are both based on data from the male mice. The number of surviving test animals is high for confidence in the results (45–49 in treated groups of 50 for each sex). The dose-response for liver tumors is excellent and highly significant ($r = 0.99$, $p < 0.001$), a linear tumor dose-response supporting the linear low dose cancer model with robust 77 to 89% tumor incidence in the high-dose groups.

Shorter-term studies did have precursor liver pathology such as liver lesions in the subchronic oral Milman study ([Milman et al., 1988](#)) and increased serum transaminase levels in the acute oral Tyson study ([Tyson et al., 1983](#)). There were different rooms for mice vs. rats, so the rat study outcomes would not affect mouse study results independently evaluated. Chemical administration was via gavage, so dosing is certain and there was no co-exposure to other chemicals due to volatilization from other dosing types such as from food or water. The best available science is using target chemical study for 1,1,2-trichloroethane and there is no read across uncertainties or time expenditures to identify and use analog data. A reliable PBPK model by the Sapphire Group as part of the HAP Task Force was utilized for the oral cancer study data extrapolation to the inhalation route to calculate the inhalation unit risk value. The PBPK model and ADME information indicates that doses did not saturate metabolism, which is also supported by the linear tumor dose-response. Body weights of male and female mice were not affected

6302 by treatment, supporting that doses did not exceed the maximum tolerated dose. The mouse cancer study
6303 has a medium systematic review rating.

Appendix D WEIGHT OF SCIENTIFIC EVIDENCE RUBRIC

The weight of scientific evidence fundamentally means that the evidence is weighed (*i.e.*, ranked) and weighted (*i.e.*, a piece or set of evidence or uncertainty may have more importance or influence in the result than another). Based on the weight of scientific evidence and uncertainties, a confidence statement was developed that qualitatively ranks (*i.e.*, robust, moderate, slight, or indeterminate) the confidence in the hazard threshold. The qualitative confidence levels are described below.

The evidence considerations and criteria detailed within ([U.S. EPA, 2021a](#)) guides the application of strength-of-evidence judgments for environmental hazard effect within a given evidence stream and were adapted from Table 7-10 of the 2021 Draft Systematic Review ([U.S. EPA, 2021a](#)).

EPA used the strength-of-evidence and uncertainties from ([U.S. EPA, 2021a](#)) for the hazard assessment to qualitatively rank the overall confidence rating for environmental hazard (Table_Apx D-1).

Confidence levels of robust, moderate, slight, or indeterminant are assigned for each evidence property that corresponds to the evidence considerations ([U.S. EPA, 2021a](#)). The rank of the *Quality of the Database* consideration is based on the systematic review overall quality determination (high, medium, or low) for studies used to calculate the hazard threshold, and whether there are data gaps in the toxicity dataset. Another consideration is the risk of bias (*i.e.*, how representative is the study to ecologically relevant endpoints?). Additionally, because of the importance of the studies used for deriving hazard thresholds, the *Quality of the Database* consideration may have greater weight than the other individual considerations. The high, medium, and low systematic review overall quality determination (OQD) ranks correspond to the evidence table ranks of robust, moderate, or slight, respectively. The evidence considerations are weighted based on professional judgment to obtain the overall confidence for each hazard threshold. In other words, the weights of each evidence property relative to the other properties are dependent on the specifics of the weight of scientific evidence and uncertainties that are described in the narrative and may or may not be equal. Therefore, the overall score is not necessarily a mean or defaulted to the lowest score. The confidence levels and uncertainty type examples are described in the appendix sections below.

D.1 Confidence Levels

- Robust confidence suggests thorough understanding of the scientific evidence and uncertainties. The supporting weight of scientific evidence outweighs the uncertainties to the point where it is unlikely that the uncertainties could have a significant effect on the exposure or 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 exposure or hazard estimates.
- Slight confidence is assigned when the weight of 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.

D.2 Types of Uncertainties

The following uncertainties may be relevant to one or more of the weight of scientific evidence considerations listed above and will be integrated into that property's rank in the evidence table:

- **Scenario Uncertainty:** Uncertainty regarding missing or incomplete information needed to fully define the exposure and dose.

- The sources of scenario uncertainty include descriptive errors, aggregation errors, errors in professional judgment, and incomplete analysis.
- **Parameter Uncertainty:** Uncertainty regarding some parameter.
 - Sources of parameter uncertainty include measurement errors, sampling errors, variability, and use of generic or surrogate data.
- **Model Uncertainty:** Uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences.
 - Modeling assumptions may be simplified representations of reality.

Table_Apx D-1 summarizes the weight of scientific evidence and uncertainties while increasing transparency on how EPA arrived at the overall confidence level for each exposure hazard threshold. Symbols are used to provide a visual overview of the confidence in the body of evidence, while de-emphasizing an individual ranking that may give the impression that ranks are cumulative (*e.g.*, ranks of different categories may have different weights).

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Table_Apx D-1. Considerations That Inform Evaluations of the Strength of the Evidence Within an Evidence Stream (*i.e.*, Apical Endpoints, Mechanistic, or Field Studies)

Consideration	Increased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Decreased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
The evidence considerations and criteria laid out here guide the application of strength-of-evidence judgments for an outcome or environmental hazard effect within a given evidence stream. Evidence integration or synthesis results that do not warrant an increase or decrease in evidence strength for a given consideration are considered “neutral” and are not described in this table (and, in general, are captured in the assessment-specific evidence profile tables).		
Quality of the database ^a (risk of bias)	• A large evidence base of high- or medium-quality studies increases strength. • Strength increases if relevant species are represented in a database.	• An evidence base of mostly <i>low</i>-quality studies decreases strength. • Strength also decreases if the database has data gaps for relevant species; <i>i.e.</i>, a trophic level that is not represented. • Decisions to increase strength for other considerations in this table should generally not be made if there are serious concerns for risk of bias; in other words, all the other considerations in this table are dependent upon the quality of the database.
Consistency	Similarity of findings for a given outcome (<i>e.g.</i> , of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across species, life stage, sex, wildlife populations, and across or within aquatic and terrestrial exposure pathways.	• Unexplained inconsistency (<i>i.e.</i>, conflicting evidence; U.S. EPA, 2005) decreases strength.) • Strength should not be decreased if discrepant findings can be reasonably explained by study confidence conclusions; variation in population or species, sex, or life stage; frequency of exposure (<i>e.g.</i>, intermittent or continuous); exposure levels (low or high); or exposure duration.
Strength (effect magnitude) and precision	• Evidence of a large magnitude effect (considered either within or across studies) can increase strength. • Effects of a concerning rarity or severity can also increase strength, even if they are of a small magnitude. • Precise results from individual studies or across the set of studies increases strength, noting that biological significance is prioritized over statistical significance. • Use of probabilistic model (<i>e.g.</i>, Web-ICE, SSD) may increase strength.	Strength may be decreased if effect sizes that are small in magnitude are concluded not to be biologically significant, or if there are only a few studies with imprecise results.
Biological gradient/dose-response	• Evidence of dose-response increases strength. • Dose-response may be demonstrated across studies or within studies and it can be dose- or duration-dependent. • Dose-response may not be a monotonic dose-response (monotonicity should not necessarily be expected, <i>e.g.</i>, different outcomes may be expected at low vs. high doses due to activation of different mechanistic	• A lack of dose-response when expected based on biological understanding and having a wide range of doses/exposures evaluated in the evidence base can decrease strength. • In experimental studies, strength may be decreased when effects resolve under certain experimental conditions (<i>e.g.</i>, rapid reversibility after removal of exposure). • However, many reversible effects are of high concern. Deciding between these situations is informed by factors such as the toxicokinetics of the

Consideration	Increased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Decreased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
	pathways or induction of systemic toxicity at very high doses). Decreases in a response after cessation of exposure (<i>e.g.</i>, return to baseline fecundity) also may increase strength by increasing certainty in a relationship between exposure and outcome (this particularly applicable to field studies).	chemical and the conditions of exposure (U.S. EPA, 1998), endpoint severity, judgments regarding the potential for delayed or secondary effects, as well as the exposure context focus of the assessment (<i>e.g.</i>, addressing intermittent or short-term exposures). - In rare cases, and typically only in toxicology studies, the magnitude of effects at a given exposure level might decrease with longer exposures (<i>e.g.</i>, due to tolerance or acclimation). - Like the discussion of reversibility above, a decision about whether this decreases evidence strength depends on the exposure context focus of the assessment and other factors. - If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased nor decreased.
Biological relevance	Effects observed in different populations or representative species suggesting that the effect is likely relevant to the population or representative species of interest (<i>e.g.</i> , correspondence among the taxa, life stages, and processes measured or observed and the assessment endpoint).	An effect observed only in a specific population or species without a clear analogy to the population or representative species of interest decreases strength.
Physical/chemical relevance	Correspondence between the substance tested and the substance constituting the stressor of concern.	The substance tested is an analog of the chemical of interest or a mixture of chemicals which include other chemicals besides the chemical of interest.
Environmental relevance	Correspondence between test conditions and conditions in the region of concern.	The test is conducted using conditions that would not occur in the environment.
^a Database refers to the entire dataset of studies integrated in the environmental hazard assessment and used to inform the strength of the evidence. In this context, database does <i>not</i> refer to a computer database that stores aggregations of data records such as the ECOTOX Knowledgebase.		

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Appendix E SPECIES SENSITIVITY DISTRIBUTION

An SSD was derived using only acute duration exposure studies that calculated LC50s. The SSD Toolbox is a resource that can fit SSDs to environmental hazard data ([Etterson, 2020a](#)). It runs on Matlab 2018b (9.5) for Windows 64 bit. For this draft TSD/assessment and 1,1,2-trichloroethane risk evaluation, EPA created one SSD with the SSD Toolbox Version 1.1 to evaluate acute aquatic vertebrate and invertebrate toxicity (Table_Apx E-1). The use of this probabilistic approach increases confidence in the hazard threshold identification as it is a more data-driven way of accounting for uncertainty. For the acute SSD, acute exposure hazard data for aquatic vertebrates and invertebrates were curated to prioritize study quality and to ensure comparability between toxicity values. For example, the empirical data set included LC50s for high, medium, and low-quality acute duration assays that measured mortality for aquatic vertebrates and invertebrates.

EPA developed an SSD for 1,1,2-trichloroethane as there were empirical toxicity data for 16 species (6 fish species and 10 invertebrate species) identified in systematic review (Table 3-1). SSDs were derived using EPA's SSD Toolbox (v1.1) ([Etterson, 2020b](#)) and plotted using R Statistical Software (v4.4.1) ([R Core Team, 2019](#)) using the ssdtools R package (v1.0.6) and the ggplot2 R package (v3.5.1). The Maximum Likelihood method and a Gumbel distribution model were used. The use of the Gumbel distribution was based on an examination of Akaike's Information Criterion (AIC) corrected for sample size, goodness of fit ([Burnham and Anderson, 2002](#)), visual examination of Q-Q (quantile-quantile) plots (Figure_Apx E-1), and evaluation of the line of best fit near the low-end of the SSD (Table_Apx E-2). The HC05 for this distribution was 31.4 mg/L 1,1,2-trichloroethane with a 95% confidence interval of 25.3 to 41.8 mg/L. After taking the lower 95th percent confidence interval of this HC05 as an alternative to the use of assessment factors, the acute aquatic COC for vertebrates and invertebrates was 25.3 mg/L 1,1,2-trichloroethane (Figure 3-2).

Table_Apx E-1. SSD Model Input for 1,1,2-Trichloroethane Acute Exposure Toxicity in Aquatic Vertebrates and Invertebrates – Empirical Data

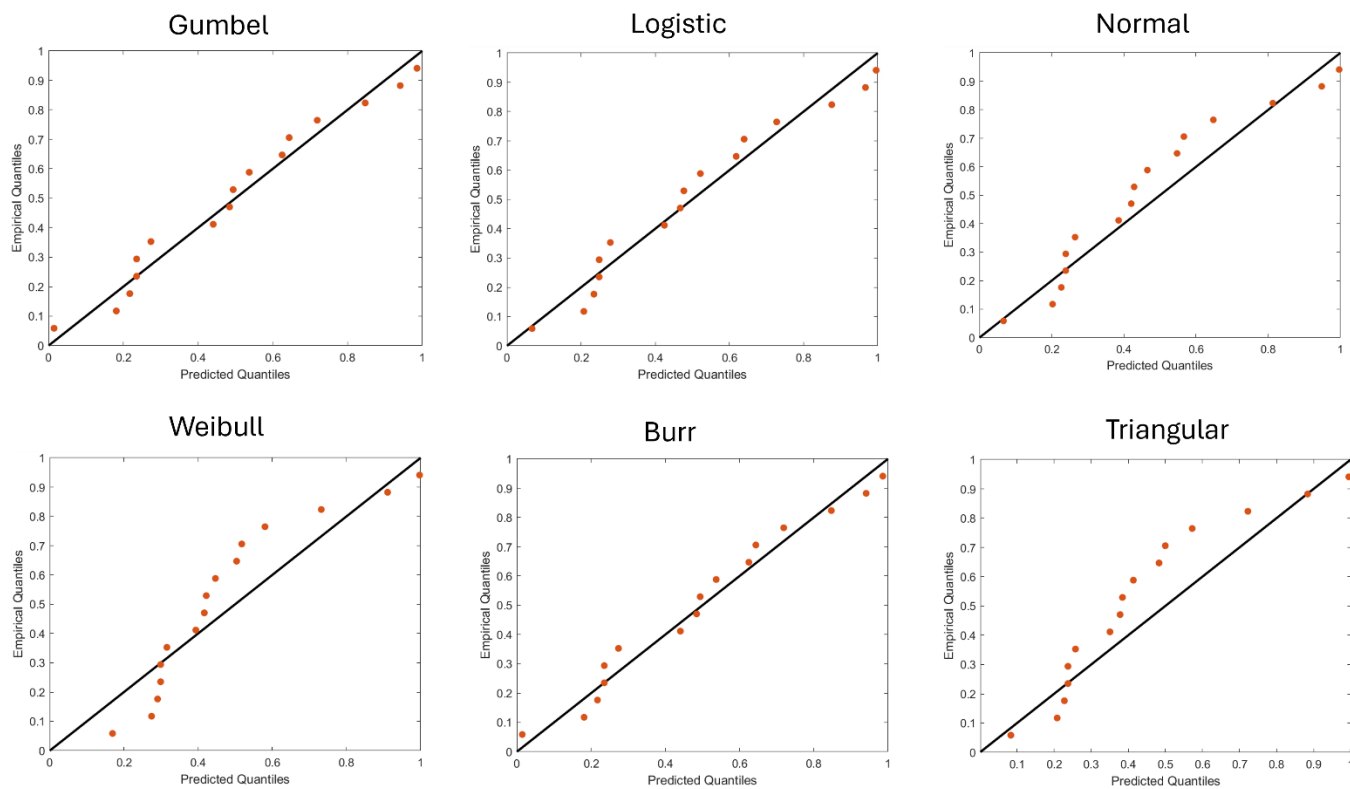
Species	Description	Acute Toxicity Value LC50 (mg/L)	Citation (Study Quality)
<i>Dreissena polymorpha</i>	Invertebrate	320	(Adema and Vink, 1981) (Low)
<i>Crepidula fornicata</i>	Invertebrate	170	(Adema and Vink, 1981) (Low)
<i>Mytilus edulis</i>	Invertebrate	110	(Adema and Vink, 1981) (Low)
<i>Pimephales promelas</i>	Vertebrate	81.6	(Geiger et al., 1985) (High)
<i>Chaetogammarus marinus</i>	Invertebrate	72	(Adema and Vink, 1981) (Low)
<i>Poecilia reticulata</i>	Vertebrate	72.5	(Adema and Vink, 1981) (Low)
<i>Artemia salina</i>	Invertebrate	62	(Adema and Vink, 1981) (Low)
<i>Daphnia magna</i>	Invertebrate	58.7	(Adema and Vink, 1981) (Low)

Species	Description	Acute Toxicity Value LC50 (mg/L)	Citation (Study Quality)
<i>Lymnaea stagnalis</i>	Invertebrate	58	(Adema and Vink, 1981) (Low)
<i>Pleuronectes platessa</i>	Vertebrate	27	(Adema and Vink, 1981) (Low)
<i>Jordanella floridae</i>	Vertebrate	45.1	(Smith et al., 1991)
<i>Temora longicornis</i>	Invertebrate	43	(Adema and Vink, 1981) (Low)
<i>Palaemonetes varians</i>	Invertebrate	43	(Adema and Vink, 1981) (Low)
<i>Crangon crangon</i>	Invertebrate	42	(Adema and Vink, 1981) (Low)
<i>Lepomis macrochirus</i>	Vertebrate	40	(Buccafusco et al., 1981) (Low)
<i>Pomatoschistus minutus</i>	Vertebrate	27	(Adema and Vink, 1981) (Low)

Table_Apx E-2. SSD Model Predictions for Acute 1,1,2-Trichloroethane Exposure and Toxicity to Aquatic Vertebrates^a

Distribution ^b	HC05 (mg/L)	Akaike Information Criterion	P-Value
Gumbel	31.40	162.88	0.75
Logistic	24.46	165.74	0.45
Normal	24.80	167.05	0.10
Weibull	10.74	174.47	0.02
Burr	31.34	165.95	0.73
Triangular	23.15	168.34	0.02

^a The SSD was generated using [SSD Toolbox v1.1](#) (accessed June 10, 2026).
^b The model with the lowest AICc value, and therefore the best model fit, is **bolded**.



Figure_Apx E-1. Q-Q Plots of 1,1,2-Trichloroethane Species Sensitivity Distribution Model Fits