

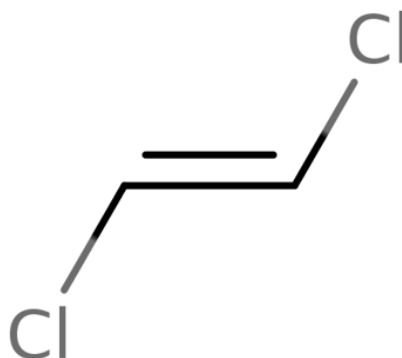


United States
Environmental Protection Agency

Draft Human Health and Environmental Hazard Assessment for *trans*-1,2-Dichloroethylene

Technical Support Document for the Draft Risk Evaluation

CASRN 156-60-5



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Docket

Supporting information can be found in the public dockets, Docket IDs ([EPA-HQ-OPPT-2026-2246](#) and [EPA-HQ-OPPT-2018-0465](#)).

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308 KEY ABBREVIATIONS AND ACRONYMS

309	AF	Assessment factor
310	AFCs	Antibody forming cells
311	AEGL	Acute Exposure Guideline Levels
312	ALP	Alkaline phosphatase
313	ALT	Alanine aminotransferase
314	AST	Aspartate aminotransferase
315	ATSDR	Agency for Toxic Substances and Disease Registry
316	BMD/C(L)	Benchmark dose/concentration (lower 95% confidence limit)
317	BMR	Benchmark response
318	BUN	Blood urea nitrogen
319	CASRN	Chemical Abstracts Service Registry Number
320	ChV	Chronic value
321	CI	Confidence interval
322	CNS	Central nervous system
323	COC	Concentration(s) of concern
324	CYP	Cytochrome P450
325	DAF	Dosimetric adjustment factor
326	EC50	Effect concentration at which 50% of test organisms exhibit an effect
327	EPA	Environmental Protection Agency (U.S.)
328	GSH	Glutathione
329	GST(Z)	Glutathione S-transferase (Zeta)
330	HC05	Hazard concentration that is protective of 95% of the species in the SSD
331	HEC	Human equivalent concentration
332	HED	Human equivalent dose
333	HV	Hazard value
334	IPM	Isopropyl myristate
335	IRIS	Integrated Risk Information System
336	K _p	Permeability coefficient
337	LC50	Lethal concentration at which 50% of test organisms die
338	LD50	Lethal dose at which 50% of test organisms die
339	LO(A)EC	Lowest-observed-(adverse)-effect-concentration
340	LO(A)EL	Lowest-observed-(adverse)-effect-level
341	MOA	Mode of action
342	NO(A)EC	No-observed-(adverse)-effect-concentration
343	NO(A)EL	No-observed-(adverse)-effect-level
344	OCSPP	Office of Chemical Safety and Pollution Prevention (EPA)
345	OECD	Organisation for Economic Co-operation and Development
346	OPPT	Office of Pollution Prevention and Toxics (EPA)
347	OR	Odds ratio
348	OQD	Overall study quality determination
349	PBPK	Physiologically-based pharmacokinetic
350	PECO	Population, exposure, comparator, and outcome
351	PESS	Potentially exposed and susceptible subpopulations
352	POD	Point of departure
353	ReCAAP	Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project
354	SACC	Science Advisory Committee on Chemicals
355	SD	Standard deviation; Sprague-Dawley (rats)
356	SSD	Species sensitivity distribution

357	TRV	Toxicity Reference Value
358	TSCA	Toxic Substances Control Act
359	UF	Uncertainty factor
360	U.S.	United States
361	Web-ICE	Web-based Interspecies Correlation Estimation

SUMMARY

This technical support document (TSD) is part of the Toxic Substances Control Act (TSCA) *Draft Risk Evaluation for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026b](#)). *trans*-1,2-Dichloroethylene is an organic substance with many uses including cleaning/degreasing, lubrication, and as an additive for several product types. This draft TSD describes the (1) use of reasonably available information to evaluate the cancer and non-cancer human health hazards, (2) environmental health hazards associated with exposure to *trans*-1,2-dichloroethylene, and (3) derivation of points of departure (PODs) used to estimate risks in the draft risk evaluation.

Human Health Hazard

Humans may be exposed to *trans*-1,2-dichloroethylene as a neat liquid or vapor, or as part of a formulation. Based on physical and chemical properties and expected exposure scenarios ([U.S. EPA, 2026b](#)), inhalation exposure is expected to be the predominant route of exposure; however, the EPA quantitatively evaluated hazards via all exposure routes. Hazards were assessed through systematic review of reasonably available evidence, which includes human epidemiology, animal toxicology, and mechanistic data (including *in vitro* studies). Previous reviews by U.S. and international governmental agencies were also consulted. The Agency for Toxic Substances and Disease Registry's (ATSDR) 2025 *Toxicological Profile for 1,2-Dichloroethene* ([ATSDR, 2025](#)) was used to identify the primary hazards and previously identified key studies. Other EPA reviews including the 2020 EPA Provisional Peer-Reviewed Toxicity Values (PPRTV) assessment ([U.S. EPA, 2020b](#)), 2010 EPA Integrated Risk Information System (IRIS) assessment ([U.S. EPA, 2010](#)), 2008 Acute Exposure Guideline Levels (AEGL) document ([U.S. EPA, 2022](#)), and 2018 CalEPA/OEHHA Public Health Goals ([CalEPA, 2018](#)) were also consulted for their hazard database. These sources were supplemented by a literature search for all reasonably available information through September 2019. An updated literature search was also performed in April 2025, refined with specific keywords to prioritize data on cancer and immunological data. EPA additionally reviewed the 2025 ATSDR assessment ([ATSDR, 2025](#)) for any post-2019 studies, however newer studies were not identified in that assessment.

The updated and refined literature pool was screened using an updated population, exposure, comparator, and outcome (PECO) statement for *in vivo* information specific to those hazard domains. Cancer was selected for a targeted literature screening to support EPA's cancer analysis due to the absence of any published carcinogenicity studies (Section 2.3.3); immunotoxicity was selected because it is the most critical repeated-dose outcome supporting hazard value derivation (see Sections 2.3.1 and 2.3.2.1.2). Following PECO screening, relevant newer studies were not identified as part of this updated search. The updated literature pool was not screened for other hazards because the recent 2025 ATSDR *Toxicological Profile* ([2025](#)) that was consulted did not contain any studies published post-2019 or any other information that would impact the weight of scientific evidence for other hazard domains. Independent systematic review was performed for all studies and outcomes. This preliminary hazard assessment builds on the hazard database and conclusions from these prior assessments, updated based on current EPA guidance, systematic review results, and in accordance with the best reasonably available science.

trans-1,2-Dichloroethylene is readily absorbed through the lungs and gastrointestinal tract. Evidence from a test order suggest that *trans*-1,2-dichloroethylene has measurable but limited dermal absorption ($\approx 1\%$ absorption based on 8 hours of exposure) when accounting for volatility of the substance from unoccluded skin ([TDCE Consortium, 2023](#)). Metabolism is unlikely to be a major contributor to the toxicity of *trans*-1,2-dichloroethylene because it undergoes "suicide inhibition" that decreases oxidative metabolism through inactivation of cytochrome P450 (CYP450) enzymes (see Section 2.2.3 for details).

Because of this unique metabolism, reasonable toxicologically similar structural analogs other than the *cis*- isomer were not identified.

In reviewing the reasonably available information, EPA concluded that the weight of scientific evidence supports dose-response analysis on two non-cancer hazard outcomes: (1) sensory irritation and acute neurotoxicity, and (2) immunological toxicity. The best representative non-cancer endpoints and PODs representing those hazard outcomes were derived for inhalation, oral, and dermal routes corresponding to either acute, intermediate, or chronic exposure. The database did not include any studies of longer than 90-day exposure duration.

EPA derived an acute human equivalent concentration (HEC) of 7,930 mg/m³ (2,000 ppm) for ocular irritation based on lacrimation in rats ([Hurtt et al., 1993](#)) with an uncertainty factor (UF) of 30, supported by a single occupational exposure study in humans with self-reported symptoms within minutes of exposure to *trans*-1,2-dichloroethylene in air ([Lehmann and Schmidt-Kehl, 1936](#)). These studies also reported signs of solvent neurotoxicity in humans and rodents at similar concentrations. Collectively these effects could result in a lack of ability to escape or may otherwise present a dangerous environment for exposed individuals. The effects reported in ([Lehmann and Schmidt-Kehl, 1936](#)) are the basis of the first threshold of Acute Exposure Guideline Levels (AEG-1) of 280 ppm for *trans*-1,2-dichloroethylene. This threshold represents exposure limits for the general public and is applicable to emergency exposure periods ranging from 10 minutes to 8 hours for high priority, acutely toxic chemicals ([U.S. EPA, 2022](#)). Because ocular irritation is based on exposure levels at peak (*i.e.*, maximal 15-minute period) air concentrations, the HEC was not duration-adjusted to continuous exposure. An acute POD for oral and dermal exposures was not derived because ocular irritation was the only endpoint relevant to acute exposure.

For repeated oral exposures via drinking water, decreased T cell-dependent humoral immune response indicated by reduced antibody-forming cells (AFCs) in mice ([Shopp et al., 1985](#)) was benchmark dose modeled and a human equivalent dose (HED) adjusted to daily exposure of 21.4 mg/kg-day was derived. As a measure of functional immunity, AFC assays are considered one of the best predictors of immunotoxicity in mice ([Ladics, 2007](#)) and demonstrate excellent concordance with immunotoxicity among immune measures ([Luster et al., 1992](#)). This was considered the most reliable POD for intermediate and chronic exposures via all exposure routes despite inconsistency in other less reliable measures of immune function. Because functional immunity was not measured in other studies, the oral HED from ([Shopp et al., 1985](#)) was also applied to dermal exposures and route-to-route extrapolation to inhalation resulted in an HEC of 116 mg/m³. The POD was derived from a 90-day experiment and increased immunotoxicity was observed at 90 days compared to a 14-day experiment in the same ([Shopp et al., 1985](#)) study at comparable doses. Because there were no other studies identified investigating chronic *trans*-1,2-dichloroethylene exposure, the observed increased toxicity at longer exposure duration supports an additional uncertainty factor for extrapolation from the intermediate POD to the chronic duration (UF_S). A 10-fold UF_S was applied for chronic oral scenarios, with a reduced 3-fold UF_S value applied to chronic dermal and inhalation scenarios because (1) only the oral database contains data indicating increased sensitivity over time, while (2) extrapolation to other routes is more uncertain. As a result, the total uncertainty factor for intermediate scenarios via all routes is 30, while the total uncertainty factors for chronic dermal/inhalation and chronic oral scenarios are 100 and 300, respectively.

There is insufficient evidence from cancer bioassays to evaluate the carcinogenicity of *trans*-1,2-dichloroethylene using standard approaches as described in EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)). Therefore, a weight of scientific evidence approach was employed to

evaluate the extent to which the lack of inhalation carcinogenicity studies imparts significant uncertainty on the human health risk assessments for *trans*-1,2-dichloroethylene using the Rethinking Chronic Toxicity and Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) framework ([OECD, 2024](#); [Hilton et al., 2022](#)). Based on the weight of scientific evidence, EPA has preliminarily concluded that quantitative cancer risk assessment of *trans*-1,2-dichloroethylene is not warranted because (1) carcinogenic effects from *trans*-1,2-dichloroethylene are not expected based on primarily negative results for genotoxicity; (2) no evidence of precancerous lesions in subchronic studies, only “marginal” carcinogenicity concern from *in silico* modeling; and (3) minimal formation of reactive metabolites (Section 2.4.6). Although there is some remaining uncertainty based on the absence of any direct cancer data or chronic toxicity data, the overall weight of scientific evidence is sufficient for making this preliminary conclusion and any additional cancer bioassays would be unlikely to provide evidence leading to a different conclusion.

Confidence ratings (Table S-1) were based on the weight of scientific evidence considering evidence integration, selection of the critical endpoint and study, relevance to exposure scenarios, dose-response considerations, and incorporation of potentially exposed or susceptible subpopulations (PESS).

Table S-1. Summary of Human Health Hazard Points of Departure for *trans*-1,2-Dichloroethylene

Target Organ System	Study Duration (Route)	Effect	HED	HEC	Uncertainty Factors	Reference (OQD)	Confidence ^a
Acute Inhalation Exposure Scenario							
Ocular/ Neurological	6 hours/ day from GD 7–16 (Whole Body Exposure)	Ocular irritation/ CNS depression	N/A	7,930 mg/m ³ (2,000 ppm)	UF _A = 3; UF _H = 3; UF _L = 3; Total UF = 30	Hurtt et al. (1993) (High)	Moderate-to-Robust
Intermediate Oral/Dermal/Inhalation Exposure Scenario							
Immune	90 days (Oral via drinking water)	Decreased humoral immune response (AFCs)	BMDL _{1SD} = 21.4 mg/kg-d	116 mg/m ³ (29.4 ppm)	UF _A = 3; UF _H = 10; Total UF = 30	Shopp et al. (1985) (High)	Moderate-to-Robust (oral/ inhalation); Moderate (dermal)
Oral Chronic Exposure Scenario							
Immune	90 days (Oral via drinking water)	Decreased humoral immune response (AFCs)	BMDL _{1SD} = 21.4 mg/kg-d	116 mg/m ³ (29.4 ppm)	UF _A = 3; UF _H = 10; UF _s = 10; Total UF = 300	Shopp et al. (1985) (High)	Moderate
Inhalation/Dermal Chronic Exposure Scenario							
Immune	90 days (Oral via drinking water)	Decreased humoral immune response (AFCs)	BMDL _{1SD} = 21.4 mg/kg-d	116 mg/m ³ (29.4 ppm)	UF _A = 3; UF _H = 10; UF _s = 3; Total UF = 100	Shopp et al. (1985) (High)	Moderate (inhalation); Slight-to-Moderate (dermal)

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Target Organ System	Study Duration (Route)	Effect	HED	HEC	Uncertainty Factors	Reference (OQD)	Confidence ^a
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AFCs = antibody-forming cells; BMDL_{1SD} = benchmark dose lower 95% confidence limit 1 standard deviation; CNS = central nervous system; GD = gestational day; HEC = human equivalent concentration; HED = human equivalent dose; OQD = overall study quality determination for the individual study that was used; POD = point of departure; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor

^a POD confidence selection based on an evaluation of the identified POD and the confidence in the alignment of this POD to the assigned route/duration and any uncertainties associated with the POD being used for risk estimates (e.g., route-to-route extrapolation, duration adjustment).

Environmental Hazard

EPA considered all reasonably available information identified through the systematic review process under the Toxic Substances Control Act (TSCA) to characterize environmental hazard endpoints for *trans*-1,2-dichloroethylene. Because available data was limited for *trans*-1,2-dichloroethylene, using a process outlined in Section 3.1.1 and further detailed in Appendix E, the analogs *cis*-1,2-dichloroethylene and trichloroethylene were selected to fill in data gaps. Upon evaluating the reasonably available information, environmental hazard thresholds were derived for acute exposures to aquatic species and chronic exposures to aquatic vertebrates, invertebrates, and for aquatic plants (algae) (Table S-2). Hazard thresholds were also derived for inhalation hazards to terrestrial vertebrates 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, is described in Section 3.

Table S-2. Summary of Environmental Hazard Toxicity Values for *trans*-1,2-Dichloroethylene

Environmental Toxicity Thresholds	Analog	Hazard Value (Units)	Assessment Factor (AF)	COC (Unit)	Confidence	Assessment Medium
Aquatic hazard toxicity values						
Acute aquatic exposure: Lower 95% CI of HC05 and HC05 from SSD	Trichloroethylene	3,005 (µg/L)	NA	3,005 (µg/L)	Robust	Water column
		4,438 (µg/L)	NA	4,438 (µg/L)	Robust	Water column
Chronic aquatic exposure	Trichloroethylene (read-across)	7,880 (µg/L)	10	788 (µg/L)	Moderate	Water column
Aquatic plant exposure: Lower 95% CI of HC05 and HC05 from SSD	Trichloroethylene	51,467 (µg/L)	NA	51,467 (µg/L)	Moderate-to-Robust	Water column
		93,364 (µg/L)	NA	93,364 (µg/L)	Moderate-to-Robust	Water column
Terrestrial hazard values						
Terrestrial plants	NA	10,350 (ppm in air)	NA	10,350 (ppm in air)	Moderate-to-Robust	Air

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Environmental Toxicity Thresholds	Analog	Hazard Value (Units)	Assessment Factor (AF)	COC (Unit)	Confidence	Assessment Medium
Terrestrial plants	NA	79 (mg/L in soil solution)	NA	79 (mg/L in soil solution)	Moderate-to-Robust	Soil pore water
Terrestrial soil-dwelling Invertebrates	Trichloroethylene	1,000 (mg/kg soil)	10	100	Moderate-to-Robust	Soil
Terrestrial soil-dwelling Invertebrates	Trichloroethylene	5.48 (mg/L in soil solution)	NA	5.48 (mg/L in soil solution)	Moderate-to-Robust	Soil Solution
Chronic inhalation toxicity reference value (TRV) for mammals	NA	6,000 ppm 23,789 (mg/cm ³)	NA	6,000 Ppm 23,789 (mg/cm ³)	Moderate	Air
Chronic oral toxicity reference value (TRV) for mammals	NA	1,504 mg/kg-bw/day	NA	1,504 mg/kg-bw/day	Robust	Diet via ingestion and Media by incidental ingestion (soil, sediment)
CI = confidence interval; HC05 = hazardous concentration (HC) for 5% of species; NA = not available/applicable; SSD = species sensitivity distribution						

1 INTRODUCTION

This technical document presents the draft human health and environmental hazard assessment in support of the TSCA *Draft Risk Evaluation for trans-1,2-Dichloroethylene* (also referred to as the “draft risk evaluation”) ([U.S. EPA, 2026h](#)) 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 and deadlines for actions related to conducting risk evaluations of existing chemicals.

In December 2019, EPA published a list of 20 chemical substances that have been designated high priority substances for risk evaluations (Docket: [EPA-HQ-OPPT-2019-0131](#)) (84 FR 71924, December 30, 2019), as required by TSCA section 6(b)(2)(B), which initiated the risk evaluation process for those chemical substances. *trans*-1,2-Dichloroethylene is one of the chemicals designated as a high priority substance for risk evaluation.

This draft TSD discusses both the human health and environmental hazard of *trans*-1,2-dichloroethylene. The risk evaluation document will summarize the results of this module and integrate the results with the exposure estimates to produce quantitative and qualitative risk estimates for all conditions of use. This draft TSD will undergo expert peer review by the Science Advisory Committee on Chemicals (SACC).

2 HUMAN HEALTH HAZARD ASSESSMENT

2.1 Approach and Methodology

EPA used systematic review processes to search, screen, evaluate, extract, and integrate reasonably available information to make conclusions about relevant adverse health effects from *trans*-1,2-dichloroethylene exposure. Following evidence integration, the Agency performed dose-response analysis to derive hazard values for use in risk characterization. These values are binned into one of four duration categories, to match the corresponding human exposure scenarios for risk estimation. The durations are provided below:

- Acute (single dose or exposure to an air concentration for no more than 24 consecutive hours);
- Intermediate (a repeated dosing ranging anywhere from a few days to <10% of lifetime, typically from short-term or subchronic studies);
- Chronic non-cancer (repeated dosing covering >10% of lifetime); and
- Chronic/lifetime cancer (repeated dosing averaged over the relevant chronic period up to a full lifetime).

EPA then evaluated the weight of scientific evidence for each aspect of the assessment and determined overall confidence ratings for each critical hazard outcome. The generalized process for conducting human health assessments under TSCA is presented below in Figure 2-1.

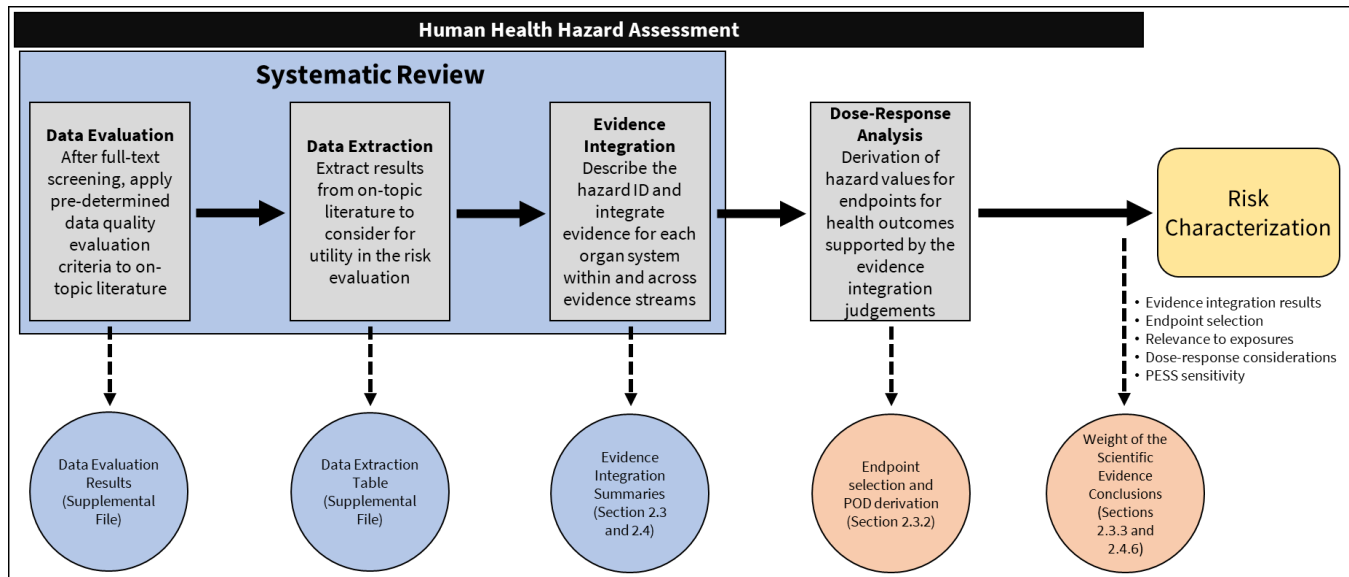


Figure 2-1. EPA Approach to Hazard Identification, Evidence Integration, and Dose-Response Analysis for *trans*-1,2-Dichloroethylene

2.1.1 Systematic Review

The searching and screening steps of the systematic review process for *trans*-1,2-dichloroethylene 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, 2021) covering all reasonably available literature published through September 2019. In short, studies were screened using population, exposure, comparator, and outcome (PECO) criteria for relevance to the hazard assessment for *trans*-1,2-dichloroethylene, with studies that passed PECO screening further considered for data evaluation and extraction. Results of PECO screening are provided for animal toxicology,

epidemiology, and dermal absorption in Appendix G. Data evaluation and extraction were performed on all PECO-relevant studies.

An updated literature search was also performed in April 2025, refined to prioritize data on cancer and immunological data. EPA additionally reviewed the 2025 ATSDR assessment ([ATSDR, 2025](#)) for any post-2019 studies, however newer studies were not identified in that assessment. The updated and refined literature pool was screened using an updated PECO statement for *in vivo* information specific to those hazard domains. Cancer was selected for a refined literature screening to support EPA's cancer analysis due to the absence of any published carcinogenicity studies (Section 2.3.3), and immunotoxicity was selected because it is the most critical repeated-dose outcome supporting hazard value derivation (see Section 2.3.1 and 2.3.2.1.2). Following PECO screening, relevant newer studies were not identified as part of this updated search. The updated literature pool was not screened for other hazards because the recent 2025 ATSDR Toxicological Profile ([ATSDR, 2025](#)) that was consulted did not contain any studies published post-2019 or any other information that would impact the weight of scientific evidence for other hazard domains, all of which had insufficient weight of scientific evidence to support dose-response analysis (Section 2.3.1). Full details and screening results for all the identified studies will be described in the *Draft Systematic Review Protocol for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026i](#)), to be released with the draft risk evaluation.

Full details on all evaluated health outcomes from all key studies are in *Draft Data Extraction Information for Environmental and Human Health Hazard Animal Toxicology and Epidemiology for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026d](#)). Data quality evaluation results can be found in *Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026m](#)) and *Data Quality Evaluation Information for Human Health Hazard Epidemiology for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026n](#)). Data quality evaluation results for dermal absorption is also provided in *Data Quality Evaluation Information for Dermal Absorption for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026l](#)).

2.1.2 Problem Formulation and Focus of Analysis

The Agency used the ATSDR *Toxicological Profile for 1,2-Dichloroethene* ([ATSDR, 2025](#)) as the starting point for this human health hazard assessment and focused on endpoints used for deriving hazard values for the *trans*- isomer in the ATSDR assessment. Although the database for *trans*-1,2-dichloroethylene is limited, ATSDR derived acute inhalation and intermediate oral minimal risk levels (MRLs). These hazard values were based on ocular irritation and immune effects, respectively. ATSDR concluded that the available data was inadequate to derive chronic MRLs (no chronic studies are available). EPA additionally consulted the 2020 EPA Provisional Peer-Reviewed Toxicity Values (PPRTV) assessment ([U.S. EPA, 2020b](#)), 2010 EPA Integrated Risk Information System (IRIS) assessment ([U.S. EPA, 2010](#)), 2008 Acute Exposure Guideline Levels document for 1,2-dichloroethene ([U.S. EPA, 2022](#)) and 2018 CalEPA/OEHHA Public Health Goals document ([CalEPA, 2018](#)) for identifying key hazard outcomes and helping summarize the hazard database. However, independent systematic review was performed for all studies and outcomes. Critical endpoints and hazard values from these prior assessments are presented in Appendix D, along with a comparison to hazard values derived in this assessment.

This hazard assessment builds off the hazard database and conclusions from these prior assessments, updated based on current EPA guidance, systematic review results, and in accordance with the best available science. All hazard outcomes were within the scope of the assessment but based on conclusions from these assessments, EPA identified the most well-supported hazard domains as critical

health outcomes for considering endpoints to undergo dose-response analysis. These critical hazard outcomes are discussed in Section 2.3.1.

2.2 Toxicokinetics and PBPK Models

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

2.2.1 Absorption

Oral

No animal or human studies were located that quantified the rate or extent of *trans*-1,2-dichloroethylene uptake following oral exposure.

Inhalation

A study exposing two volunteers for 30 minutes to a *cis:trans*-1,2-dichloroethylene mixture of unknown ratios¹ reported a 72 to 75% decrease in the levels of *trans*-1,2-dichloroethylene in the exposure chamber from initial concentrations, suggesting that inhaled *trans*-1,2-dichloroethylene was absorbed through the lungs ([Lehmann and Schmidt-Kehl, 1936](#)). Closed-chamber uptake studies in rats indicate rapid absorption in animals exposed to *trans*-1,2-dichloroethylene vapor ([Andersen et al., 1980](#); [Filser and Bolt, 1979](#)). A rapid uptake phase, occurring within 1.5 to 2 hours, was followed by a slower uptake phase that approached a steady state. During the slow uptake phase, the reduction of *trans*-1,2-dichloroethylene in the exposure chambers showed a first-order decline when initial concentrations were low (≤ 15 ppm) ([Filser and Bolt, 1979](#)), but zero-order elimination was observed with higher gas concentrations, suggesting metabolic saturation. Blood:air coefficients for *trans*-1,2-dichloroethylene (6.04 ± 0.38 in humans, 9.58 ± 0.94 in rats ([Gargas et al., 1989](#)), and 5.8 in an unspecified species ([Sato and Nakajima, 1979](#))) also suggest that pulmonary absorption is likely to occur.

Dermal

There is limited available information concerning *trans*-1,2-dichloroethylene dermal absorption. Dermal absorption is relatively low under non-occluded conditions due to it being highly volatile (vapor pressure = 331 mmHg at 25 °C ([NLM, 2018](#))). In Part E of the *Risk Assessment Guidance for Superfund Volume I* ([U.S. EPA, 2004](#)), the permeability coefficient (K_p) in cm/hour for *trans*-1,2-dichloroethylene dissolved in water is estimated using an equation based on the log K_{ow} and molecular weight of a given chemical (volatility not accounted for in this equation). The equation was derived based on fit to an experimental database of *in vitro* absorption data on human skin for about 90 chemicals. Based on this equation, the predicted K_p for *trans*-1,2-dichloroethylene is 7.7×10^{-3} cm/hour. The lower and upper confidence intervals for this estimate were 3.1×10^{-4} and 1.9×10^{-1} cm/hour, respectively. It should be noted that the experimental database used to derive the K_p equation had a low number of results for halogenated compounds, which may influence the K_p predictions for *trans*-1,2-dichloroethylene.

In response to a TSCA section 4 test order (Docket: [EPA-HQ-2018-0465-0045](#)), an OECD (Organisation for Economic Co-operation and Development) 428 guideline study ([TDCE Consortium, 2023](#)) was conducted to determine and compare absorption rates and measured permeability coefficients of radiolabeled [^{14}C]- *trans*-1,2-dichloroethylene following *in vitro* dermal applications to excised human skin at multiple concentrations. For non-occluded (with a vapor trap for mass recovery) scenarios of finite loading for determination of fractional absorption, multiple concentrations (0.1, 1, and 10%) were tested using either isopropyl myristate (IPM) or toluene. Infinite dosing scenarios were tested

¹ Study was photocopied and in German so tables are not fully legible. The ratios are not legible; however, the concentrations were listed as 40.1 mg/L or 0.25% w/v.

under occluded conditions at multiple concentrations (10%, 50%, or neat), using either IPM or receptor fluid.

For fractional dermal absorption of a finite loading of *trans*-1,2-dichloroethylene, skin samples were exposed to the test material for 8 hours, after which time the dose remaining on the skin was washed off the skin with a mild detergent solution. Receptor fluid samples were collected at multiple intervals throughout the duration of the experiment of 24 hours (receptor fluid sampling conducted at 10 and 30 minutes and 1, 2, 4, 8, 12, 16, and 20 hours; all compartments were collected at 24 hours). Volatile radioactivity was trapped using a charcoal filter. At the end of the experiment, the skin samples were tape stripped to remove residual surface dose and the stratum corneum, and the amount of chemical remaining in the skin compartment was also quantified. The distribution of radioactivity in the skin was determined by radioassay of samples collected from each compartment of the static diffusion cell. Finite application of *trans*-1,2-dichloroethylene as 10, 1 and 0.1% solutions in IPM or toluene, under semi-occlusive conditions, indicated potentially absorbable dose (dermal delivery + stratum corneum strips 3–20) of 0.43 to 1.43% of applied dose, where detectable. The mass balance was only 28 to 66% and the coefficient of variation was 19 to 55%, adding uncertainty to these findings. At each concentration, the majority of radioactivity was unabsorbed, indicating that under finite conditions, *trans*-1,2-dichloroethylene was most likely to quickly volatilize from the skin surface. Mean absorption across concentrations and solvents ranged from 0.43 to 1.43%, albeit without a consistent concentration-response.

For dermal permeability of infinite loading of *trans*-1,2-dichloroethylene, receptor fluid samples were collected at multiple intervals throughout the duration of the 24-hour experiment. Radioactivity in the receptor fluid was analyzed to determine the rate of penetration and the K_p of the test item. Following infinite application of *trans*-1,2-dichloroethylene, the maximum absorption rate and permeability coefficients were lower in the IPM solutions as compared to those in receptor fluid. Permeability coefficients for the 10 and 50% IPM solutions were 9.63×10^{-4} and 7.6×10^{-4} cm/hour, respectively, while the permeability coefficients for the 10 and 50% receptor fluid solutions were 9.16×10^{-3} cm/hour and 2.0×10^{-3} cm/hour, respectively. The permeability coefficient for the neat *trans*-1,2-dichloroethylene solution was 6.66×10^{-4} cm/hour. Coefficients of variation ranged from 16 to 61%, indicating uncertainty in the estimate for infinite scenarios as well. An inverse concentration-response was observed, with K_p increasing for more dilute formulations, consistent with the higher K_p values estimated by (U.S. EPA, 2004) for dilute aqueous solutions.

More details on how EPA interpreted the results of the test order data, including statistical adjustments to account for variability, are presented in Appendix C. In summary: a range of 0.7 to 1.7% fractional absorption (adjusted to account for variability in the results) was applied for use in Monte Carlo modeling of occupational exposure scenarios. Consumer exposure scenarios used fractional absorption estimates of 0.6% and 1.2% at the 4-hour and 24-hour timepoints, respectively. Screening of general population incidental dermal exposure from swimming in an impacted body of water used a K_p of 9.16×10^3 cm/hour from the 10% receptor fluid formulation to best resemble exposure to a dilute aqueous solution.

2.2.2 Distribution

In Vivo

No *in vivo* oral, inhalation, or dermal studies were identified in humans or animals that investigated the tissue distribution of *trans*-1,2-dichloroethylene throughout the body.

In Vitro

Tissue-air partition coefficients calculated using a vial equilibration method and tissues obtained from male Fischer 344 rats (see Table 2-1) suggest that *trans*-1,2-dichloroethylene in the blood will be distributed to the liver and will accumulate preferentially in fat ([Gargas et al., 1989](#); [Gargas et al., 1988](#)).

Table 2-1. *trans*-1,2-Dichloroethylene Tissue:Air Partition Coefficients in Rats

Partition Coefficient			
Blood:Air	Liver:Air	Muscle:Air	Fat:Air
9.58 ± 0.94	8.96 ± 0.61	3.52 ± 0.54	148 ± 11
Source: (Gargas et al., 1989 ; Gargas et al., 1988)			

2.2.3 Metabolism***Human Studies***

No human studies on the metabolism of *trans*-1,2-dichloroethylene were identified.

Laboratory Animal Studies

The primary metabolic pathways (see Figure 2-1) for *trans*-1,2-dichloroethylene, elucidated from *in vitro* and *in vivo* studies in rats, include cytochrome P450 (CYP) oxidation and metabolism by alcohol and aldehyde dehydrogenases and glutathione-S-transferase zeta (GSTZ). Multiple isozymes of CYP are involved in oxidation of *trans*-1,2-dichloroethylene including, but not limited to, CYP2E1 and CYP3A4 ([Lilly et al., 1998](#); [Costa and Ivanetich, 1982](#)). Epoxidation of the *trans*-1,2-dichloroethylene ethylene double bond yields an unstable epoxide intermediate that rearranges non-enzymatically to form 2,2-dichloroacetaldehyde, which is the primary metabolite arising from CYP oxidation. Enzymatic conversion of 2,2-dichloroacetaldehyde by alcohol and aldehyde dehydrogenases (ADH, ALDH) forms the metabolites, 2,2-dichloroethanol, and 2,2-dichloroacetic acid (DCA) ([Nakajima, 1997](#); [Barton et al., 1995](#); [Costa and Ivanetich, 1984](#); [Filser et al., 1982](#); [Leibman and Ortiz, 1977](#); [Bonse et al., 1975](#)). GSTZ mediates the dechlorination of DCA—eventually leading to the formation of glycolic acid ([Costa and Ivanetich, 1984](#)).

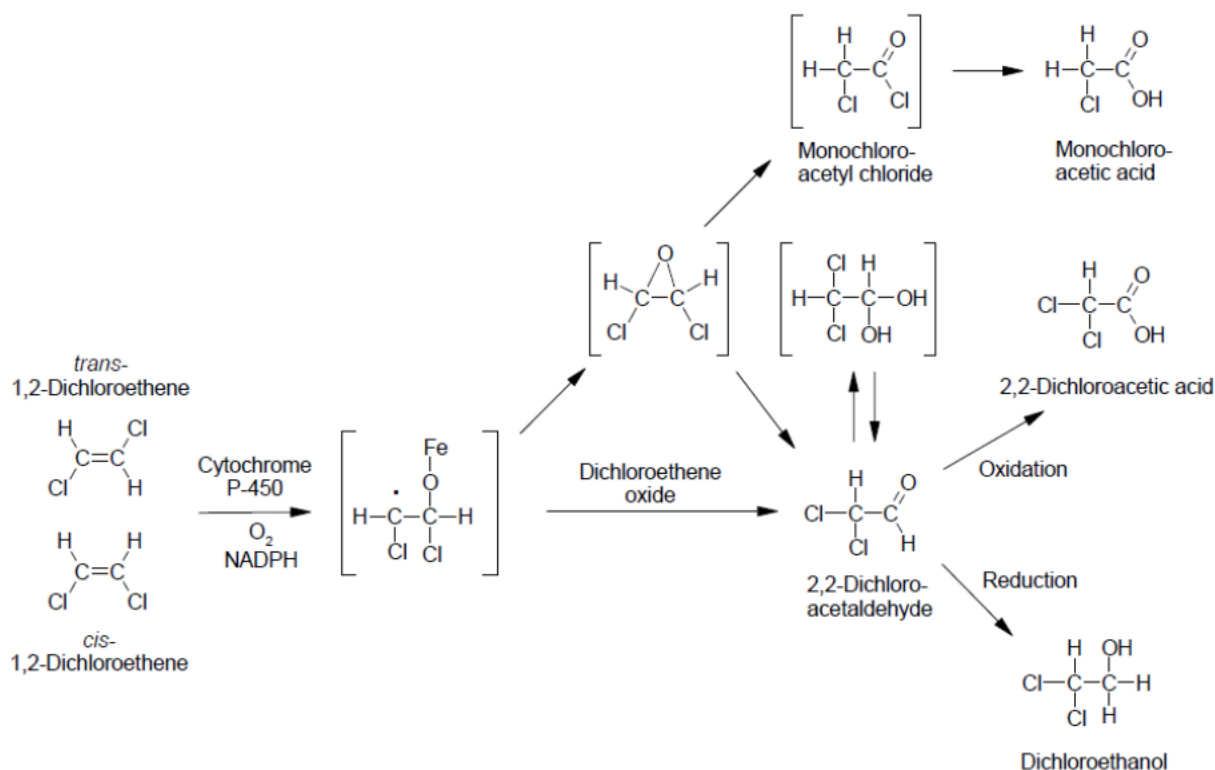


Figure 2-1. Proposed Metabolic Scheme for *cis*- and *trans*-1,2-Dichloroethylene (ATSDR, 2025)

Oral: A high-quality 90-day drinking water study in mice evaluated liver glutathione (GSH) levels, microsomal protein content, and CYP enzyme activity (Barnes et al., 1985). Exposure to *trans*-1,2-dichloroethylene in drinking water resulted in decreased liver GSH levels in males (but not females) and decreased liver microsomal enzyme activity (aniline hydroxylase) in females (but not males).

Inhalation: An *in vivo* inhalation study evaluated hexobarbital sleeping time, zoxazolamine paralysis time, and metabolism of aminopyrine in rats exposed for 8-hours to 200, 600, or 1,000 ppm *trans*-1,2-dichloroethylene (Freundt and Macholz, 1978). There was a dose-dependent increase of the hexobarbital sleeping time and the zoxazolamine paralysis time, suggesting inhibition of oxidative metabolism.

Inactivation of CYP2E1 enzyme activity and subsequent competitive inhibition of the metabolism of other compounds was demonstrated experimentally in rats following pre-exposure to *trans*-1,2-dichloroethylene (Barton et al., 1995). Based on data from gas uptake studies in male Fisher 344 rats, (Clewett and Andersen, 1994) estimated the zero-order enzyme resynthesis rate to be 2.5% of the steady-state activity per hour. The metabolic rate constants for *trans*-1,2-dichloroethylene were estimated for male Fischer 344 rats using a gas uptake method. The zero-order turn-over velocity ($V_{\max}$) of 3.0 mg/hour-kg was first determined by (Gargas et al., 1988) using a suicide inhibition model, which was optimized by assuming that the reactive metabolites produced during metabolism interacted with the enzyme-*trans*-1,2-dichloroethylene complex; this was later updated to 2.49 mg/hour-kg after taking into account both enzyme inhibition and resynthesis (Gargas et al., 1990). Csandy (1995) reported an experimentally derived $V_{\max}$ in rats of 7 $\mu\text{mol/hour per kg}$, which was consistent with the zero-order $V_{\max}$ reported for rats by (Filser and Bolt, 1979), but no additional details of the study methods were provided. Lilly (1998) optimized the rate constants to obtain the best fit of gas uptake results using different models of enzymatic inhibition, which indicated suicide inhibition (a form of enzyme inactivation in which the compound inhibits its own metabolism), was the most likely mechanism of

CYP2E1 inhibition by *trans*-1,2-dichloroethylene. The inhibitory effect on oxidative CYP enzymes indicates that *trans*-1,2-dichloroethylene is expected to exhibit time- and dose-dependent effects attributable to its suicide inhibition, or mechanism-based inactivation, of CYP enzymes, which leads to self-limiting bioactivation. As a result, the formation of reactive oxidative metabolites is initially high but declines as the enzyme is inactivated, resulting in a time-dependent decrease in formation and a nonlinear relationship between dose/duration and metabolite exposure at the site of action. In addition, recovery of enzyme activity requires new enzyme (protein) synthesis, which additionally contributes to time-dependency.

In contrast to the oral route, GSH conjugation is not expected to play a role in *trans*-1,2-dichloroethylene metabolism via the inhalation route; no changes in the levels of nonprotein sulfhydryl were observed in the livers of Sprague-Dawley (SD) rats exposed to *trans*-1,2-dichloroethylene gas (Barton et al., 1995). The formation of the DCA metabolite *in vivo* was indirectly supported by the production of acetone in a closed-system inhalation study, in which rats were exposed to 3,000 ppm or more for up to 50 hours (allowing for zero-order metabolism); DCA and other haloacetic acids are typically associated with acetonemia—though the mechanisms are poorly understood (Filser et al., 1982).

Dermal: EPA did not identify *in vivo* animal data that evaluated metabolism of *trans*-1,2-dichloroethylene by the dermal route of exposure. Given the limited dermal absorption (approximately 1%), the contribution of metabolism via dermal exposure is likely not significant.

Other Routes: Strain-specific inhibition of CYP activities by *trans*-1,2-dichloroethylene has also been demonstrated in rats treated intraperitoneally (Nakahama et al., 2000; Hanioka et al., 1998; Mathews et al., 1998). These studies also suggest organ specificities as well as differences in inhibition of metabolism based on exposure route and rodent strain. CYP3A, but not CYP2E1, was suppressed in liver microsomes of Wistar rats injected with *trans*-1,2-dichloroethylene either once at 500 mg/kg, or for 4 consecutive days at 727 mg/kg-day (Nakahama et al., 2000; Hanioka et al., 1998); however, in male F344 rats intraperitoneally injected, albeit at a lower dose (100 mg/kg), inhibition of CYP2E1 was observed with no changes in CYP3A (Mathews et al., 1998). These studies also suggest organ specificities in the expression and activity of *trans*-1,2-dichloroethylene metabolism. Wistar rats intraperitoneally injected once with *trans*-1,2-dichloroethylene demonstrated suppressed CYP2B activity and protein levels in lung microsomes (Nakahama et al., 2000) but not in liver microsomes. In the same study, CYP2E1 activity and proteins levels were decreased in liver microsomes and not detected in lung microsomes.

An *in vivo* study evaluated species, sex, and tissue specificity of CYP2B1-mediated induction of enzyme activity (measured as pentoxyresorufin *O*-dealkylase [PROD] activity) in liver, kidney, and lung microsomes from rats, mice, and hamsters treated with *trans*-1,2-dichloroethylene via intraperitoneal injection (Paolini et al., 1995). Rats and mice demonstrated increased CYP2B1 enzyme activity in all tissues. In hamsters, CYP2B1 activity was only significantly increased in the liver. While sex differences were not compared for statistical significance, *trans*-1,2-dichloroethylene-induced enzymatic activity of males was generally higher in liver and lung and lower in kidney of mice, with essentially no sex difference in rats. In hamsters, male liver activation was greater while female kidney and lung activation was greater.

Conclusion

Although *trans*-1,2-dichloroethylene is metabolized into various oxidative moieties including a reactive epoxide intermediate, the predominant metabolic outcome is inhibition, whereby *trans*-1,2-

dichloroethylene reaction with oxidative CYP enzymes leads to subsequent inhibition of those enzymes and overall reduction in oxidative metabolic activity. This response appears to vary across organs, species, and study design, with CYP2E1 as the major target of suicide inhibition.

2.2.4 Elimination

There is limited excretion data available for *trans*-1,2-dichloroethylene. No studies on the elimination of *trans*-1,2-dichloroethylene in animals or humans were identified. The downstream metabolism and subsequent elimination of the DCA metabolite has been described (see the Integrated Risk Information System [IRIS] *Toxicological Review for Dichloroacetic Acid* ([U.S. EPA, 2003c](#))). DCA is metabolized to glyoxylate through oxidative dichlorination catalyzed by GSTZ. The glyoxylate is then oxidized to oxalate that can then be excreted in urine or will eventually form serine by transamination into glycine followed by transfer of a formyl group. DCA can also be metabolized to form carbon dioxide ([Costa and Ivanetich, 1984, 1982](#)). Trace amounts of dichloroethanol are expected to be exhaled.

PBPK Model Considerations

Several physiologically-based pharmacokinetic (PBPK) models for *trans*-1,2-dichloroethylene have been described; however, there is uncertainty extrapolating to humans due to the lack of human data on *trans*-1,2-dichloroethylene. Filser ([1979](#)) used a simplified compartmental model to describe the distribution and elimination of *trans*-1,2-dichloroethylene following inhalation exposure but did not account for CYP inhibition. Gargas ([1990](#)) later used a model including CYP2E1 suicide inhibition and resynthesis of the enzyme during exposure. Lilly ([1998](#)) generated a four-compartment model for inhalation exposure that included the liver, fat, and slowly and rapidly perfused tissues and that used kinetic constants from experimentally obtained animal data that also accounted for inhibition and resynthesis. Using a simulated steady-state model that included parameters for alveolar ventilation, cardiac output, liver blood flow, blood:air and liver:blood partition coefficients, and first order metabolism clearance coefficients ($V_{\max}/K_m$), ([Aylward et al., 2010](#)) extrapolated the rat model to humans to predict a blood/dose inhalation slope of 1.9 $\mu\text{g/L}$ per mg/m^3 , and an oral slope of 3.4 $\mu\text{g/L}$ per $\text{mg}/\text{kg}\cdot\text{day}$. Finally, ([Peyret and Krishnan, 2012](#)) used animal data from multiple volatile organic compounds (VOCs) to develop quantitative property-property relationship (QPPR) models to predict human clearance coefficients ($V_{\max}/K_m$).

It is expected that these values could be incorporated into PBPK models for humans to simulate blood concentration profiles; however, there is no model currently available that integrates these parameters into a validated model usable for human health risk assessment. Instead, the Agency relied on standard approaches based on EPA guidance for dosimetry across species and route-to-route extrapolations (Section 2.3.2.2).

2.3 Non-Cancer Hazard Assessment

The sections below describe adverse outcome and mechanistic data available, evidence integration, and weight of scientific evidence conclusions for the most relevant human health hazard outcomes for *trans*-1,2-dichloroethylene. Based on review of existing assessments (see Section 2.1.2), EPA focused on hazard identification and evidence integration of sensory irritation, immunotoxicity, and hepatic toxicity, which are the most well-supported human health hazard outcomes associated with *trans*-1,2-dichloroethylene.

Full details on all evaluated health outcomes from all key studies are in *Draft Data Extraction Information for Environmental and Human Health Hazard Animal Toxicology and Epidemiology for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026d](#)). Data quality evaluation results can be found in *Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for trans-1,2-*

Dichloroethylene ([U.S. EPA, 2026m](#)) and *Data Quality Evaluation Information for Human Health Hazard Epidemiology for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026n](#)). Additional details for key studies are provided in the dose-response analysis (Section 2.3.2).

2.3.1 Hazard Identification for Critical Human Health Hazard Outcomes

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 *trans*-1,2-dichloroethylene.

2.3.1.1 Sensory Irritation and Acute Solvent Neurotoxicity

2.3.1.1.1 Human Evidence

EPA identified a single epidemiological study that evaluated potential sensory irritation hazards following *trans*-1,2-dichloroethylene exposure.

Two human subjects were exposed to 275 to 2,220 ppm of *trans*-1,2-dichloroethylene for 5 to 30 minutes. Subjects exposed to 275 ppm did not exhibit any effect at 5 minutes. At 825 ppm slight dizziness after 5 minutes from a 10-minute exposure was identified. Slight burning of the eyes was observed at a concentration of 950 ppm at a 5-minute exposure duration and also seen at 30 minutes due to the 1,000 ppm exposure and at 10 minutes due to a 1,200 ppm exposure concentration of *trans*-1,2-dichloroethylene. Symptoms such as dizziness occurred at concentrations of 1,000 to 2,200 ppm increasing in severity with concentration, drowsiness occurred at 1,200 ppm, intracranial pressure and nausea were noted at 1,700 and 2,200 ppm. The purity of the test substance was not reported, and accurate measurement of exposure concentrations is uncertain. No additional information on exposure conditions was reported ([U.S. EPA, 2022](#); [Lehmann and Schmidt-Kehl, 1936](#)).

2.3.1.1.2 Laboratory Animal Evidence

EPA identified acute, short-term, and subchronic studies indicating sensory irritation and solvent neurotoxicity following *trans*-1,2-dichloroethylene exposure.

Inhalation

Animal studies showed *trans*-1,2-dichloroethylene inhalation exposure can cause eye irritation. A high-quality developmental toxicity study in rats evaluated clinical signs of ocular irritation in dams exposed by whole-body inhalation at 2,000, 6,000, or 12,000 ppm on gestation days (GD) 7 to 16 ([Hurtt et al., 1993](#)). Concentration-related increases in the incidence of lacrimation (at all concentrations) and periocular staining ($\geq 23,800$ mg/m³ [6,000 ppm]) were observed. These clinical signs were assessed before and after each dose administration and gross postmortem examinations (GD 22) were stated to be consistent with clinical findings; incidence data was reported per animal (15/24 at 2,000 ppm, 22/24 at 6,000 ppm, and 24/24 at 12,000 ppm) and did not specify if that was during or after exposure. In a range finding component of the same study ([Hurtt et al., 1993](#)), at 6,000 and 12,000 ppm dams demonstrated evidence of narcosis (incoordination) immediately following exposure—a sign of solvent neurotoxicity analogous to the dizziness reported in the human study. Clinical signs consistent with central nervous system (CNS) depression include lethargy and salivation, which was observed in the 12,000 ppm dose group ([Hurtt et al., 1993](#)).

A study in New Zealand White rabbits ([DuPont, 1988b](#)) further supports eye irritation after installation of 0.01 mL *trans*-1,2-dichloroethylene (99.64% pure) into the lower conjunctival sac induced irritation, including transient moderate iritis and conjunctivitis in both washed and unwashed eyes. In addition, the eye washed for 1 minute after 20 seconds of *trans*-1,2-dichloroethylene exposure severe corneal opacity

and moderate to severe corneal injury, which persisted for 2 days following exposure and first resolved at day 3. In contrast, an inhalation study in male and female rats reported no lacrimation or other clinical signs of ocular irritation, ophthalmological lesions, and histopathology changes in the eyes or lacrimal glands at exposure concentrations up to 4,000 ppm (15,900 mg/m³) (DuPont Haskell Lab, 1998). Veterinary ophthalmologists examined both eyes of each animal via focal illumination and indirect ophthalmoscopy prior to exposure and on all surviving rats on days 90 and 91 of the study. Clinical signs indicating solvent neurotoxicity were not evaluated by a functional observational battery to identify chemical-induced sensory impairment. A statistically significant, dose-responsive increase in wet/stained perineal areas in female rats exposed to 1,000 or 4,000 ppm was observed; however, the authors noted that the effect was transient and may merely be due to the stress of the experimental procedure.

Dermal

A study in rabbits evaluated skin irritation 24, 48, and 72 hours following occluded topical exposure to 630 mg/kg *trans*-1,2-dichloroethylene and reported mild to moderate erythema in rabbits after 48 hours (DuPont, 1988c). More severe dermal effects were reported in another DuPont study in rabbits, including edema, necrosis, fissuring, and epidermal scaling, in rabbits after occluded dermal exposure to 5,000 mg/kg *trans*-1,2-dichloroethylene for 24 hours (DuPont, 1988a).

Oral

An acute oral gavage lethality study in mice administered observed clinical signs of neurotoxicity at 1,600, 2,000, 2,400, 2,800, 3,000, and 3,500 mg/kg (LD50 = 2,122 mg/kg in male mice or 2,391 mg/kg in female mice). Observations in the 10 days after dosing included decreased activity, ataxia, impaired righting reflex, and hunchback appearance (Barnes et al., 1985). Decreased activity and ruffled fur were observed at the lower end of this range at 1,600 to 2,400 mg/kg within 2 hours of dosing. Males were affected more than females, and no clinical signs were reported at the 800 or 1,200 mg/kg dose levels. Effects seen at doses approaching and beyond the LD50 range might represent non-specific overt toxicity, however.

2.3.1.1.3 Mechanistic and Supporting Evidence

Although lacrimation and ocular discharge in rats are likely indicating ocular irritation, signs of solvent neurotoxicity seen in humans (Lehmann and Schmidt-Kehl, 1936) suggest that neurological responses might be involved. There is evidence in rats that lacrimation can involve a neurological response as lacrimation in response to bright light involved trigeminal neuronal signaling (Okamoto et al., 2012). While there is no indication of *trans*-1,2-dichloroethylene targeting the cholinergic system, the observed symptoms of lacrimation and salivation (and potential urination indicated by wet perineal areas) could be associated with overactive acetylcholine and overactivation of muscarinic/nicotinic receptors (Adeyinka and Kondamudi, 2020). More likely, the anesthetic/depressive symptoms reported in both rats (Hurt et al., 1993; DuPont, 1988b) and humans (Lehmann and Schmidt-Kehl, 1936) are indicative of generalized CNS depression common to many organic solvents (Van Thriel and Boyes, 2022).

2.3.1.1.4 Evidence Integration Summary and Conclusions

There is *slight* human evidence for sensory irritation and solvent neurotoxicity based on a 90-year old case study of human volunteers (Lehmann and Schmidt-Kehl, 1936). The evidence in animals is *moderate* based on high-quality studies in rats and rabbits that assessed ocular irritation (Hurt et al., 1993; DuPont, 1988b). The evidence in animals is *moderate* based on high quality studies in rats and rabbits that assessed sensory irritation. The irritation was shown to persist for 2 days after a direct single exposure in rabbits (DuPont, 1988b) before resolving on day 3. Irritation persisted until termination 6 days after a more prolonged inhalation exposure (6 hour/day, 10 days) in rats (Hurt et al., 1993).

Inhalation studies in rats showed lacrimation in pregnant rats, but no effects in non-pregnant female or male rats exposed at higher concentrations for longer duration. Eye instillation in rabbits resulted in irritation. Mild-to-severe dermal effects were observed in two rabbit studies after 24 hours of occluding dermal exposure (DuPont, 1988c). There is slight human evidence and slight-to-moderate animal evidence for sensory irritation and CNS depression/solvent neurotoxicity. A summary of the database including strengths and weaknesses and evidence integration conclusions is presented in Table 2-2.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse sensory irritation effects, dose-response analysis is considered appropriate for assessing sensory irritation and acute neurotoxicity.

Table 2-2. Evidence Integration Summary Table for Sensory Irritation and Acute Neurotoxicity Effects

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence in studies of exposed humans considered for deriving toxicity values			
• A single case report on 2 volunteers exposed via air (U.S. EPA, 2022; Lehmann and Schmidt-Kehl, 1936).	• Dose- and duration-responsive outcomes noted for eye irritation and solvent neurotoxicity effects over only minutes of exposure to <i>trans</i>-1,2-dichloroethylene in air (U.S. EPA, 2022; Lehmann and Schmidt-Kehl, 1936).	• Only 2 subjects with subjective reporting of symptoms. • Study is 90 years old with questionable scientific validity, scored Low for data quality (U.S. EPA, 2022; Lehmann and Schmidt-Kehl, 1936).	<i>Overall wieght of scientific evidence (WOSE) judgement for sensory irritation and solvent neurotoxicity effects based on human evidence:</i> • Slight for effects on eye irritation and CNS depression.
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
• High-quality inhalation developmental toxicity study in rats (Hurtt et al., 1993). • High-quality 90-day inhalation study in male and female rats (DuPont Haskell Lab, 1998). • High-quality single eye instillation study in rabbits (DuPont, 1988b). • High-quality single dermal application study in rabbits (DuPont, 1988c). • Single dermal application study in rabbits (DuPont, 1988a). • Medium quality oral lethality study in mice (Barnes et al., 1985).	<i>Effects on eye</i>		<i>Overall WOSE judgement for sensory irritation and acute neurotoxicity effects based on animal evidence:</i> • Moderate for effects on lacrimation/eye irritation identified in two species by two administration routes. • Moderate for effects on dermal erythema. • Slight-to-moderate for solvent neurotoxicity.
	• Concentration-related increases in the incidence of lacrimation (at ≥7,930 mg/m³ [2,000 ppm]) and periocular staining (≥23,800 mg/m³ [6,000 ppm]) observed in pregnant rats (Hurtt et al., 1993). • Instillation of 0.01 mL <i>trans</i>-1,2-dichloroethylene in the eyes of rabbits induced irritation (DuPont, 1988b). • <i>High</i> quality studies.	• No lacrimation or other clinical signs of ocular irritation, no treatment-related ophthalmological lesions, and no histopathology changes in the eyes or lacrimal glands of rats reported in a 90-day inhalation study (DuPont Haskell Lab, 1998).	
	<i>Effects on skin</i>		
	• Mild to moderate erythema in rabbits 48 h after dermal application (DuPont, 1988c). • Severe erythema in rabbits 24 h after dermal application rabbits (DuPont, 1988a).		
	<i>Neurological effects</i>		

Database Summary	Factors that Increase Strength	Factors that Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
	- Lacrimation, salivation, and lethargy in female dams exposed via inhalation (Hurt et al., 1993). - Dose-responsive increase in wet perineal area in one inhalation study potentially indicating urination (DuPont Haskell Lab, 1998). - Clinical signs of acute neurotoxicity in an LD50 study (Barnes et al., 1985).	- Effects not consistent across studies and primarily at very high concentrations. - Perineal wetness only observed in females and was transient (DuPont Haskell Lab, 1998).	
Evidence in mechanistic studies and supplemental information			
- No direct evidence available. - Indirect connections between observed clinical signs.	- Indirect connections between observed clinical signs and trigeminal neuronal signaling or the cholinergic system. - Solvent neurotoxicity resulting in depressive symptoms is a common phenomenon from volatile organic chemicals (Van Thriel and Boyes, 2022).	No mechanistic evidence indicates potential activation of muscarinic or nicotinic receptors.	<i>Overall WOSE judgement for sensory irritation and acute neurotoxicity effects based on mechanistic evidence:</i> Indeterminate-to-slight

2.3.1.2 Immunological and Hematological

2.3.1.2.1 Human Evidence

EPA did not identify epidemiological studies that evaluated any potential immunological or hematological hazards for *trans*-1,2-dichloroethylene.

2.3.1.2.2 Laboratory Animal Evidence

EPA identified short-term, subchronic, and chronic oral and inhalation studies indicating immunological or hematological effects following *trans*-1,2-dichloroethylene exposure.

Oral

Immune Effects: In a high-quality 14-day oral gavage study ([Shopp et al., 1985](#)), male mice administered up to 210 mg/kg-day demonstrated a decrease of 29% in producing IgM antibody forming cells (AFCs)/spleen against sheep red blood cell (sRBC), trending towards immune suppression at the highest dose, but did not reach statistical significance. The magnitude of this decrease suggests potential concern for the effect at longer exposure duration or higher doses. Spleen weight mirrored the AFC response, with a non-significant reduction of approximately 20% at 210 mg/kg-day. A smaller change of only 9% at the highest dose was reported for AFC/10⁻⁶ cells, suggesting that much of the observed change was due to reduced spleen size. The 14-day results are not considered reliable for measures of humoral immunity, as EPA published testing guidelines ([OPPTS 870.7800](#)) recommend a minimum of 28 days exposure for AFC assays. No effects on cell-mediated (*i.e.*, antibody-independent) immune response were observed. Overall, no significant findings for any measure of functional immunity were identified from the 14-day study.

The same publication included a high-quality 90-day drinking water study in mice that demonstrated statistically significant suppression of humoral immunity in male mice exposed to 0.1, 1.0, or 2.0

mg/mL of *trans*-1,2-dichloroethylene *ad libitum* was equivalent to time-weighted average doses of 17, 175 or 387 mg/kg/day *trans*-1,2-dichloroethylene. This derivation of dosing was based on calculated water consumption rate with less than 10% of *trans*-1,2-dichloroethylene lost during the 3 to 4 days between bottle changes confirmed by gas-liquid chromatography, as described in a prior publication ([Barnes et al., 1985](#)). Additionally, fluid consumption was comparable between treatment groups and the control group treated with deionized water, suggesting no aversion and palatability issues to the test chemical. Together, these findings indicate that chemical volatility and palatability, concerns raised during Science Advisory Committee on Chemicals (SACC) review for similar studies performed from the same laboratory on 1,1-dichloroethane ([EPA-HQ-OPPT-2024-0114-0086](#)) do not apply to this 90-day drinking water study ([Shopp et al., 1985](#)), and the actual delivered dose is likely not substantially different than the nominal dose.

Dose-related reductions in splenic IgM AFCs against sheep red blood cells were observed in male (but not female) mice, with a statistically significant reduction in AFCs/spleen (normalized per spleen) at all doses (maximum of 36% reduction at the high doses) and in AFCs/ 10^{-6} cells (normalized to the number of total cells in one spleen) at the two highest doses (28% reduction at the highest dose). There was also a 15 to 19% reduction in spleen weight observed in males at day 4 following antigen presentation ([Shopp et al., 1985](#)). While the text narrative of the manuscript switched references to AFCs/spleen and AFCs/ 10^{-6} cells in male mice, the narrative for female mice makes it clear that the data tables are correct. This is consistent with the study interpretation by ([U.S. EPA, 2010](#)) and ([ATSDR, 2025](#)). Similar results were observed on day 5 post-antigen presentation, with a 37% reduction at the highest dose on a per-spleen basis and 22% reduction per 10^{-6} cells. The biological relevance of the reduced spleen weight is unclear because of a flat dose-response and the changes were not statistically significant. Other tests of humoral immunity did not demonstrate suppression in male or female mice (*i.e.*, hemagglutination, response to lipopolysaccharide). No effects on cell-mediated immunity were observed in male or female mice as evaluated by delayed-type hyper-sensitivity response to sRBCs, popliteal lymph node proliferation responses to sRBC, and spleen cell response to the T-lymphocyte mitogen concanavalin A. The methods as described in ([Shopp et al., 1985](#)) and the sister methodology paper, ([White et al., 1985](#)), are ambiguous on the timing of sRBC immunization, but they suggest that sRBC immunization only occurred *after* the cessation of exposure on day 91 (the study repeatedly references investigating immunity “following” 90 days of exposure). If this was the case, then the study would have reduced sensitivity for detecting immunosuppression since the sRBC immunization and subsequent humoral immunity measurements would be occurring during the recovery period.

In another high-quality 90-day drinking water study, indicators of immune effects were evaluated in male and female mice, including hematology, spleen and thymus weights, and gross necropsy ([Barnes et al., 1985](#)). Decreased absolute and relative thymus weights of 23 to 24% were observed in female mice (but not males) exposed to 452 and 224 (or more) mg/kg-day, respectively. Leukocyte levels were not consistently changed in one direction in either sex (significantly increased in females at 224 but not 452 mg/kg-day), while lymphocytes showed a consistent dose-response but not a statistically significant decrease (as high as 13.5% in males).

No changes in immune cell counts were observed in male rats up to 3,210 mg/kg-day or in female rats up to 3,245 mg/kg-day ([NTP, 2002](#)). Furthermore, no changes in relative thymus weight (spleen weight was not measured) or histopathology of the spleen, thymus, or lymph nodes were observed in male rats up to 3,210 mg/kg-day or in female rats up to 3,245 mg/kg-day. In contrast, immune cell counts were not measured for mice of either sex from dietary exposure to *trans*-1,2-dichloroethylene ([NTP, 2002](#)). Additionally, no effect on relative thymus weight (spleen weight also not measured) or changes in the histopathology of the spleen, thymus, or lymph nodes were observed up to 7,925 or 8,065 mg/kg-day in

male or female mice, respectively, in the National Toxicology Program (NTP) 14-week dietary studies for *trans*-1,2-dichloroethylene ([NTP, 2002](#)).

Hematological Effects: Non-immune hematological parameters such as hematocrit, hemoglobin, platelets, fibrinogen, and erythrocyte counts demonstrated no changes in either sex in the 90-day drinking water study ([Barnes et al., 1985](#)). Prothrombin time was significantly decreased in males however not in a dose-responsive manner, so this effect is not considered relevant. The same study also included a 14-day oral gavage experiment where hematological parameters remained unchanged. No changes in leukocyte counts were also observed in mice of both sexes from dietary exposure ([NTP, 2002](#)).

Studies in rats also demonstrated inconsistent hematological findings. A 90-day drinking water study ([Hayes et al., 1987](#)) showed no effects on hematological parameters, including erythrocyte counts, hematocrit, and hemoglobin in rats exposed at doses up to 2,809 and 3,114 mg/kg-day in males and females, respectively. At similar and lower doses, erythrocyte counts were significantly decreased ($\leq 7\%$ relative to controls) in male rats at doses at or exceeding 380 mg/kg-day (males) in a 14-week dietary exposure study (using microencapsulated *trans*-1,2-dichloroethylene, ([NTP, 2002](#))). Male rats showed dose-related decreases in hematocrit and hemoglobin concentration at doses at or exceeding 770 mg/kg-day. In female rats, hematocrit and blood hemoglobin concentrations were decreased at doses at or exceeding 1,540 mg/kg-day. The 14-week dietary study ([NTP, 2002](#)) dosed animals *trans*-1,2-dichloroethylene in starch microcapsules mixed into the feed with analytically confirmed administered dosages to be within 10% of the target, homogeneous, and stable—though analysis of some batches, animal room feed samples showed significant loss (37–58% in rats, 50–75% in mice). The study authors attributed the loss as due to degradation of the starch microcapsule from moisture condensation or the presence of urine (perhaps due to adding moisture or chemical reaction with the starch microcapsule). The drinking water dose in ([Hayes et al., 1987](#)) was not verified to confirm that *trans*-1,2-dichloroethylene did not volatilize. However, that concern is mitigated for ([Barnes et al., 1985](#)) and ([Shopp et al., 1985](#)) because less than 10% of chemical was lost between bottle changes.

Interpretation of drinking water studies—especially those with negative results—is difficult due to chemical volatility and lack of analytical verification of drinking water concentrations as the actual received doses may have been much lower than estimated, although concern for ([Barnes et al., 1985](#)) and ([Shopp et al., 1985](#)) is mitigated because less than 10% of chemical was lost between bottle changes. Similarly, the negative ([NTP, 2002](#)) study may have overestimated exposure by as high as 4-fold in some samples (meaning the absence of results occurred at lower doses than expected) based on analysis of feed samples.

Inhalation

Inhalation studies were limited to two high-quality studies in rats that demonstrated changes in hematological markers and/or immune cell types in response to *trans*-1,2-dichloroethylene exposures. An inhalation study in six female rats evaluated hematology and spleen histopathology after a single 8-hour exposure and after 1-, 2-, 8-, or 16-week exposures ([Freundt et al., 1977](#)). In the only measurement of immunology outcomes, leukocyte counts were decreased by 23% in female rats exposed to at or exceeding 793 mg/m³ (200 ppm) for 8 hours (no other immunological measures were assayed). Hematology endpoints were examined only for the single 8-hour exposure at 0, 200, and 1,000 ppm *trans*-1,2-dichloroethylene. Female rats exposed to 1,000 ppm for 8 hours (highest dose tested) showed a statistically significant 9% decrease in erythrocyte count, compared to controls, with no effects observed at 200 ppm.

A 90-day inhalation study in male and female rats evaluated hematology and histopathology of spleen, thymus, bone marrow, and mesenteric and mandibular lymph nodes after exposure to 0, 200, 1,000, 4,000 ppm *trans*-1,2-dichloroethylene ([DuPont Haskell Lab, 1998](#)). A statistically significant decrease (26%) in lymphocyte count was reported at 4,000 ppm in male rats. Other immune cells such as neutrophils and monocytes showed inconsistent responses between 45- and 90-day timepoints, while eosinophils demonstrated a non-significant increase. Total white blood cell count (*i.e.*, leukocytes) was significantly reduced at the highest concentration of 4,000 ppm. In females, there was a consistent negative dose-response trend in lymphocytes and overall white blood cells, but statistical significance was only achieved for monocytes following 45 but not 90 days of exposure to 4,000 ppm (eosinophils non-significantly increased at the highest dose). These changes in immune cell levels were not accompanied by histological changes in the spleen, thymus, bone marrow, or lymph nodes at concentrations up to 15,860 mg/m³ (4,000 ppm). No other hematological effects were observed. The evaluation of this study for respiratory tract toxicity is summarized in Section 2.3.1.7.2.

2.3.1.2.3 Mechanistic and Supporting Evidence

Phagocytosis is an important element of innate immunity. An *in vitro* study evaluated the phagocytic activity of mouse peritoneal macrophages exposed to a single dose of *trans*-1,2-dichloroethylene for 15 to 20 hours ([Utsumi et al., 1992](#)). *trans*-1,2-Dichloroethylene decreased phagocytic activity by 28% at 1 mM. It is not known whether the parent *trans*-1,2-dichloroethylene or metabolites have the primary immunosuppressive activity, however the observed “suicide inhibition” of oxidative metabolism by *trans*-1,2-dichloroethylene suggests that metabolism is unlikely to be a major driver of toxicity.

For the isomer *cis*-1,2-dichloroethylene, limited information was available to support the weight of scientific evidence for immunotoxicity. In an oral 90-day gavage study, no effects on immune organs of thymus, spleen, and lymph nodes were identified in male and female rats. No results were provided for leukocyte counts, and there were no other measures of immunity ([McCauley et al., 1995](#)).

2.3.1.2.4 Evidence Integration Summary and Conclusions

The evidence for immunological effects in animals is *moderate* based on high-quality studies that assessed humoral immunity, however with some studies demonstrating null or inconsistent effects even at elevated doses. A drinking water study reported dose-related reductions in T-cell dependent antibody responses in male mice, indicating immunosuppression. However, sex differences in the AFC response and the lack of immune suppression in other tests of humoral immune function (spleen cell response to B cell mitogen lipopolysaccharide and hemagglutination titers) adds uncertainty. Inhalation and dietary studies in rats and mice that evaluated hematology, organ weights, and histopathology, reported slight decreases in erythrocyte and leukocyte counts in some experiments but without consistency across sexes, routes, and studies. Mechanistic evidence for immunological effects was *slight* based on a single *in vitro* study that showed decreased phagocytic activity in mouse macrophages exposed to *trans*-1,2-dichloroethylene. Human evidence is *indeterminate* due to the lack of any relevant human data. There is only *slight* evidence for hematological effects based on mild changes in erythrocytes, hematocrit, and hemoglobin in a single animal study. A summary of the database including strengths and weaknesses and evidence integration conclusions is presented in Table 2-3.

The database shows indications of immunosuppression across most studies, however individual measurements are not consistent across sexes or studies. In an analysis of immune cell assays for risk assessment (this is a review/methods paper that does not discuss *trans*-1,2-dichloroethylene ([Luster et al., 1992](#))), concordance with other evidence of immunotoxicity was among the highest of all immune measures for AFC assays with 78% concordance. This is consistent with AFC assays being considered one of the best predictors of immunotoxicity in mice ([Ladics, 2007](#)). The only measure that scored

higher was lymphocyte cell surface markers (83% concordance). The lack of specific surface markers, along with the high variability seen across these studies, complicates interpretation of the biological significance of those results. Other immune measures such as spleen weight/cellularity and overall leukocyte count did not significantly correlate with immunotoxicity, while reduced relative thymus weight was significant but with reduced concordance relative to the top two measures. The reduced importance of immune cell counts in immunotoxicity risk assessment compared to measures of functional immunity is consistent across public health organizations ([Johnson et al., 2024](#)).

While specific lymphocyte cell surface markers were not utilized, lymphocytes specifically were significantly reduced in males (but not females, though they demonstrated a dose-responsive decrease) in a 90-day inhalation study ([DuPont Haskell Lab, 1998](#)), matching the sex with reduced AFCs following 90 days of oral exposure ([Shopp et al., 1985](#))—albeit in very different study designs, in different species, and at quite different relative dose/concentration levels (17–387 mg/kg-day in drinking water from ([Shopp et al., 1985](#)); 4,000 ppm in air from ([DuPont Haskell Lab, 1998](#))). There was also a dose-responsive decrease in lymphocytes in males (not females) in another 90-day drinking water study ([Barnes et al., 1985](#)), however this did not achieve statistical significance. Females demonstrated more inconsistent responses across studies, with an overall lack of evidence for immune effects other than decreased immune cell types in two studies ([DuPont Haskell Lab, 1998](#); [Freundt et al., 1977](#)) and reduced thymus weight in a single study ([Barnes et al., 1985](#)). Lymphocytes and immune cell weights were not reduced in the 90-day feeding study ([NTP, 2002](#)); however, losses of up to 75% in some batches of microencapsulated *trans*-1,2-dichloroethylene indicate that actual dosing was likely lower than nominal targets. Regardless, there was a lack of any immune effects at dose levels well above the standard limit dose of 1,000 mg/kg-day.

The discussion section from ([Shopp et al., 1985](#)) mentions that the decrease in AFC “was not severe enough to depress the functional ability of the humoral immune system” because a statistically significant change in hemagglutination and the B cell mitogen lipopolysaccharide (LPS) was not observed. These three measures represent different aspects of humoral (antibody-based) immunity, however. LPS activation indicates normal B cell proliferation processes, independent of antibody function or response to a particular antigen, while hemagglutination represents function of total existing antibody independent of when they were created. sRBC-mediated AFC decrease is specific to T cell-dependent antibody responses following antigen presentation ([Malynn and Wortis, 1984](#); [Koller, 1982](#)). The methods for ([Shopp et al., 1985](#)) imply that sRBC immunization only occurred after the 90 days of exposure ceased, with AFC measurements taken after 4 to 5 days of recovery. This differs from 1998 OCSPP immunotoxicity test guidelines ([OPPTS 870.7800](#)) which recommend timing immunization prior to the last day of exposure (*e.g.*, on day 24 of a 28-day study). This could further explain why hemagglutination changes were negative, since that was measured 7 days after immunization, which would add an additional 2 to 3 days of recovery. Therefore, the positive response for reduced IgM AFCs even with potential recovery time is sufficient to indicate potential T cell-mediated immune suppression in mice, especially given the consistent results at day 4 and 5 post-antigen presentation.

Although inconsistent, indications of reduced lymphocytes increase the combined concordance with reduced AFCs for identifying immunotoxicants ([Luster et al., 1992](#)). Studies utilizing lymphocyte cell surface markers would be necessary for determining whether affected lymphocyte levels were T cell-specific, correlating with deficient T-cell dependent antibody responses. In the absence of these data, only indirect connections can be made from the available results. The lack of consistent responses for overall immune cell counts and effects on immune organs along with no effect on other general markers of antibody response suggests that *trans*-1,2-dichloroethylene may target T cell-mediated humoral immunity specifically.

In addition, there is evidence of immune effects from structurally similar chlorinated solvents the *Risk Evaluation for 1,1-Dichloroethane* ([U.S. EPA, 2025c](#)) and the *Risk Evaluation for 1,2-Dichloroethane* ([U.S. EPA, 2026k](#)) considered several studies with immune effects in rodents and concluded that there was suggestive evidence that these chlorinated solvents may cause immune system suppression under relevant exposure conditions. While this endpoint was not selected for POD selection and there were concerns about that specific dataset, the suggestive evidence supports the consistency of immune suppression observed across chlorinated solvents. In the *Risk Evaluation for Perchloroethylene* ([U.S. EPA, 2020c](#)), EPA considered epidemiological and animal studies of immune effects associated with perchloroethylene exposure and determined that “despite some lack of precision and uncertainties in the results of immunotoxicity studies, evidence suggests PCE exposure may lead to immunotoxicity.” While immune suppression was not a critical endpoint, other immune effects (increased immune cells, IgE, IL-4) from a case-control study ([Emara et al., 2010](#)) were considered sufficient for dose-response analysis of perchloroethylene. In the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#)), EPA identified both autoimmunity and immunosuppression in mice and rats ([Selgrade and Gilmour, 2010](#); [Keil et al., 2009](#); [Woolhiser et al., 2006](#); [Kaneko et al., 2000](#); [Sanders et al., 1982](#)) and considered this a target organ system for derivation of the acute and chronic POD (immunosuppression in the form of reduced response to infection was the basis of the acute POD). While these chemicals are structurally similar, they are metabolized to a much greater extent (Section 2.2.3) and the relative role of metabolites in immunotoxicity is uncertain.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse immunological and hematological effects, dose-response analysis is considered appropriate for assessing immunotoxicity. There is insufficient support for other hematological outcomes.

Table 2-3. Evidence Integration Summary Table for Immune/Hematological Effects

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence in studies of exposed humans considered for deriving toxicity values (no data)			• Indeterminate
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
- High-quality 14-day oral gavage study in male mice evaluated cell-mediated and humoral immunity (Shopp et al., 1985). - High-quality 90-day drinking water study in male and female mice evaluated cell-mediated and humoral immunity (Shopp et al., 1985). - High-quality inhalation study in female rats after a single 8-hour exposure and after 1-, 2-, 8-, or 16-week exposures (Freundt et al., 1977). - High-quality 90-day inhalation study in male and female rats (DuPont	<i>Immune Effects</i>		In a high-quality study in mice using a well-established assay, humoral immunity was suppressed in males but not females. Thymus weights, spleen weights, and white blood cell counts and spleen weights were inconsistently impacted, with 1 study showing no effect on these parameters (NTP, 2002). Hematology changes were mild and were not consistently seen across studies. <i>Overall WOSE judgement for immune/hematological effects based on animal evidence:</i> Moderate for immune effects
	- Dose-related reductions in splenic IgM antibody-forming cells (one of the most well-established immunotoxicity functional assays for T cell-dependent humoral immunity) against sheep red blood cells were observed in male (but not female) mice exposed to ≥ 175 mg/kg-day via drinking water for 90 days at both 4 and 5 days post-antigen presentation (Shopp et al., 1985). - Decreased absolute and relative thymus weights of 23–24% were observed in female mice (but not males) exposed to 452 and	<i>trans</i>-1,2-dichloroethylene did not affect cell-mediated immunity or other measures of humoral immunity in male or female mice or any indicator of cell-mediated immunity in mice exposed to as high as 387–452 mg/kg-day in drinking water for 90 days (Shopp et al., 1985). <i>trans</i>-1,2-dichloroethylene did not affect thymus weights in mice exposed via diet to doses up to 8,065 mg/kg-day for 14 weeks or in rats exposed subchronically to doses up to 3,114 mg/kg-day for 90 days in drinking water or by	

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Haskell Lab, 1998). - High-quality 90-day drinking water study in male and female mice (Barnes et al., 1985). - Medium-quality 90-day drinking water study in male and female rats (Hayes et al., 1987). - High-quality dietary study in male and female rats and mice after 14 weeks of exposure (NTP, 2002). - High-quality oral gavage study in male mice after 14 days of exposure (Barnes et al., 1985).	≥224 mg/kg-day, respectively, in drinking water for 90 days (Shopp et al., 1985). - Leukocyte counts were decreased in female rats exposed to ≥793 mg/m³ (200 ppm) for 8 hours (DuPont Haskell Lab, 1998). - Lymphocytes were reduced by 26% in male rats exposed to 4,000 ppm for 90 days (DuPont Haskell Lab, 1998).	diet to doses up to 3,245 mg/kg-day for 14 weeks (though delivered dose levels in diet may have been overestimated) (NTP, 2002). <i>trans</i>-1,2-dichloroethylene did not alter the histology of the spleen, thymus, bone marrow, or lymph nodes in rats exposed via inhalation to concentrations up to 15,860 mg/m³ (4,000 ppm) for up to 90 days (DuPont Haskell Lab, 1998), or in mice or rats exposed via diet to doses up to 8,065 mg/kg-day for 14 weeks (NTP, 2002).	Slight for hematological effects
	Blood Effects		
	- Erythrocyte counts were decreased in female rats exposed to 3,965 mg/m³ (1,000 ppm) by inhalation for 8 hours (DuPont Haskell Lab, 1998). - Erythrocyte counts were slightly decreased (≤7%, compared to controls) in rats exposed via diet at doses ≥380 mg/kg-day (males) or ≥1,580 mg/kg-day (females) for 14 weeks (NTP, 2002). In the same study, rats of both sexes showed decreases in hematocrit and/or hemoglobin concentration at doses ≥770 mg/kg-day (males) or ≥1,540 mg/kg-day (females) (NTP, 2002).	No other relevant hematological effects were observed in mice exposed by gavage for 14 days (Barnes et al., 1985), in rats exposed by inhalation for 90 days (DuPont Haskell Lab, 1998), in mice or rats exposed via drinking water for 90 days (Shopp et al., 1985; Barnes et al., 1985), or in mice exposed by diet for 14 weeks (NTP, 2002).	
Evidence in mechanistic studies			
An <i>in vitro</i> study evaluated phagocytic activity of mouse peritoneal macrophages exposed to <i>trans</i>-1,2-dichloroethylene for 15-20 hours (Utsumi et al., 1992).	<i>trans</i>-1,2-dichloroethylene decreased phagocytic activity by 28% in mouse peritoneal macrophages at 1mM (Utsumi et al., 1992).	The database lacks studies specifically designed to identify mechanisms of the observed immune and hematological effects.	The available data are limited to a single <i>in vitro</i> experiment showing a decrease in phagocytosis in macrophages exposed to <i>trans</i>-1,2-dichloroethylene. <i>Overall WOSE judgement for immune/hematological effects based on mechanistic evidence:</i> Slight

2.3.1.3 Hepatic

2.3.1.3.1 Human Evidence

EPA did not identify epidemiological studies that evaluated any potential hepatic hazards for *trans*-1,2-dichloroethylene.

2.3.1.3.2 Laboratory Animal Evidence

EPA identified acute, short-term, subchronic, and chronic studies evaluating potential hepatic effects following *trans*-1,2-dichloroethylene exposure.

Inhalation

A high-quality inhalation study in male and female rats exposed to concentrations of 0, 200, 1,000, or 4,000 ppm *trans*-1,2-dichloroethylene for 90 days evaluated serum chemistry. Serum chemistry measures of liver damage included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), sorbitol dehydrogenase (SDH), bilirubin, albumin, cholesterol, and total protein. Liver weight and liver histopathology were also tested ([DuPont Haskell Lab, 1998](#)). No treatment-related changes in liver histopathology or increases in serum liver enzymes (ALT, ALP, and AST) were observed in male and female rats. Notably, serum glucose levels were elevated in male (19%) and female (17%) rats at 4,000 ppm at 90 days, with the increase in males (18%) starting at Day 45. An acute inhalation lethality study in male and female rats further supports no adverse liver effects via inhalation after a single 4-hour exposure to 48,767 mg/m³ (12,300 ppm) *trans*-1,2-dichloroethylene showed no changes in histopathology ([\[Redacted\], 1999](#)).

Oral

Oral exposure studies in rodents showed inconsistent hepatic toxicity. Acute and short-term studies in mice and rats demonstrated no effects on serum chemistry and/or liver weight ([Nakahama et al., 2000](#); [Hanioka et al., 1998](#); [Jenkins et al., 1972](#)).

In contrast, subchronic and chronic studies demonstrated changes in liver weight or serum chemistry although these changes were inconsistent in directionality across studies. A 14-week NTP dietary study reported increased, but not dose-responsive, relative liver weights in female rats (5.5–9.6% above control) at ≥ 395 mg/kg-day, and male (8.9–14% above control) and female (11% above control) mice at ≥ 1900 and $\geq 3,760$ mg/kg-day, respectively ([NTP, 2002](#)). No differences from control were observed in male rats. Liver necrosis was observed in a female mouse at each of the 1,830 and 7,925 mg/kg dose levels, with an increase in serum ALT in females reaching 197% of controls at 1,830 mg/kg-day. Neither of these outcomes were observed consistently or in a dose-responsive manner across sexes or species and they were generally observed only at very elevated doses well above a typical limit dose of 1,000 mg/kg-day. There is suspected loss of *trans*-1,2-dichloroethylene from microencapsulation pellets however as reported in the study, so nominal dosing is not reliable and the true average daily dose is likely lower.

A 14-day oral gavage experiment in male mice by ([Barnes et al., 1985](#)) with doses of 21 mg/kg-day and 210 mg/kg-day indicated a non-statistically significant *decrease* in absolute and relative liver weight in male mice following 14 days of 210 mg/kg-day; the biological relevance of this, however, is unclear. In a high-quality drinking water study in mice also in ([Barnes et al., 1985](#)), serum chemistry (ALP, AST, ALT, lactate dehydrogenase [LDH], protein, cholesterol) and liver weight were evaluated after 90 days of exposure to 17, 175 or 387 mg/kg-day (in males, female doses were slightly higher) ([Barnes et al., 1985](#)). In this 90-day study, significant increases in serum glucose (27, 20 and 24%) were also seen in male mice at 17, 175 and 387 mg/kg-day, respectively compared to control. Significant increases in

serum ALP were seen at 175 and 375 mg/kg-day (62% and 33%, respectively) and a significant decrease in liver glutathione (21%) at 375 mg/kg/day, but no exposure related changes in gross pathology. Relative organ weights did not indicate a dose-responsive change different from control at 17 mg/kg/day, but a significant increase in relative liver weight (8%) was observed at 175 mg/kg/day but not in the highest dosage of 375 mg/kg/day in male mice. In female mice, significant *decreases* in serum ALT (33 and 39%) and AST (27 and 36%) were seen at 224 and 452 mg/kg/day, respectively; the biological significance of decreased liver enzymes is unclear and exposure related changes in gross pathology were not observed in male or female mice. Female mice also showed increases in serum glucose at 23 (28%), 224 (20%) and 452 (28%) mg/kg/day.

In another subchronic drinking water study of similar duration in rats, no effects on serum chemistry (ALT, ALP, AST, 5'-Nucleotidase [5'-NT], protein, cholesterol, bilirubin) or statistically significant liver weight or histopathology changes were observed, although a non-significant 15% increase in relative liver weight was seen in males at the highest dose (3,114 mg/kg-day) after 90 days of exposure ([Hayes et al., 1987](#)). However, there are uncertainties related to the actual doses received due to chemical volatility and lack of analytical verification of drinking water concentrations.

2.3.1.3.3 Mechanistic and Supporting Evidence

An inhalation study in female Wistar rats evaluated serum chemistry (ALP, AST, ALT, cholesterol, albumin, total protein) and liver histopathology up to 16 weeks after exposure (8 hours/day, 5 days/week, for 1-, 2, 8-, or 16 weeks) ([Freundt et al., 1977](#)). Incidences of fat accumulation and degeneration in liver lobules and Kupffer cells were increased with exposure duration after exposure to 793 mg/m³ (200 ppm) for up to 16 weeks. This study did not contain detailed analyses and only tested a small number of animals (n = 6)

An acute gavage study in male rats evaluated activities of liver enzymes (glucose-6-phosphatase and tyrosine transaminase) after a single exposure ([Jenkins et al., 1972](#)). Exposure of male rats to *trans*-1,2-dichloroethylene resulted in a statistically significant decrease in liver tyrosine transaminase activity at the highest dose (1,500 mg/kg) and an increase in liver glucose-6-phosphatase (G6P) activity at 400 mg/kg. Liver G6P is a key regulatory enzyme in generating glucose and maintaining blood glucose levels. Exposure of mice to the highest dose of 387 mg/kg/day *trans*-1,2-dichloroethylene in drinking water for 90 days resulted in decreased liver GSH levels in males (but not females), without consistent effects on microsomal protein in either sex ([Barnes et al., 1985](#)).

2.3.1.3.4 Evidence Integration Summary and Conclusions

There are *indeterminate* human evidence and mechanistic support to assess hepatic toxicity. The database lacks animal studies specifically designed to identify mechanisms of hepatic effects. The evidence in animals is *slight* because findings were not consistently dose-responsive and usually only one indicator of toxicity was observed (*e.g.*, only liver weight or serum enzymes but not both). These studies include inhalation, gavage, dietary, drinking water, and intraperitoneal injection exposures. The findings suggest some changes in liver weight and serum chemistry, but consistent histopathological changes in the liver were not observed across studies. In one inhalation study, increased incidences of hepatic fat accumulation were observed in rats exposed to *trans*-1,2-dichloroethylene, but other rat inhalation studies did not show changes in hepatic histopathology. High-quality dietary studies in rats and mice showed some increases in liver weights, but in the absence of serum chemistry and histopathology changes. Increases in serum glucose and liver enzymes were observed in rats and mice in inhalation and oral 90-day studies, respectively, and an increase in liver G6P activity was observed in an acute gavage study in male rats suggesting changes in glucose homeostasis. However, the biological significance for metabolic impacts remains unclear without additional evidence. Interpretation is further

complicated by a lack of analytical verification of delivered doses in drinking water studies. A summary of the database including strengths and weaknesses and evidence integration conclusions is presented in Table 2-4.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse liver effects, dose-response analysis *is not* considered appropriate for assessing liver toxicity. While some studies demonstrated multiple parameters indicating liver toxicity, other studies were conflicting and, in some cases, even demonstrated responses in the opposite direction.

Table 2-4. Evidence Integration Summary Table for Hepatic Effects

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence in studies of exposed humans considered for deriving toxicity values (no data)			• Indeterminate
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
• High-quality inhalation lethality study in rats ([Redacted], 1999). • High-quality 90-day inhalation study in rats (DuPont Haskell Lab, 1998). • Medium-quality gavage study in male rats (Jenkins et al., 1972). • High-quality 14-week dietary studies in rats and mice (NTP, 2002). • High-quality 90-day drinking water study in mice (Barnes et al., 1985). • Medium-quality 90-day drinking water study in rats (Hayes et al., 1987). • Medium-quality intraperitoneal injection study in male rats (Nakahama et al., 2000). • High-quality intraperitoneal injection study in rats (Hanioka et al., 1998). • High-quality gavage study in male mice (Barnes et al., 1985).	• In dietary studies, absolute and relative liver weights were increased in female rats, but not in male rats, at ≥ 395 mg/kg-day and relative (but not absolute) liver weights were increased in male and female mice at $\geq 1,900$ and $\geq 3,760$ mg/kg-day, respectively, after 14 weeks of exposure (NTP, 2002). • In oral and inhalation studies in mice and rats, serum glucose levels were increased in both males and females after 90 days (DuPont Haskell Lab, 1998). • Evidence of necrosis in female mice (NTP, 2002). • High-quality studies.	• Rat inhalation studies did not show changes in hepatic histopathology (DuPont Haskell Lab, 1998; [Redacted], 1999). • No liver histopathology or serum chemistry changes were seen in rats or mice exposed via diet for 14 weeks (NTP, 2002). • Most observed outcomes were not dose-responsive and/or were not consistently seen across sexes and species.	High-quality dietary studies in rats and mice showed some increases in liver weights, but in the absence of serum chemistry and histopathology changes are not considered adverse. <i>Overall WOSE judgement for hepatic effects based on animal evidence:</i> • Slight
Evidence in mechanistic studies			
• High-quality inhalation study in female rats (Freundt et al., 1977). • High-quality 90-day drinking water study in mice (Barnes et al., 1985). • Medium-quality acute oral gavage study in male rats	• Incidences of fat accumulation in liver lobules and Kupffer cells were increased with exposure duration after exposure to 793 mg/m³ (200 ppm) for up to 16 weeks in Wistar rats (Freundt et al., 1977). • Exposure of mice to <i>trans</i>-1,2-	• The database lacks studies specifically designed to identify mechanisms of hepatic fat accumulation. • Group sizes (n = 6) were small and incidences of fat	A single inhalation study in rats showed increased incidences of hepatic fat accumulation without additional mechanistic evidence. Inconsistent effects on metabolic activity indicate that

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
(Jenkins et al., 1972).	dichloroethylene in drinking water resulted in decreased liver GSH levels in males (but not females) only at the highest dose of 387 mg/kg-day (Barnes et al., 1985). Exposure of male rats to <i>trans</i>-1,2-dichloroethylene resulted in decreased liver tyrosine transaminase activity and increased liver glucose-6-phosphatase (G6P) activity after a single gavage exposure (Jenkins et al., 1972).	accumulation in the liver were generally lower for shorter duration exposures (increased with exposure duration) in the high-quality rat inhalation study (Freundt et al., 1977). Changes in metabolic parameters were inconsistent and occurred at higher doses than observed apical effects.	metabolism likely does not significantly contribute to liver toxicity. <i>Overall WOSE judgement for hepatic effects based on mechanistic evidence:</i> Indeterminate

2.3.1.4 Reproductive

2.3.1.4.1 Human Evidence

EPA did not identify epidemiological studies that evaluated potential reproductive hazards for *trans*-1,2-dichloroethylene.

2.3.1.4.2 Laboratory Animal Evidence

EPA identified short-term and subchronic studies that evaluated potential reproductive effects following *trans*-1,2-dichloroethylene exposure.

Inhalation

Reproductive toxicity was examined in two high-quality rat studies. In a developmental toxicity study, pregnant dams exposed by whole-body inhalation at 2,000, 6,000, or 12,000 ppm on GDs 7 to 16 demonstrated a dose-dependent increase in early resorptions ([Hurtt et al., 1993](#)). All resorptions were early and the total number per litter were 0.3 in controls and significantly increased to 0.8 in the 6,000-ppm group and 1.1 in the 12,000-ppm group. The number of resorptions per litter in the 2,000-ppm group was not statistically significantly different from controls. The study authors reported that the values for all three treatment groups were within the historical control limits, noting that the mean control values from five studies in the previous 2 years ranged between 0.6 and 1.0 resorptions per litter. In male and female rats exposed to similar concentrations of *trans*-1,2-dichloroethylene for 90 days no histopathological changes to male or female reproductive organs were observed ([DuPont Haskell Lab, 1998](#)).

Oral

A small number of high-quality rodent studies ([NTP, 2002](#); [Barnes et al., 1985](#); [Hayes et al., 1987](#)) showed no changes in histopathology or weights of reproductive organs, consistent across species and exposure durations. No consistent effects on sperm counts, sperm motility, vaginal cytology, or estrous stages or cycle length were observed in male and female rats and mice dosed with less than or equal 3,210 and 7,925 mg/kg-day, respectively in a 14-week dietary study ([NTP, 2002](#)). There were significantly reduced rat spermatid heads per gram testis at 3,760 mg/kg-day but this was not dose-

responsive and the other measures of spermatid counts were not significantly different. In addition, no histopathological changes were observed in male and female reproductive tissues (testes, epididymis, prostate, seminal vesicle, and/or preputial gland for males; clitoral gland, mammary gland, ovaries, and/or uterus for females). Similarly, in subchronic drinking water and short-term gavage studies in mice, no treatment related changes in testes or ovary weights, gross pathology, or histology were observed at up to 387 mg/kg/day (Barnes et al., 1985). Another drinking water study in rats of similar duration (Hayes et al., 1987) showed no changes to testes weights or gross pathology in rats at up to 3,114 mg/kg-day; however, there are uncertainties related to dosing as noted in Section 2.3.1.3.2 above.

Mechanistic and Supporting Evidence

EPA did not identify mechanistic studies that contributed to the understanding of potential reproductive hazards for *trans*-1,2-dichloroethylene.

2.3.1.4.3 Evidence Integration Summary and Conclusions

There are *indeterminate* human evidence and mechanistic support to assess reproductive toxicity of *trans*-1,2-dichloroethylene. The evidence in animals is *indeterminate* based on four high-quality studies. In one inhalation rat study there was a mild, dose dependent increase in early resorptions in pregnant dams, but these were within the historical control range, while in another rat study with similar exposure concentrations, no histopathological changes were observed in males or females after 90 days. Oral studies in rats and mice showed no changes in reproductive histopathology or function at similar concentrations over similar exposure durations.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse reproductive effects, dose-response analysis *is not* considered appropriate for assessing reproductive toxicity. The functional impact of reduced spermatid counts is unclear because the number of matings were unaffected and the magnitude of resorptions was below what would be considered adverse. The evidence integration summary for reproductive effects is presented together with developmental outcomes in Table 2-5.

2.3.1.5 Developmental

2.3.1.5.1 Human Evidence

EPA identified one epidemiological study that evaluated potential developmental hazards following *trans*-1,2-dichloroethylene exposure.

Review of the case-control study in children born to mothers exposed to *trans*-1,2-dichloroethylene in drinking water at Camp Lejeune in North Carolina found no association between exposure to *trans*-1,2-dichloroethylene and birth defects (neural tube or oral cleft defects). A nested case-control study was performed in a cohort of 12,598 children born between 1968 and 1985 to women residing at Camp Lejeune, North Carolina, while pregnant. The drinking water at Camp Lejeune was contaminated with *trans*-1,2-dichloroethylene as well as vinyl chloride, trichloroethylene, tetrachloroethylene, and benzene (Ruckart et al., 2013). Cases identified during surveys of the women were confirmed via medical and vital records. Verified cases included 15 neural tube defects and 24 oral cleft defects; 526 control children were included in the analysis. Maternal exposures during the first trimester were calculated via historical reconstruction of chemical concentrations in drinking water. When considering exposed versus unexposed, *trans*-1,2-dichloroethylene exposure was not associated with neural tube defects (odds ratio [OR] = 1.1, 95% confidence interval [CI]: 0.4–3.1) or oral cleft defects (OR = 0.5, 95% CI: 0.2–1.3). Additionally, when *trans*-1,2-dichloroethylene exposure

levels were stratified to low (>0 to <5 ppb) or high (≥ 5 ppb), no associations were identified for *trans*-1,2-dichloroethylene exposure and oral cleft defects. The study did not confirm that *trans*-1,2-dichloroethylene was the only isomer present in drinking water.

2.3.1.5.2 Laboratory Animal Evidence

EPA identified short-term inhalation studies evaluating potential developmental effects following *trans*-1,2-dichloroethylene exposure.

Inhalation

A high-quality inhalation study in rats evaluated developmental effects in pregnant dams exposed by whole-body inhalation for 6 hours/day at 2,000, 6,000, or 12,000 ppm on GD 7 to 16 (Hurt et al., 1993). Statistically significant decreases in mean fetal body weights for females (5.9% decrease) and all fetuses (4.2% decrease) were observed at 12,000 ppm. No statistically significant effects were identified for fetal body weight of males alone. No external, internal, or skeletal anomalies or variations were observed.

2.3.1.5.3 Mechanistic and Supporting Evidence

EPA did not identify mechanistic studies that contributed to the understanding of potential developmental hazards for *trans*-1,2-dichloroethylene.

2.3.1.5.4 Evidence Integration Summary and Conclusions

The *trans*-1,2-dichloroethylene database lacks sufficient studies evaluating developmental toxicity. There is *indeterminate* human evidence to assess developmental toxicity based on a single medium-quality case-control study. Children born to mothers exposed to *trans*-1,2-dichloroethylene, along with other chemicals, during pregnancy in drinking water showed no associations with birth defects. Information confirming the presence of *trans*-1,2-dichloroethylene as the only isomer present in drinking water was not reported. The evidence in animals is *indeterminate* based on a single high-quality developmental study in rats that showed a small increase ($<6\%$) in mean female fetal weight (not males) and only at the highest dose tested. Mechanistic data pertaining to developmental effects of *trans*-1,2-dichloroethylene were not located. A summary of the database for developmental effects together with reproductive effects, including strengths and weaknesses and evidence integration conclusions, is presented in Table 2-5.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse developmental effects, dose-response analysis is not considered appropriate for assessing developmental toxicity. There are some indications of detrimental fetal outcomes, but of very low magnitude below which would be considered adverse and amenable for dose-response analysis.

Table 2-5. Evidence Integration Summary Table for Reproductive and Developmental Effects

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence in studies of exposed humans considered for deriving toxicity values			
Nested case-control study (data quality not performed because PECO-relevance could not		No associations identified between <i>trans</i>-1,2-dichloroethylene exposure and neural tube defects or oral cleft defects in a small case-	Available data are limited to a single case-control study with a small number of subjects that reported no association between <i>trans</i> -

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
be confirmed) of developmental effects among infants born to mothers living at Camp LeJeune (North Carolina, USA) during pregnancy (Ruckart et al., 2013).		control study (526 controls, 52 cases) (Ruckart et al., 2013). Drinking water at Camp Lejeune was contaminated with mixture of <i>trans</i>-1,2-dichloroethylene, vinyl chloride, trichloroethylene, tetrachloroethylene, and benzene. No confirmation <i>trans</i>-1,2-dichloroethylene was the only isomer present (Ruckart et al., 2013).The effect of <i>trans</i>-1,2-dichloroethylene exposure could not be definitively isolated from other co-exposures.	1,2-dichloroethylene exposure and neural tube or oral cleft birth defects. <i>Overall WOSE judgement for reproductive and developmental effects based on human evidence:</i> Indeterminate
Evidence from <i>In Vivo</i> mammalian animal studies considered for deriving toxicity values			
- High-quality 14-week dietary studies in male and female rats and mice (NTP, 2002). - High quality 90-day inhalation study in male and female rats (DuPont Haskell Lab, 1998). - High-quality developmental toxicity study of rats exposed by inhalation (Hurtt et al., 1993). - High-quality 90-day drinking water study in male and female mice (Barnes et al., 1985). - Medium-quality study in male and female rats (Hayes et al., 1987). - High-quality 14-day gavage study in male mice (Barnes et al., 1985).	<i>Effects on Male and Female Reproductive Organs</i>		No effects were observed on male or female reproductive organs. A high-quality study in rats showed a mild, dose dependent increase in early resorptions in pregnant dams. Developmental effects consisted of reduced fetal body weights in rats. <i>Overall WOSE judgement for reproductive and developmental effects based on animal evidence:</i> Indeterminate
	A single indication of reduced spermatid counts in rats (NTP, 2002).	- No histopathology changes to male or female reproductive organs in subchronic oral studies of rats and mice (Barnes et al., 1985;Hayes et al., 1987) or in a subchronic inhalation study in rats (DuPont Haskell Lab, 1998). - No effects on sperm parameters or estrous cyclicity in subchronic studies (NTP, 2002) or developmental studies of rats and mice besides a single spurious result (Hurtt et al., 1993).	
	<i>Effects on Reproduction or Offspring</i>		
	- Decreased fetal body weight (5.9% in females and 4.2% in both sexes combined) in offspring of rats exposed to 12,000 ppm during gestation in a <i>high</i>-quality study (Hurtt et al., 1993). - A dose-dependent increase in early resorptions in pregnant dams exposed by whole-body inhalation at 2,000, 6,000, or 12,000 ppm during gestation in a <i>high</i>-quality study (Hurtt et al., 1993).	Resorption rates for all three treatment groups were within the historical control limits (Hurtt et al., 1993).	

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence in mechanistic studies and supplemental information			
No data. <i>Overall judgement for reproductive and developmental effects based on mechanistic evidence:</i> Indeterminate			

2.3.1.6 Renal

2.3.1.6.1 Human Evidence

EPA did not identify epidemiological studies that evaluated any renal hazards for *trans*-1,2-dichloroethylene.

2.3.1.6.2 Laboratory Animal Evidence

EPA identified acute, subchronic and chronic studies evaluating renal effects following *trans*-1,2-dichloroethylene exposure.

Oral

The lack of renal effects was consistent across exposure durations and species. A high-quality gavage study in male and female mice found no changes in serum chemistry or kidney weights after a 14-day exposure ([Barnes et al., 1985](#)). No biologically relevant, treatment-related effects on serum chemistry, kidney weight, or histopathology were observed in high-quality studies of male or female mice exposed by diet for 14 weeks (<8,065 mg/kg-day) or male and female rats exposed by diet at doses up to 3,245 mg/kg-day ([NTP, 2002](#)). Similarly, 90-day drinking water study reported no effects on serum chemistry (blood urea nitrogen [BUN], creatinine, glucose, calcium, chloride, phosphorous), urinalysis, and kidney histopathology in male and female mice exposed up to 452 mg/kg-day ([Barnes et al., 1985](#)). In Hayes et al. ([1987](#)), a statistically significant increase in absolute and relative (to brain weight) kidney weights ($\geq 10\%$ difference from control) in female rats exposed to at least 1,257 mg/kg-day, and a statistically nonsignificant 12% increase in relative (to body weight) kidney weight in male rats exposed to 3,114 mg/kg-day were observed. However, the biological relevance of these findings without changes in serum chemistry or kidney histopathology is unclear and organ weight effects only above a standard limit dose of 1,000 mg/kg-day, with additional uncertainty surrounding dosing as described in Section 2.3.1.3.2.

Inhalation

No renal effects were observed in acute studies of rats and male mice ([\[Redacted\], 1999](#); [Plaa and Larson, 1965](#)). This is further supported by high-quality subchronic and chronic inhalation studies in male and female rats that also demonstrated no renal effects based on markers of renal function or kidney histopathology ([DuPont Haskell Lab, 1998](#); [Freundt et al., 1977](#)).

2.3.1.6.1 Mechanistic and Supporting Evidence

EPA did not identify mechanistic studies that contributed to the understanding of potential renal hazards for *trans*-1,2-dichloroethylene.

2.3.1.6.2 Evidence Integration Summary and Conclusions

There is *indeterminate* human, animal, and mechanistic evidence to assess renal toxicity. Among the six high-quality studies available, rats and mice showed no renal effects. In a single medium-quality study in rats, *trans*-1,2-dichloroethylene exposure was associated with marginally increased kidney weights, but without changes in serum chemistry, urinalysis, or histopathology after a 90-day exposure in

drinking water. There is compelling evidence of no effect over acute to intermediate exposures, however in the absence of any chronic studies it is unknown whether longer exposures would cause adverse renal effects. A summary of the database, including strengths and weaknesses and evidence integration conclusions, is presented in Table 2-6.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse renal effects, dose-response analysis is not considered appropriate for assessing renal toxicity. There was only a single effect observed in any study and it was above a traditional limit dose and without evidence of adversity; however, the possibility of effects following chronic exposure cannot be ruled out.

Table 2-6. Evidence Integration Summary Table for Renal Effects

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence in Studies of Exposed Humans Considered for Deriving Toxicity Values (no data)			• Indeterminate
Evidence from <i>In vivo</i> Mammalian Animal Studies Considered for Deriving Toxicity Values			
- High-quality inhalation lethality study in rats ([Redacted], 1999). - High-quality 90-day inhalation study in rats (DuPont Haskell Lab, 1998). - High-quality 16-week inhalation study in female rats (Freundt et al., 1977). - High quality 14-week dietary study in rats and mice (NTP, 2002). - High-quality 90-day drinking water study in mice (Barnes et al., 1985). - Medium-quality 90-day drinking water study in rats (Hayes et al., 1987). - High-quality gavage study in mice (Barnes et al., 1985). - Uninformative intraperitoneal injection study in male mice (Plaa and Larson, 1965).	Statistically significant increased absolute and relative (to brain weight) kidney weights ($\geq 10\%$ difference from control) were observed in female rats exposed to ≥ 1.257 mg/kg-day via drinking water for 90 days. A nonsignificant 12% increase in relative (to body weight) kidney weight was observed in male rats exposed to 3.114 mg/kg-day (Hayes et al., 1987).	No treatment-related effects on serum chemistry, kidney weight, or histopathology changes were observed in dietary or inhalation studies in rats and mice ([Redacted], 1999; DuPont Haskell Lab, 1998; Freundt et al., 1977; NTP, 2002; Barnes et al., 1985; Hayes et al., 1987; Barnes et al., 1985).	In a single medium-quality study, marginal increases in kidney weights (without histopathology changes) in rats exposed via drinking water, with consistent null results otherwise in high-quality studies. <i>Overall WOSE judgement for renal effects based on animal evidence:</i> Indeterminate ^a
Evidence in mechanistic studies and supplemental information			
No data. <i>Overall judgement for renal effects based on mechanistic evidence:</i> Indeterminate			
^a Compelling evidence of no effect over acute to intermediate exposure durations.			

2.3.1.7 Respiratory

2.3.1.7.1 Human Evidence

EPA did not identify epidemiological studies that evaluated any respiratory hazards for *trans*-1,2-dichloroethylene.

2.3.1.7.2 Laboratory Animal Evidence

EPA identified short-term, subchronic, chronic studies that evaluated potential respiratory hazards for *trans*-1,2-dichloroethylene.

Inhalation

High-quality inhalation studies showed no treatment-related effects on lung weights or histopathology observed in male or female rats exposed to concentrations up to 15,900 mg/m³ (4,000 ppm) for 90 days (DuPont Haskell Lab, 1998). Instances of hyperplasia, degeneration, or metaplasia were reported in 1/10 female rats at 1,000 or 4,000 ppm; however, this is not considered biologically significant. An inhalation study in female rats reported slight to severe capillary hyperemia and alveolar septal distention in the lungs after a single inhalation exposure to at or exceeding 793 mg/m³ (200 ppm) for 8 hours or repeated exposures to 793 mg/m³ (8 hours/day, 5 days/week) for up to 16 weeks. Severe effects were only observed at concentrations at or exceeding 3,970 mg/m³ (1,000 ppm) in the single exposure experiment (Freundt et al., 1977). These findings have not been corroborated in other studies at higher exposure levels and this study had notable weaknesses as discussed above in Section 2.3.1.3.3.

Oral/Other

No treatment-related effects on lung weights or histopathology were observed in male or female rats or mice exposed by diet or drinking water for 13 to 14 weeks (NTP, 2002; Hayes et al., 1987; Barnes et al., 1985). These findings are consistent with no changes in lung weights observed in a high-quality 14-day gavage study in mice (Barnes et al., 1985) and a medium-quality intraperitoneal study in rats (Nakahama et al., 2000).

2.3.1.7.1 Mechanistic and Supporting Evidence

EPA did not identify mechanistic studies that contributed to the understanding of potential respiratory hazards for *trans*-1,2-dichloroethylene.

2.3.1.7.2 Evidence Integration Summary and Conclusions

There is *indeterminate* human, animal, and mechanistic evidence to assess respiratory toxicity. While lung histopathology changes were reported in an inhalation study of Wistar rats (Freundt et al., 1977), no treatment-related effects on lung weights or histopathology were observed in an inhalation study of SD rats exposed for a similar duration to higher exposure concentrations (DuPont Haskell Lab, 1998). Strain differences could certainly explain the differential sensitivity. The (Freundt et al., 1977) was limited by small sample size (n=6) and did not examine any other relevant respiratory outcomes. A summary of the database including strengths and weaknesses and evidence integration conclusions is presented in Table 2-7.

Based on the weight of scientific evidence, evidence integration judgements, and available dose-response data for adverse renal effects, dose-response analysis *is not* considered appropriate for assessing respiratory toxicity. The positive outcome is conflicted by another study at higher doses and deriving a quantitative hazard value for respiratory toxicity is not supported.

Table 2-7. Evidence Integration Summary Table for Respiratory Effects

Database Summary	Factors That Increase Strength	Factors That Decrease Strength	Summary of Key Findings and Within-Stream Strength of the Evidence Judgement
Evidence from human studies considered for deriving toxicity values (no data)			• Indeterminate
Evidence from <i>in vivo</i> mammalian animal studies considered for deriving toxicity values			
• High-quality 90-day inhalation study in rats (DuPont Haskell Lab, 1998). • High-quality inhalation study in female rats (Freundt et al., 1977). • High-quality 90-day drinking water study in rats (Barnes et al., 1985). • Medium-quality 90-day drinking water study in mice (Hayes et al., 1987). • High-quality 14-week dietary studies in rats and mice (NTP, 2002). • Medium-quality single intraperitoneal injection study in male rats (Nakahama et al., 2000). • High-quality gavage study in mice (Barnes et al., 1985).	• Slight to severe capillary hyperemia and alveolar septal distention were observed in the lungs of female Wistar rats after a single inhalation exposure to ≥ 793 mg/m³ (200 ppm) for 8 hours or repeated exposures to 793 mg/m³ (8 hours/day, 5 days/week) for up to 16 weeks (Freundt et al., 1977).	• Group sizes (6/group) were small, and histopathology findings were reported qualitatively in the study that observed lung effects. • Lung histopathology changes reported in an inhalation study of Wistar rats (Freundt et al., 1977) but not in an inhalation study of SD rats exposed for a similar duration to higher exposure concentrations (DuPont Haskell Lab, 1998).	A single inhalation study in rats <i>Overall WOSE judgement for respiratory effects based on animal evidence:</i> • Indeterminate for effects on the respiratory tract.
Evidence in mechanistic studies and supplemental information			
No data. <i>Overall judgement for respiratory effects based on mechanistic evidence:</i> Indeterminate			

2.3.2 Non-Cancer Dose-Response Assessment

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

When considering non-cancer PODs for estimating risks for acute, intermediate, and chronic exposure scenarios, EPA reviewed the suite of studies in animals, humans, and *in vitro* systems and individual critical hazard outcomes for which sufficient data was available to support dose-response analysis. From among the database supporting those outcomes, the Agency selected the best individual studies and most relevant endpoints based on the following considerations:

- Overall quality determinations
- Exposure duration
- Dose range
- Relevance (*e.g.*, what species was the effect in, was the study directly assessing the effect, is the endpoint the best marker for the tox outcome?)
- Uncertainties not captured by overall quality determination
- Endpoint sensitivity
- Uncertainty and sensitivity of BMR selection from BMD modeling.

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).

2.3.2.1.1 Non-Cancer Points of Departure (PODs) for Acute Exposures

Given the limited database for *trans*-1,2-dichloroethylene, few observed health effects are relevant to acute exposures. Increased resorptions indicating early pregnancy loss could present from a single exposure. Evidence indicates that certain developmental effects may result from a single exposure during a critical window of development ([Davis et al., 2009](#); [Van Raaij et al., 2003](#)), consistent with EPA's *Guidelines for Developmental Toxicity Risk Assessment* ([U.S. EPA, 1991](#)). Irreversible and binary developmental outcomes such as resorptions/abortions typically fall within this classification. However, the overall database for reproductive and developmental effects was indeterminate. The increase in resorptions is of uncertain biological significance because the magnitude of resorptions was a maximum of only 1.1 per litter at the highest concentration of 12,000 ppm ([Hurtt et al., 1993](#)), which is just barely above the historical control range of 0.6 to 1.0 resorptions/litter.

Reduced leukocytes counts of 23% were reported following 8 hours of exposure to 200 or 1,000 ppm *trans*-1,2-dichloroethylene ([Freundt et al., 1977](#)). This study did not investigate any other immunological measures and this result is an outlier considering that a reduction in immune cells was only observed at 4,000 ppm administered for 90 days in ([DuPont Haskell Lab, 1998](#)). There is no evidence to support a compensatory mechanism that would explain an inverse duration-response, and further evidence would be needed to associate a temporary reduction in leukocytes with an adverse health effect in humans. Therefore, reduced leukocytes were not considered further as a candidate for an acute POD.

A more reliable acute endpoint is sensory irritation, which does not require exposure for an extended period of time and is considered to be a peak exposure effect independent of exposure duration. Animal models showed the acute irritation was associated with neurotoxicity in the form of narcosis, which aligns with the dizziness observed in an epidemiological study ([Lehmann and Schmidt-Kehl, 1936](#)). Both dermal and ocular irritation were observed following acute or short-term exposures (Section 2.3.1.1). These effects as reported in ([Lehmann and Schmidt-Kehl, 1936](#)) are the basis of the first threshold of Acute Exposure Guideline Levels (AEGL-1) of 280 ppm for *trans*-1,2-dichloroethylene ([U.S. EPA, 2022](#)). AEGL-1 is the level above which one "could experience notable defined as notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure." Above the AEGL-2 level of 1,000 ppm for up to a 60-minute duration, individuals "could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape." Narcosis/anesthetic effects were the basis of the AEGL-2. A summary of the AEGLs for *trans*-1,2-dichloroethylene are presented in Table_Apx D-2. Although these effects may be reversible after exposure ceases and they are not severe on their own, together they could lead to dangerous situations in the workplace. As stated in the [Formaldehyde SACC Meeting Minutes and Final Report](#), "eye or other mucous membrane irritation can have adverse impacts if the worker or individual in the general population is hampered in the safe performance of their occupation or transportation."

Evidence of neurotoxicity in the form of either CNS depression (e.g., dizziness, incoordination, lethargy) or less likely, other neurological dysfunction through the trigeminal ([Okamoto et al., 2012](#)) or cholinergic system ([Adeyinka and Kondamudi, 2020](#)), is apparent in multiple rodent studies and is supported by the human case study with a limited sample size ([Lehmann and Schmidt-Kehl, 1936](#)). These effects are primarily qualitatively reported and cannot be easily applied for dose-response analysis. In contrast, there is evidence of dose-response for ocular irritation from a rat study ([Hurtt et al., 1993](#)), which is supported by a human study, both of which also reported indications of solvent neurotoxicity ([U.S. EPA, 2022](#); [Lehmann and Schmidt-Kehl, 1936](#)). Endpoints from both studies are highly relevant to acute exposures; symptoms of eye irritation and dizziness were reported by subjects in

([Lehmann and Schmidt-Kehl, 1936](#)) within minutes of exposure to *trans*-1,2-dichloroethylene in air, while lacrimation and incoordination were observed in rodents immediately and/or routinely across the exposure period study ([Hurt et al., 1993](#)). The human study ([Lehmann and Schmidt-Kehl, 1936](#)) scored a Low (but not “uninformative for dose-response”), however it contains precise dose-response information directly applicable to the hazard endpoints. These two studies were considered for acute exposures to *trans*-1,2-dichloroethylene in air; they are considered representative of both sensory irritation and associated acute neurotoxicity. There are no appropriate studies or endpoints relevant to dermal or oral exposures. Key information from these studies is summarized below in Table 2-8.

Table 2-8. Candidate Endpoints for Acute Exposure Scenarios

Study	Hurt et al. (1993) ^a	U.S. EPA (2022); Lehmann and Schmidt-Kehl (1936) ^a
Route	<i>Inhalation/Ocular</i>	
Endpoint/Effects	Lacrimation, ocular discharge	Dizziness, burning of eyes
Duration	10 days	5–30 minutes
LO(A)EL	2,000 ppm (7,930 mg/m ³)	825 ppm (3,271 mg/m ³)
NO(A)EL	None	275 ppm (1,090 mg/m ³)
Species	Rats	Humans
Notes	Developmental toxicity study with signs of ocular irritation as the most sensitive health outcome	Single 90-year old case report, not a well-controlled experiment; subjective reporting of symptoms based on only 2 subjects
OQD	High	Low
LO(A)EL = lowest observed (adverse) effect; NO(A)EL = no observed (adverse) effect; OQD = overall quality determination from systematic review.		
^a Study was considered for dose-response analysis.		

Ocular irritation was detected in rats based on both lacrimation (tearing) and discharge of a brown periocular stain following 10 days of exposure to *trans*-1,2-dichloroethylene in air. While these may not be the most sensitive measures of irritation, they followed a dose-response and can be directly associated with adverse eye effects. The dose-response for ocular irritation is also representative of the depressive symptoms associated with general solvent neurotoxicity ([Van Thriel and Boyes, 2022](#)). The [Lehmann \(1936\)](#) study (as discussed in ([U.S. EPA, 2022](#))) was in humans and demonstrates a dose-response relationship with increasing symptoms at higher concentrations for exposures of 30 minutes or less. Although there is substantial uncertainty based on the age of the study and the qualitative nature, it will be considered alongside the animal data for determining the most appropriate representative POD for the endpoint due to presenting human data and a more sensitive identification of irritation together with solvent neurotoxicity.

2.3.2.1.2 Non-Cancer PODs for Intermediate and Chronic Exposures

Immune system toxicity is the most well-supported hazard for repeat-dose effects. The two studies with dose-responsive effects on lymphocytes or function are ([DuPont Haskell Lab, 1998](#)) and ([Shopp et al., 1985](#)). The Dupont study identified dose dependent reductions in immune cells at elevated concentrations about 1,000 ppm, with decreased lymphocytes in males as the only statistically significant effect following 90 days of exposure. The [Shopp et al., \(1985\)](#) study reported decreased AFCs, a functional measure of humoral immunity, in male mice (observed at both 4 and 5 days post-antigen presentation). Other indicators of immune response such as immune organ weights or total

leukocyte counts were inconsistent or showed null effects ([Barnes et al., 1985](#)), however these are considered less reliable measures of immunity ([Ladics, 2007](#)). There were no indications of less sensitive immune effects (*i.e.*, thymus weight, immune organ histopathology, and/or immune cell counts) seen in ([NTP, 2002](#)) at nominal doses up to 3,265 mg/kg-day in rats and 8,000 mg/kg-day in rats); however, there was uncertainty in the dosing in that study using microencapsulation of *trans*-1,2-dichloroethylene; the dosing formulations were shown to be homogenous, stable, and with 10% of target dosage—however, samples of feed from the animal rooms on the last day of each preparation were consistently below the targeted dose (8–52% in rats, 44–75% in mice). Feed consumption reported weekly for cages of 1 to 5 animals was fairly consistent throughout the study and body weights increased substantially over the course of the study, so daily dose decreased over the 14 weeks. In addition to the typical uncertainties in a dietary study, the animal room samples indicate that the high exposures reported in the study may be an overestimate of exposure, which is an important consideration when weighing the lack of immune effects. The studies selected for dose-response consideration are summarized below in Table 2-9.

Table 2-9. Candidate Endpoints for Intermediate/Chronic Exposure Scenarios

Study	DuPont Haskell Lab (1998)	Shopp et al. (1985) ^a
Route	<i>Inhalation</i>	<i>Oral</i>
Endpoint/Effects	Decreased number of lymphocytes	Reduced humoral immune response in males
Duration	90 days	90 days
LO(A)EL	4,000 ppm (15,859 mg/m ³)	175 mg/kg-day
NO(A)EL	1,000 ppm (3,965 mg/m ³)	17 mg/kg-day
Species	Rats	Mice
Notes	Consistent reductions in several other immune cells; reduced lymphocytes in males most consistent/sensitive	Strong result for functional measure of immunity (AFC) but inconsistent results otherwise
OQD	High	High
LO(A)EL = lowest observed (adverse) effect; NO(A)EL = no observed (adverse) effect; OQD = overall quality determination from systematic review.		
^a Study was considered for dose-response analysis.		

The implications of the observed decrease in immune cells in Dupont ([1998](#)) is unclear. Overall white blood cell counts were decreased by up to 20% in males and 18% in females. Lymphocytes were decreased at 4,000 ppm by over 25% in males and over 22 % in females (statistically non-significant) compared to control, however it is difficult to relate this change to human immune function and disease susceptibility. A clinical diagnosis of lymphopenia (low lymphocyte count) may result from less than 1,500 cells/μL blood; up to 4,800 cells/μL is normal (<https://www.nhlbi.nih.gov/health/lymphopenia/diagnosis>, accessed January 9, 2026), but lymphocyte counts were almost 13,000 cells/μl in control male rats. An investigation of the historical control data for the laboratory ([Giknis and Clifford, 2006](#)) shows a wide range for lymphocyte and white blood cell levels, both of which overlap the counts reported in study controls. Additionally, no effect on lymphocytes or other leukocytes were observed in a 14-week oral study ([NTP, 2002](#)) (however there is some uncertainty about dosing in this study). Therefore, it is unclear whether these reductions are biologically significant or adverse. The reduced sensitivity of immune cell counts compared to functional measures is well-established, due both high variability and uncertain adverse thresholds ([Johnson et al., 2024](#)) for cell counts.

Although responses were inconsistent for all measures or between sexes in (Shopp et al., 1985), decreased AFCs represents a well-established functional measure of humoral immunity that is considered one of the best predictors of immunotoxicity in mice based on extensive intra- and inter-laboratory validation for T-cell dependent antibody responses (Ladics, 2007). Additionally, EPA published 1998 test guidelines (OPPTS 870.7800) that chemicals intended for use as pesticides be evaluated for immunosuppressive potential based on the primary humoral immune response using the AFC assay or ELISA following repeated chemical exposures along with data from routine toxicity testing, to provide more accurate information on risk to the immune system. Furthermore, as discussed in Section 2.3.1.2.4, concordance with other evidence of immunotoxicity has been shown to be among the highest of all immune measures for AFC assays (Luster et al., 1992). Reduced lymphocytes when identified by cell surface markers showed the greatest concordance, but reductions in overall leukocytes were not significantly associated with immunotoxicity. Given the above considerations, this endpoint from (Shopp et al., 1985) is selected as the most robust endpoint for dose-response analysis of repeated dose effects. Despite uncertainties and inconsistencies, this endpoint will be applied to both intermediate and chronic exposure durations.

Shopp et al. (1985) reported AFCs both on a per spleen basis and per 10^6 spleen cells. Because there was a reduction (albeit not statistically significant) in spleen weight at all exposure concentrations, AFCs per 10^6 spleen cells was considered the more relevant measure to normalize for spleen size and this outcome will be used for dose-response analysis. It is important to note that there is inconsistency in immune responses both within and across studies, and no other AFC assays are available within the limited database.

2.3.2.2 Dose-Response Derivation for Non-Cancer Hazard Values

As described in Section 2.3.2.1, EPA identified the best studies for *trans*-1,2-dichloroethylene for quantitative dose response analysis. The sections below describe the steps used to derive the hazard values used to calculate risks.

2.3.2.2.1 Duration, Dosimetric, and Unit Adjustments

Duration, Dosimetric, and Unit Adjustments for Inhalation/Ocular Hazard Values

Dosimetric Adjustments: In the absence of a PBPK model or other chemical specific data-derived extrapolation factors (U.S. EPA, 2014), EPA follows established guidance for dosimetric adjustments across species (U.S. EPA, 2012a, 1994). The endpoints selected are not applicable to inhalation dosimetry however; immune effects in (Shopp et al., 1985) were from oral administration and ocular irritation in (Hurt et al., 1993) and (Lehmann and Schmidt-Kehl, 1936) are based on external air concentration only. Therefore, inhalation dosimetry is not required for these endpoints.

Duration Adjustments: The studies selected for dose-response assessment utilized differing exposure durations and frequencies. Typically, to better compare results across studies and exposure scenarios, administered doses/concentrations were linearly adjusted to continuous exposure (24 hours/day, 7 days/week) prior to POD derivation. For sensory irritation, effects are driven by peak concentration and not accumulation of aggregate dose over time. Consistent with the AEGL document (U.S. EPA, 2022), concentrations associated with ocular irritation were not duration-adjusted and will be compared to the shortest relevant duration of peak air concentration for risk estimation.

Unit Conversion: It is often necessary to convert between ppm and mg/m^3 due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all inhalation hazard values to be used for risk estimation in in both units (Table 2-16). The following equation (Equation 2-1) presents the conversion of the HEC from ppm to mg/m^3 .

Equation 2-1. Converting ppm to mg/m³

$$\text{HEC (mg/m}^3\text{)} = \text{HEC (ppm)} * (\text{molecular weight} / 24.45^2)$$

Dosimetric and Unit Adjustments for Oral Hazard Values

Dosimetric Adjustments: In the absence of a PBPK model or other chemical specific data-derived extrapolation factors, EPA adjusted the HEDs using allometric BW^{3/4}-scaling based on guidance from ([U.S. EPA, 2011b](#)). 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 2-2.

Equation 2-2. Dosimetric Adjustment Factor (DAF)

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

Where:

DAF	=	Dosimetric adjustment factor (unitless)
BW_A	=	Body weight of species used in toxicity study (kg)
BW_H	=	Body weight of adult human (kg)

[U.S. EPA \(2011b\)](#) presents DAFs for extrapolation to humans from several species. However, because those DAFs used a human body weight of 70 kg, EPA has updated the DAFs using a human body weight of 80 kg for this risk evaluation ([U.S. EPA, 2011a](#)). EPA used the body weights of 0.025 and 0.25 kg for mice and rats, respectively, as presented in ([U.S. EPA, 2011a](#)). The resulting DAFs for mice and rats are 0.13 and 0.24, respectively.

Duration Adjustments: Similar to inhalation values, oral values are adjusted to daily exposure by removing the hours/day factor from the equation as shown in Equation 2-3. When a POD is applied to acute exposures, days per week are not adjusted.

Equation 2-3. Adjusting Average Dose or Oral/Dermal POD for Differences in Days Exposure Across Scenarios

$$Dose_{continuous} = Dose_{study} \times \left(\frac{D_s}{7} \right)$$

Where:

$Dose_{continuous}$	=	Adjusted air concentration/inhalation POD
$Dose_{study}$	=	Air concentration/inhalation POD from study dataset
D_s	=	Days per week/year exposure in study dataset

Unit Conversion

Oral values in mg/kg-day and inhalation values in mg/m³ can then be interconverted based on default exposure factors from ([U.S. EPA, 2011a](#)). EPA applies a default body weight of 80 kg and breathing rate of 14.7 m³/day (based on continuous exposure at rest). OPPT typically assumes 100% oral and

² 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.

inhalation absorption in the absence of data. Dermal absorption is accounted for in the exposure estimate; oral HEDs can therefore be directly applied to the dermal route. HECs and HEDs can be interconverted using Equation 2-4 and the exposure factors above. Respiratory effects are only relevant to the inhalation route and will not be extrapolated to other exposure routes.

Equation 2-4. Converting HEC to HED

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

2.3.2.2.2 Non-Cancer Benchmark Dose Analysis and HEC/HED Derivation

EPA conducted benchmark dose (BMD) modeling in accordance with guidance ([U.S. EPA, 2012b](#)) to refine PODs for the endpoints and studies described in Section 2.3.1. EPA decisions on modeling of specific data sets and results are described below. See Appendix A for a summary of all BMD modeling results, including model selection and alternative endpoint options. See *Draft Benchmark Dose Modeling Results for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026a](#)) for full BMD modeling details including statistical tests, results from all models, and any associated graphs. All modeling was performed using EPA's BMDS online modeling suite (<https://bmdsonline.epa.gov/>, last accessed January 30, 2026).

Non-Cancer PODs for Acute Exposure

As discussed in Section 2.3.2.1.1, there are two studies relevant to acute exposures that are appropriate for dose-response analysis, both involving sensory irritation. Sensory irritation (and associated neurotoxicity such as dizziness) was considered adverse because it can cause notable discomfort and lead to dangerous situations in the workplace. The developmental toxicity study ([Hurtt et al., 1993](#)) was intended to test developmental and reproductive outcomes following inhalation exposure, however the animals were exposed whole-body to *trans*-1,2-dichloroethylene in air. Lacrimation (*i.e.* tear formation) and induction of periocular brown staining were observed at all concentrations, indicating ocular irritation. Periocular staining was not considered a reliable or sensitive measure of eye irritation; however, it was BMD-modeled along with lacrimation for comparison. Both outcomes were modeled as dichotomous variables with the default benchmark response (BMR) of 10% extra risk. Air concentrations from ([Hurtt et al., 1993](#)) were not duration-adjusted to continuous exposure because sensory irritation is based on peak air concentration and not an accumulation of chemical (*i.e.*, area under the curve, AUC) over time.

The BMCL₁₀ for lacrimation was 914 mg/m³. While modeling was successful, the BMCL was almost 9-fold below the LOAEC and lowest concentration tested. The BMD to BMDL ratio was also flagged as a warning in BMDS for being greater than 3-fold, indicating large uncertainty in the estimate. The BMCL₁₀ for ocular staining was 4,440 mg/m³. There were no modeling concerns for this BMCL; however, the relationship between the presence of ocular stain and irritation is uncertain and the staining likely a much less sensitive marker. These results were compared to the human no-observed-adverse-effect-concentration (NOAEC) of 1,090 mg/m³ from ([Lehmann and Schmidt-Kehl, 1936](#)), data presented in ([U.S. EPA, 2022](#)). This NOAEC is based on reports of dizziness and burning of the eyes at higher concentrations over durations of only minutes. The dataset cannot be modeled because only two volunteers were studied and differing subjective symptoms were reported at various exposure concentrations (as opposed to increasing intensity of a single outcome). Considering these uncertainties, the LOAEC value from ([Hurtt et al., 1993](#)) is considered the most reliable value for POD selection.

Table 2-10. Dose-Response Analysis of Selected Studies and Endpoints Considered for Deriving Acute PODs

Study Parameters	Study POD (HEC)	BMD Modeling Result	Measured Outcome (Organ System)	Comments
Inhalation				
Hurtt et al. (1993) Female Crl:CD BR rats exposed 6 h/day for 10 days via inhalation during gestational days 7-16	LOAEC = 7930 mg/m ³ (7930 mg/m ³)	BMCL ₁₀ = 914 mg/m ³	Lacrimation (Sensory Irritation)	The BMCL is not considered reliable for POD derivation because it is almost 9-fold below the LOAEC and lowest concentration tested. The LOAEC value is more appropriate.
		BMCL ₁₀ = 4,440 mg/m ³	Periocular Staining (Sensory Irritation)	This endpoint is not considered a sensitive measure of eye irritation.
U.S. EPA (2022); Lehmann and Schmidt-Kehl (1936) Humans exposed once to air concentrations for 5 to 30 min	NOAEC = 1,090 mg/m ³ (1,090 mg/m ³)	Not BMD-modeled due to small sample size (n = 2) and differing reported symptoms	Dizziness, burning of eyes (Neurotoxicity, sensory irritation)	Study results summarized in AEGL document (U.S. EPA, 2022). LOAEC = 3,271 mg/m ³ for slight dizziness, with burning of eyes and more severe dizziness symptoms at higher concentrations.
BMCL ₁₀ = benchmark dose concentration lower limit 10%; BMD = benchmark dose; LOAEC = lowest observed adverse effect concentration; NOAEC = no observed adverse effect concentration; POD = point of departure;				

Non-Cancer PODs for Intermediate and Chronic Exposures

Decreased humoral immunity from ([Shopp et al., 1985](#)) is the only repeat-dose endpoint considered for dose-response analysis as it represents an adverse outcome based on a reliable, well-established assay. The measurement of AFCs per 1 million total spleen cells is a reliable indicator of functional humoral immunity, and this measurement at day 4 was modeled as a continuous variable with the default BMR of 1 standard deviation (SD). A similar dose-response relationship was observed on day 5, however only day 4 results were modeled because they demonstrate a stronger AFC induction and starker dose-response. BMD modeling was successful for the dataset with a BMDL of 21.4 mg/kg-day, however visual fit was poor (potentially due to the large dose spacing between the first and second dose) and the selected model had elevated scaled residual near the BMD indicating statistical uncertainty in the modeling result (see Appendix A.1). EPA therefore also modeled the dataset with the highest dose dropped because the response appeared to plateau at the highest doses, causing inconsistent model fit across all dose groups. BMD modeling was also successful for the trimmed dataset with a more sensitive BMDL of 9.33 mg/kg-day and substantially reduced scaled residual at the BMD. However, given that modeling was successful for the complete dataset and the BMD is closer to the highest dose in both modeling runs, there is additional uncertainty in whether dropping the high dose is appropriate (leaving only two doses plus a control). With only three groups total (0, dose 1, dose 2), a model fit may be supported, however, modeling is limited to a lower number of applicable models ([U.S. EPA, 2012b](#)). Therefore, only the BMDL of the complete dataset was considered for POD derivation.

Table 2-11. Dose-Response Analysis of Selected Studies and Endpoints Considered for Deriving Intermediate and Chronic PODs

Study Parameters	Study POD (HED)	BMD Modeling Result	Measured Outcome (Organ System)	Comments
Oral				
Shopp et al. (1985) Male and female CD-1 mice exposed daily via drinking water for 90 days, then exposed to sRBC with AFCs measured 4 or 5 days later.	NOAEL = 17 mg/kg-day ^a (2.2 mg/kg-d)	BMDL _{1SD} = 21.4 mg/kg-day	Decreased humoral immune response – AFCs/10 ⁶ spleen cells at day 4 post-antigen presentation (Immunotoxicity)	This endpoint is considered one of the best predictors for evaluating humoral immunity (Ladics, 2007). While functional immune assays are expected to be more precise indicators of immune toxicity (Johnson et al., 2024), this endpoint is conservative considering inconsistent outcomes at higher doses for other immune measures,
AFC = antibody forming cells; BMDL _{1SD} = benchmark dose lower 95% confidence limit 1 SD; POD = point of departure; sRBC = sheep red blood cells ^a The lowest dose can be interpreted as either a NOAEL or LOAEL depending on whether AFCs/spleen or AFCs/10 ⁶ cells are counted. As discussed in Section 2.3.2.1.2, AFCs/10 ⁶ cells is considered the most appropriate measure. There is inconsistency in the study text and tables, however consensus across prior assessments is that the dataset selected represents AFCs/10 ⁶ cells.				

2.3.2.2.3 POD Selection for Use in Risk Estimation

Acute Exposure Scenarios

Three POD options (from across 2 studies) were presented in Section 2.3.2.2.2 for acute sensory irritation and associated solvent neurotoxicity. The NOAEC from ([U.S. EPA, 2022](#); [Lehmann and Schmidt-Kehl, 1936](#)) cannot be considered representative of population responses because it is based on only two volunteers and there is concern for bias since the volunteers were from the laboratory performing the study. Additionally, the study is 90-years-old, which gives substantial concern about scientific rigor and ethics of human study criteria. The study is the basis of the current AEGL recommendation, but given the above considerations and the *low* rating for data quality, it was considered less reliable than the high-quality animal study. Regardless, it provides important quantitative weight of scientific evidence support for the human relevance of these effects.

The results from ([Hurtt et al., 1993](#)) on rodent responses are dose-responsive with indications of ocular irritation, however the endpoints are visually apparent changes from the eye (*i.e.*, lacrimation, discharge) that may not be the most sensitive. Periocular staining resulted in a BMCL₁₀ of 4,400 mg/m³ 5-fold higher than the BMCL₁₀ for lacrimation (914 mg/m³) and 4-fold higher than the human NOAEC from ([Lehmann and Schmidt-Kehl, 1936](#)). On the other hand, the BMCL₁₀ for lacrimation is not reliable because the value is almost 9-fold below the LOAEC and lowest concentration tested.

When considering all of the above options, balancing reliability, sensitivity, and the strength of the dataset, the LOAEC of 7,930 mg/m³ from ([Hurtt et al., 1993](#)) with a UF_L of 3 applied provides the most robust option for risk estimation. A larger UF is not justified because while ocular irritation is adverse, it is unlikely to have a steep dose-response curve and severe signs of eye damage were not seen. With a total uncertainty factor of 30 (UF_A = 3; UF_H = 3; UF_L = 3), the effective hazard threshold (POD/UF) is 264.3 mg/m³—compared to a risk threshold of 363.3 mg/m³ based on the NOAEC from ([Lehmann and Schmidt-Kehl, 1936](#)) when applying a UF of 3. For comparison, the risk threshold for the lacrimation BMCL₁₀ (UF = 30) from ([Hurtt et al., 1993](#)) is approximately an order of magnitude lower at 30.4 mg/m³ and the threshold for the periocular staining BMCL₁₀ (UF = 10) from ([Hurtt et al., 1993](#)) is 444 mg/m³. Therefore, the LOAEC for lacrimation in rats results in a risk threshold that is sensitive and

robust, falling in the middle of the range among these options. This selected POD is consistent with the basis of the ATSDR MRL ([ATSDR, 2025](#)), which also used lacrimation from ([Hurtt et al., 1993](#)). ATSDR applied 10× UF for both inter- (UF_A) and intra- (UF_H) species variability, to account for both toxicodynamic and toxicokinetic uncertainties between and within species for a total uncertainty factor of 100× (Appendix D). In contrast, EPA determined that metabolism is not a significant contributor to this endpoint, thus eliminating the need for a toxicokinetic uncertainty factor (3). Since only toxicodynamic variability was relevant (3) to both interspecies and intraspecies uncertainty, lower 3× UF_A and 3× UF_H were applied in this assessment.

The weight of scientific evidence also supports solvent neurotoxicity based on observations in rodents and humans. Solvent irritation, or perhaps lacrimation itself; therefore, appears to either be associated with neurotoxicity or serve as a quantifiable clinical marker.

Intermediate/Chronic Exposure Scenarios

As previously discussed in Section 2.3.2.2.2, the BMDL_{1SD} for decreased AFCs (indicating decreased humoral immunity) from ([Shopp et al., 1985](#)) on the full dataset is the only result considered for risk estimation. BMD modeling was also performed with the high dose dropped for comparison; while visual fit was improved, losing a dose group introduces too much uncertainty with only two non-zero doses remaining for the result to be reliable when modeling of the full dataset was successful.

Shopp et al. ([1985](#)) evaluated immunotoxicity from *trans*-1,2-dichloroethylene under 14- and 90-day exposure durations, and chronic toxicity studies are not available. The BMDL_{1SD} of 21.4 mg/kg-day from this study is thus applied to both intermediate and chronic repeat-dose exposures. A concern raised by the SACC for the *Draft Risk Evaluation for 1,1-Dichloroethane* was the use of a short-term 14-day gavage study by Munson ([1982](#)) for the intermediate duration as opposed to using a longer study duration (*i.e.*, the 90-day exposure duration from the same study) that would, according to the SACC, better represent the onset of toxicity due to human exposures ([EPA-HQ-OPPT-2024-0114-0086](#)). Reduced AFCs were observed following a 14- but not 90-day exposure to the analog 1,2-dichloroethane ([Munson et al., 1982](#)). In contrast, AFCs were significantly reduced in the 90-day exposure to *trans*-1,2-dichloroethylene ([Shopp et al., 1985](#)) and EPA is using the 90-day data, consistent with SACC recommendations. As previously discussed, AFC assays are considered one of the best predictors of immunotoxicity in mice ([Ladics, 2007](#)) and are a part of a 1998 test guideline assay for immunotoxicity ([OPPTS 870.7800](#)). Therefore, despite inconsistent or negative results for other immune outcomes (considered less reliable for immunotoxicity risk assessment ([Johnson et al., 2024](#); [Luster et al., 1992](#))), the POD derived from this endpoint was selected.

For *trans*-1,2-dichloroethylene, immunotoxicity was not observed in the short-term, 14-day study, suggesting that a longer exposure duration is necessary to elicit this health effect (although the 14-day duration is shorter than recommended by EPA test guidelines ([OPPTS 870.7800](#))). In accordance with EPA guidance, the Agency applied an additional UF for subchronic to chronic (*i.e.*, intermediate-to-chronic extrapolation UF_S). A 10-fold UF_S was applied for chronic oral/dermal scenarios.

Because irritation/solvent neurotoxicity occurs at a higher concentration than immunotoxicity, that effect would not be naturally limiting of immune effects occurring at lower inhaled concentrations and immunotoxicity could be expected to result from inhalation exposure. However, there is uncertainty in extrapolating across routes given that there are no inhalation studies for functional immunity and reduction in lymphocytes from inhalation exposure was observed at much higher concentrations. In the absence of a POD from an inhalation study, the oral POD was extrapolated to an HEC using the calculations from Section 2.3.2.2.1. For the resulting inhalation HEC of 116 mg/m³, a 3-fold UF_S value

was applied because as stated above the database suggests that the oral route may be more sensitive and in order to minimize compounding uncertainties. EPA applied dosimetric adjustments consistent with EPA guidance ([U.S. EPA, 2011a](#)) in deriving an HED in order to reduce the UF_A to 3.

PODs to be used in risk estimation are presented in Table 2-16, organized by applicable route and duration.

2.3.2.3 Uncertainty Factors Used for Non-Cancer Endpoints

Considerations for the application of uncertainty factors are below based EPA guidance and reports from ([U.S. EPA, 1994, 1993](#)), ([2002](#)), and ([2012a](#)) further discuss considerations for application of UFs in human health hazard dose-response assessment. Only uncertainty factors applicable to this assessment are discussed below. A summary of how these are applied for each endpoint across exposure scenarios is provided in Table 2-12.

1) Interspecies Uncertainty Factor (UF_A) of 1 or 3

EPA uses data from oral toxicity studies in animals to derive relevant HEDs, and U.S. EPA ([2011b](#)) recommends allometric scaling (using the $3/4$ -power of body weight) to account for interspecies toxicokinetics differences for oral data. When applying allometric scaling, EPA guidance recommends using a UF_A of 3. The remaining uncertainty is associated with interspecies differences in toxicodynamics. EPA also uses a UF_A of 3 for the intermediate and chronic inhalation HEC and dermal HED values for immunotoxicity because these values are derived from the oral HED.

For ocular irritation a UF_A of 3 is also applied to account for toxicodynamic variability. Ocular irritation may vary between humans and animals, and the irritation threshold for lacrimation in animals may also vary across animals. Toxicokinetic variability across species is unlikely to be significant for ocular irritation that impacts the outer surface of the eye.

An UF_A is not applied for human data such as the sensory irritation and dizziness reported in ([Lehmann and Schmidt-Kehl, 1936](#)), so the effective UF_A value is 1 for that HEC.

2) Intraspecies Uncertainty Factor (UF_H) of 3 or 10

EPA uses a default UF_H of 10 to account for variation in sensitivity within human populations due to limited information regarding the degree to which human variability may impact the disposition of or response to *trans*-dichloroethylene. The UF_H of 10 is applied to immunotoxicity from intermediate or chronic exposures.

As with UF_A , UF_H is reduced to 3 for ocular irritation to account for variability in the sensitivity to *trans*-1,2-dichloroethylene as an irritant, with expected minimal contribution from metabolism as toxicokinetic differences across people are unlikely to contribute to human variability in the sensory irritation response.

The UF_H was established to account for uncertainty and variability that includes susceptible subpopulations, and research indicates that a factor of 10 (when considering both toxicokinetics and toxicodynamics) is sufficient in most cases ([U.S. EPA, 2002](#)). EPA expects that the UF_H used in the risk evaluation accounts for a significant portion of the intraspecies variability that includes all susceptible subpopulations applicable to *trans*-1,2-dichloroethylene, including those in occupational scenarios. A refinement to the UF_H would be warranted in cases where the susceptible subpopulation is specifically defined (*e.g.*, through knowledge of the chemical's

mode of action); however, EPA does not have any reasonably available data that would support modifying the UF beyond the standard 10 $\times$, or a further reduction of the 3 $\times$ value applied for acute ocular irritation.

3) LOAEL-to-NOAEL Uncertainty Factor (UFL) of 1 or 3

When PODs are based on a NOAEL or BMDL, the value represents an absence of adverse effect and therefore, an additional UF is not needed. For an endpoint based on a LOAEL (*i.e.*, lacrimation in [Hurt et al., 1993](#)), a UFL of 3 was applied to account for the uncertainty inherent in extrapolating from the LOAEL to the NOAEL. A larger UFL of 10 was considered but not applied because ocular irritation is a mild effect and a larger UFL would result in a NOAEL-equivalent POD below that of the BMDL value that was dismissed.

The HED for immunotoxicity (extrapolated to an HEC) was BMD modeled, so a UFL does not apply (equivalent to a value of 1).

4) Subchronic-to-Chronic Uncertainty Factor (UFs) of 3 or 10

In the absence of a chronic study, EPA used a UFs of 10 for oral chronic exposure. This is supported by findings from [Shopp et al., 1985](#) showing no reduction in humoral immunity response at 14 days, but a statistically significant decrease seen at 90 days, indicating a duration response. Decreased humoral immunity based on decreases in AFCs is considered an adverse effect of biologically relevant concern ([Ladics, 2007](#); [Luster et al., 1992](#)); see Section 2.3.1.2.4).

EPA applied a reduced UFs of 3 for chronic inhalation because extrapolating from the oral HED is likely already conservatively health protective since the extrapolated HEC from [Shopp et al., 1985](#) is 116 mg/m³ (29.4 ppm) and repeated-dose effects on immune cells following inhalation exposure were only reported in the literature at 4,000 ppm (15,542 mg/m³).

Table 2-12. Uncertainty Factors Applied Across Exposure Scenarios

Endpoint	Reference	Duration	Route	Total UF
Ocular irritation/ CNS depression	Hurtt et al., 1993)	Acute	Inhalation	30 (UF _A = 3; UF _H = 3; UF _L = 3)
Decreased humoral immune response (AFCs)	Shopp et al. (1985)	Intermediate	Oral	30 (UF _A = 3; UF _H = 10)
			Inhalation	30 (UF _A = 3; UF _H = 10)
			Dermal	30 (UF _A = 3; UF _H = 10)
		Chronic	Oral	300 (UF _A = 3; UF _H = 10; UF _s = 10)
			Inhalation	100 (UF _A = 3; UF _H = 10; UF _s = 3)
			Dermal	100 (UF _A = 3; UF _H = 10; UF _s = 3)
CNS – central nervous system; UF = uncertainty factor; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; UF _s = subchronic-to-chronic uncertainty factor;				

2.3.3 Weight of Scientific Evidence Conclusions for Non-Cancer Human Health Hazard

EPA considered evidence integration conclusions and dose-response considerations from the above sections additional factors to choose overall hazard confidence levels based on the following characteristics:

- evidence integration/weight of scientific evidence judgements;
- selection of most critical endpoint and study;
- relevance to exposure scenario;
- dose-response considerations; and
- PESS sensitivity.

The following section summarizes the strengths and limitations from summary table of confidence for each hazard endpoint and exposure duration, drawing upon information from previous sections and additional considerations as needed. Appendix B presents the overall rankings for the above characteristics.

2.3.3.1 Strengths, Limitations, Assumptions, and Key Sources of Uncertainty for the Hazard Identification and Selection of PODs for Human Health Hazard Assessment

2.3.3.1.1 Acute Non-Cancer

Evidence Integration Conclusions

As summarized in Section 2.3.1.1, there is slight human evidence for eye irritation from a single study on two volunteers exposed for less than an hour ([Lehmann and Schmidt-Kehl, 1936](#)). There is moderate animal evidence for both ocular and dermal irritation in the form of lacrimation and erythema, respectively. There is slight human evidence and slight-to-moderate animal evidence for sensory irritation and CNS depression/solvent neurotoxicity, which is associated with ocular irritation in both human and animal studies. Although these effects may not be severe or permanent, they can cause adverse effects and potentially impact performance in the workplace.

Selection of Most Critical Endpoint and Study

EPA has moderate confidence in the selection of ocular irritation and the representative study ([Hurtt et al., 1993](#)). Although it is uncertain whether lacrimation is the most sensitive measure of irritation, the response was observed in a dose-response manner, is corroborated by another outcome observed in the study (periocular staining), and can be directly associated with adverse eye effects. EPA derived a POD for risk estimation of acute exposures based on ocular irritation (lacrimation) effects in female rats following gestational exposure, with additional support from a single study in humans on two volunteers ([Lehmann and Schmidt-Kehl, 1936](#)). Ocular irritation is also associated with neurotoxicity, whether from lacrimation as a symptom of cholinergic/trigeminal responses or based on general CNS depression ([Van Thriel and Boyes, 2022](#)). Both effects together contribute to a reduced ability to escape which could endanger an exposed individual, especially in an occupational setting.

Relevance to Exposure Scenarios

The ocular irritation (and associated neurotoxicity) endpoint is highly relevant to the assigned acute exposure scenario. While the selected study is repeat-dose, irritation is based on peak concentration and is not duration-dependent; these effects were observed either immediately and/or routinely across the exposure period study ([Hurtt et al., 1993](#)). Therefore, the shortest unit of exposure resulting in a peak air concentration is most relevant for risk estimation of ocular irritation. This assumption is confirmed by the evidence from ([Lehmann and Schmidt-Kehl, 1936](#)) that reported effects on eye irritation (along with signs of solvent neurotoxicity such as dizziness) within minutes of exposure.

Dose-Response Considerations

Both lacrimation and periocular discharge from ([Hurt et al., 1993](#)) were successfully modeled, however the resulting BMCL values were likely too low or too high, respectively, when considering comparison to the human data from ([Lehmann and Schmidt-Kehl, 1936](#)). The LOAEC value was selected as the POD because when considering UFs, the risk thresholds falls in the middle of all options. There is reduced confidence in this value due to the use of a LOAEC, but this concern is mitigated because it is supported by the alternative options below or above the POD selected, and the LOAEC/UF is a very similar value to the NOAEC/UF from the humans study.

PESS Sensitivity

Laboratory inbred animal strains were used for examination of key endpoints and limited human evidence was available for acute non-cancer endpoints. Therefore, EPA was unable to quantify considerations from unique sensitivities. However, the risk threshold (POD/UF) for the LOAEC from the animal study is slightly lower than the equivalent threshold from the human study on only two volunteers and is expected to account for increased variability that might be expected from a larger sample size. While metabolism is not expected to contribute to ocular irritation (or associated neurotoxicity), EPA maintained a $3\times$ UF_A and UF_H to account for toxicodynamic differences in sensitivity of symptoms to the chemical in the air around the eyes. See Section 2.5 for more details on how PESS considerations were incorporated into the preliminary hazard assessment.

2.3.3.1.2 Intermediate/Chronic Non-Cancer

Evidence Integration Conclusions

Immune effects were observed across multiple rodent studies in both inhalation and oral studies, although several measures of immunity also demonstrated no effect in different study types or sexes. The totality of the dataset supports a general indication of immunosuppression, however for any individual measurement the results were inconsistent. One 14-week oral study using microencapsulated *trans*-1,2-dichloroethylene in feed demonstrated no change in organ weights or immune cell counts ([NTP, 2002](#)); however, there was substantial chemical loss of up to 75% in certain batches that do not appear to have been accounted for in dosing estimates (though even accounting for loss doses were generally higher than standard limit doses). There were no relevant human studies, but moderate confidence was assigned based on animal studies. Immune effects primarily presented as indicators of immune suppression, specifically T cell-dependent antibody responses based on reduced AFCs, and this was further supported by a single mechanistic study providing evidence of decreased phagocytosis following *trans*-1,2-dichloroethylene exposure *in vitro*.

As mentioned above, other indicators of immunosuppression were inconsistent across sexes, routes, and durations (although evidence of reduced lymphocytes appeared across multiple studies), so confidence is lower for immunosuppression more broadly. However, positive response for reduced IgM AFCs is sufficient to indicate T cell-mediated immune suppression and represents a functional immune deficit.

Selection of Most Critical Endpoint and Study

EPA had the strongest confidence in the selection of study and endpoints representing immunotoxicity. The endpoint used for POD selection from ([Shopp et al., 1985](#)) was reduced antibody-forming cells, considered one of the best predictors for measuring T cell-dependent humoral immunity ([Ladics, 2007](#)). There was some variability in the immune responses reported within that study between sexes and across different assays which contribute to uncertainty in endpoint selection, but the selected endpoint represents the best representative option among endpoints supported by the weight of scientific evidence when accounting for all the factors described in Section 2.3.2.1 (*i.e.*, study quality, dose range, exposure duration, relevance, and endpoint sensitivity, etc).

Relevance to Exposure Scenarios

The ([Shopp et al., 1985](#)) study exposed rats for 90 days, which is highly relevant to intermediate exposure scenarios. There is uncertainty in extrapolating this study to chronic exposures however, requiring an additional subchronic to chronic uncertainty factor. Similarly, the ([Shopp et al., 1985](#)) was oral and is directly applicable to oral exposure scenarios. Route-to-route extrapolation is required for dermal and inhalation routes; the database does not contain a dermal immunotoxicity study and there are no inhalation studies investigating functional immunity, so uncertainty is increased when applying the immunotoxicity POD to those exposure routes. However, the expected minimal contribution of metabolism to the toxicity of *trans*-1,2-dichloroethylene (Section 2.2.3) suggests that toxicokinetic differences across routes (such as first-pass metabolism through the liver via ingestion) are likely minor, and toxicological responses should be similar regardless of exposure route.

Dose-Response Considerations

BMD modeling was successful for the ([Shopp et al., 1985](#)) dataset. However, visual fit was questionable in the range of the BMD/BMDL. EPA additionally BMD modeled the dataset with highest dose dropped which provided improved fit and a lower BMDL value, however this result was not used for POD selection. While visual fit was improved, losing a dose group introduces too much uncertainty with only two non-zero doses remaining for the result to be reliable when modeling of the full dataset was successful. Overall, while successful BMD modeling improves the precision of the estimate compared to a NOAEL or LOAEL, confidence in the specific value is reduced due to the large spacing between dose groups resulting in large-scaled residuals near the BMD. For extrapolation of the oral POD to the dermal route there is additional quantitative uncertainty because of the highly variable results from the dermal absorption data (Appendix C and ([U.S. EPA, 2026f](#)))

PESS Sensitivity

As stated for acute exposures, laboratory inbred animal strains were used for examination of key endpoints and limited human evidence was available for acute non-cancer endpoints. However, the intermediate/chronic POD is considered protective of individuals sensitive to disruptors of immunity because EPA selected the most sensitive endpoint, sex, and biological response from ([Shopp et al., 1985](#)) among several immune assays in that study, and the findings in ([Shopp et al., 1985](#)) are health-protective when considering all reliable studies for repeated-dose outcomes. See Section 2.5 for more details on how PESS considerations were incorporated into the hazard assessment.

2.4 Evaluation of the Carcinogenicity of *trans*-1,2-Dichloroethylene Using the ReCAAP Weight-of-Evidence Framework

2.4.1 Introduction

No adequate chronic toxicity or cancer bioassays are available to evaluate the carcinogenicity of *trans*-1,2-dichloroethylene using standard approaches as described in EPA *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005](#)). To evaluate the extent to which the lack of sufficient carcinogenicity studies imparts significant uncertainty on the human health risk assessments, a read-across and weight-of-the-scientific evidence analysis was employed to assess potential cancer risks for *trans*-1,2-dichloroethylene in the absence of any direct cancer evidence. EPA has used the ReCAAP Framework along with considerations of the Integrated Approach to Testing and Assessment (IATA) case studies demonstrating applicability of the weight of evidence ReCAAP Framework ([OECD, 2024](#); [Hilton et al., 2022](#)).

Although initially developed for evaluating cancer bioassay testing requirements for agrochemicals, EPA believes many of the same scientific principles in the ReCAAP Framework apply to TSCA risk

evaluations; this framework was used in the risk evaluations for diisobutyl phthalate (DIBP) and dicyclohexyl phthalate (DCHP) ([U.S. EPA, 2025a](#)) and was reviewed favorably by the SACC ([U.S. EPA, 2025d](#)). The ReCAAP Framework takes into consideration multiple lines of evidence including information pertaining to nomenclature, physical and chemical properties; exposure and use patterns; ADME properties; and toxicological data (e.g., genetic toxicity, acute toxicity, subchronic toxicity, hormone perturbation, immunotoxicity, mode of action [MOA]). The framework was developed by a workgroup comprised of scientists from academia, government (including EPA), non-governmental organizations, and industry stakeholders. Recently, the OECD has published several IATA case studies demonstrating applicability of the weight of evidence ReCAAP framework to risk assessment ([OECD, 2024](#)). Goetz et al. (2024) also published three retrospective case studies demonstrating application of the ReCAAP Framework for three agrochemical active substances.

EPA used some, but not all, elements of the ReCAAP framework and OECD case studies. The weight of scientific evidence for cancer hazard was evaluated based on data from *trans*-1,2-dichloroethylene and the analogous *cis*- isomer (or a mixture of both) informing direct evidence of carcinogenicity (Section 2.4.2), non-cancer health effects in cancer target organs (Section 2.4.3), genotoxicity (Section 2.4.4), and mechanistic data on MOA (Section 2.4.5). Conclusions are provided in Section 2.4.6.

The limited database for *trans*-1,2-dichloroethylene was supplemented with reasonably available information on the *cis*- and unspecified or mixed isomers based on existing and recent governmental assessments ([ATSDR, 2025](#); [U.S. EPA, 2010](#)). Although other chlorinated solvents including several TSCA chemicals could serve as reasonable structural analogs (see details on read-across analysis for environmental hazard in Appendix E), the unique metabolism of *trans*-1,2-dichloroethylene (with suicide inhibition of oxidative CYP metabolism, resulting in a nonlinear relationship between dose/duration and metabolite exposure at the site of action, see Section 2.2.2) does not resemble any other TSCA chemicals with finalized or ongoing risk evaluations and the toxicokinetics would therefore be quite different for non-isomer chemicals. Suicide inhibitors irreversibly inactivate target enzymes by forming covalent adducts after enzyme-mediated activation, which complicates hazard because toxicity depends on metabolism of the parent and the enzyme's capacity to bioactivate it. Irreversible inhibition alters enzyme activity and changes rates of metabolite formation; a surrogate chemical that produces the same primary metabolites at the same rate under normal enzyme activity may not cause an analogous reaction if the parent compound inactivates the enzyme. Additionally, since suicide inhibition is dose- and time-dependent, structural similarity assumptions may be difficult to characterize. Lastly, if internal toxicity arises from metabolites, an analog without suicide inhibition might not be bioactivated to the same reactive species and might not share the same MOA as *trans*-1,2-dichloroethylene. Consequently, inter-individual variability in genetic polymorphisms may become more uncertain.

2.4.2 Evidence of Carcinogenicity

2.4.2.1 Epidemiology Studies

A case-control study evaluating children born to mothers exposed during pregnancy to *trans*-1,2-dichloroethylene in drinking water (also containing vinyl chloride, trichloroethylene, tetrachloroethylene, and benzene) at U.S. Marine Corps Base Camp Lejeune in North Carolina did not find associations between exposure and childhood cancer ([Ruckart et al., 2013](#)). The study population included 539 children, with 13 cases of hematopoietic cancers diagnosed before 20 years of age. The OR for combined leukemia and non-Hodgkin's lymphoma was 1.5 (95% CI 0.5, 4.7; $p = 0.44$). Another study found no associations between male breast cancer and exposure to *trans*-1,2-dichloroethylene in drinking water at Camp Lejeune ([Ruckart et al., 2015](#)). The study population consisted of 444 males, with 71 cases of breast cancer. Odds ratios for low cumulative exposure (>0 to <472 ppb-months) and

high cumulative exposure (≥ 472 ppb-months) were 0.67 (95% CI 0.03, 4.25) and 1.99 (95% CI 0.42, 7.47), respectively. Additionally, although the exposures were considered to be to *trans*-1,2-dichloroethylene, no information was reported to confirm that the *trans*- form was the only isomer present in drinking water.

There are no available epidemiological cancer studies for *cis*-1,2-dichloroethylene. However, there is one additional study on non-specified isomers of 1,2-dichloroethylene. In a case-control occupational study ([Kernan et al., 1999](#)), there was no association between increased 1,2-dichloroethene exposure (based on categorical ordinal binning) and pancreatic cancer.

2.4.2.2 Animal Studies

EPA did not identify laboratory animal studies that evaluated carcinogenic effects for *trans*-1,2-dichloroethylene, and there are no available chronic duration studies of more than a year for the chemical generally. There are also no rodent bioassays for the *cis*- or unspecified isomer mixture. No tumors were observed in rats administered *trans*-1,2-dichloroethylene for 90 days via inhalation ([DuPont Haskell Lab, 1998](#)).

The only chronic duration study was from Dow Chemical Company, a 6-month inhalation exposure using an unspecified isomer mixture of dichloroethylene on several different laboratory animals ([1994](#)). This study did not investigate any measures of carcinogenicity, however.

2.4.2.3 Existing Weight-of-Evidence Cancer Classifications

1,2-Dichloroethylene as either isomer (*cis*-/*trans*-) is not listed in the NTP 15th Report on Carcinogens ([NTP, 2021](#)). It has also not been evaluated by the International Agency for Research on Cancer (IARC).

EPA's *Toxicological Review of 1,2-Dichloroethylene* ([U.S. EPA, 2010](#)) determined that there is "inadequate information to assess the carcinogenic potential" of *trans*-1,2-dichloroethylene. The same classification was applied to the *cis*- isomer.

2.4.3 Non-Cancer Health Effects in Potential Cancer Target Organs

While there are not any direct investigations of carcinogenicity in animal studies and a very limited database of epidemiological data, non-cancer health effects can provide indirect evidence of potential early key events in carcinogenic pathways such as metaplasia. Organ systems with the most non-cancer evidence potentially informing carcinogenicity are summarized below. Generally, there was low toxicity for most organ systems—especially when considering concentrations/doses below standard toxicity testing upper limits (1,000 mg/kg-day or ppm). The critical non-cancer endpoints of sensory irritation/CNS depression and immunosuppression (Section 2.3.2.1) are potentially temporarily disabling or may increase susceptibility to infection. Although sensory irritation/CNS depression is not being associated with mechanisms of carcinogenesis, immunosuppression can result in a depletion of tumor cell antigen recognition resulting in cells escaping immune surveillance and facilitating their proliferation to form tumors.

Blood

As summarized in Section 2.3.1.1, *trans*-1,2-dichloroethylene exposure generally caused either no effects or a reduction in humoral immune function. While decreased immunity could impair immune surveillance and could be a risk factor for cancer susceptibility (as mentioned in the ReCAAP Framework), increased inflammation is more directly associated with key events in carcinogenesis and immunosuppression would not lead to tumor formation alone. A 90-day oral study on the *cis*- isomer

only identified an increase of 11% relative thymus weight at the highest dose of 870 mg/kg-day without any corresponding histopathology ([ATSDR, 2025](#); [McCauley et al., 1995](#)).

Inconsistent observations of reduced erythrocytes and hematocrit were reported across several studies for *trans*-1,2-dichloroethylene ([NTP, 2002](#); [Hayes et al., 1987](#)) and *cis*-1,2-dichloroethylene ([McCauley et al., 1995](#)) isomers. Inhalation exposure to 1,000 ppm for up to 6 months on an isomer mixture did not result in any change to hematocrit or hemoglobin ([Dow Chemical, 1994](#)).

Liver

As summarized in Section 2.3.1.3, there is some evidence of liver toxicity from *trans*-1,2-dichloroethylene exposure, primarily via the oral route, but reported findings were inconsistent across routes, doses, species, and sexes and the lowest dose inducing an effect was 175 mg/kg-day. The only relevant mechanistic evidence observed was fat accumulation/degeneration following 16 weeks of inhalation exposure to 200 ppm ([Freundt et al., 1977](#)), but this study was only described qualitatively.

The *cis*- isomer induced increased liver weight following 90 days of oral exposure to 32 or 870 mg/kg-day ([McCauley et al., 1995](#)) but without any effect on serum enzymes or histopathology; mixed isomers did not cause effects on serum enzymes in rats or rabbits via inhalation for up to 6 months ([Dow Chemical, 1994](#)). Overall, there is insufficient information on liver effects to inform whether any early key events for liver cancer may be induced.

Other Organ Systems

There is no indication of renal toxicity from *trans*-1,2-dichloroethylene exposure based on available rodent studies (Section 2.3.1.6) and only qualitative histopathological evidence of respiratory tissue damage in a single study ([Freundt et al., 1977](#)), Section 2.3.1.7). There is also no indication of altered histopathology in reproductive organs (Section 2.3.1.3), changes in adrenal or thyroid glands ([NTP, 2002](#)), or evidence of endocrine disruption based on aromatase activity inhibition ([ATSDR, 2025](#)).

There is no evidence of cancerous precursors in kidney, respiratory tissue, or thyroid from *cis* ([McCauley et al., 1995](#)) or mixed isomers (only kidney examined, ([Dow Chemical, 1994](#))).

2.4.4 Genotoxicity and *In Silico* Evidence

Genotoxicity

trans-1,2-Dichloroethylene: *trans*-1,2-dichloroethylene has mixed but primarily negative genotoxicity results when tested *in vitro* or *in vivo*. *In vitro* genotoxicity experiments (Table 2-13) include two studies of mutagenicity in yeast, three bacterial mutagenicity studies, several studies of sister chromatid exchange and chromosomal aberrations in mammalian cell lines, and a study of unscheduled DNA synthesis in rat hepatocytes. There is conflicting evidence for the mutagenicity of *trans*-1,2-dichloroethylene in bacterial and yeast studies. A study with *Saccharomyces cerevisiae* yielded positive results for reverse mutations with S9 activation ([Bronzetti et al., 1984](#)). Another study in *S. cerevisiae* found increased revertants at the highest dose tested but severe effects on survival made a positive result unreliable ([Koch et al., 1988](#)). Of the three studies in *Salmonella typhimurium*, only one study found evidence of mutations with and without S9 activation ([Strobel and Grummt, 1987](#)). The other two bacterial studies had negative results ([NTP, 2002](#); [Mortelmans et al., 1986](#); [Simmon et al., 1977](#)). *trans*-1,2-Dichloroethylene did not increase the frequency of chromosomal aberrations or sister chromatid exchange in any mammalian cell line tested ([NTP, 2002](#); [Sawada et al., 1987](#)). A study of unscheduled DNA synthesis in Long-Evans rat hepatocytes also yielded negative results ([Costa and Ivanetich, 1984](#)). Onfelt ([1987](#)) reported increased percentages of cells with aneuploidy in experiments using V79 Chinese

hamster lung cells exposed to *trans*-1,2-dichloroethylene, but there was no evidence of a concentration-response relationship at the exposure levels tested (6.5-26 mM).

Table 2-13. *In Vitro* Genotoxicity Studies on *trans*-1,2-Dichloroethylene

Reference(s)	Test System	Doses and Exposure Conditions	Endpoint	Results	Comment
(NTP, 2002) ; Mortelmans et al. (1986)	<i>Salmonella typhimurium</i> TA1535, TA1537, TA97, TA98, TA100	Up to 10,000 µg/plate or cytotoxic dose	Mutation	Negative (± S9)	
Simmon et al. (1977)	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA98, TA100, <i>Escherichia coli</i> WP2, <i>Saccharomyces cerevisiae</i> D3	Up to 5 mg/plate or cytotoxic dose	Mutation	Negative (± S9)	Chemical purity not determined
Strobel and Grummt (1987)	<i>S. typhimurium</i> TA97, TA98, TA100, TA104	0.01, 0.025, 0.05, 0.1, 0.25, 0.5, 1.0 mg/plate	Mutation	Positive (± S9)	Positive in 3 of 4 strains; weaker mutagenicity observed without S9
Greim et al. (1975)	<i>E. coli</i> K12 (gal+, arg+, nad+, MTR)	2.3 mM	Mutation	Negative (± liver microsomes)	
Bronzetti et al. (1984)	<i>Saccharomyces cerevisiae</i> D7	40, 80, 100 mM, <i>trans</i> -1,2-dichloroethylene dissolved in DMSO vehicle	Mutation	Positive (+S9)	Cytotoxicity was observed at positive doses.
Koch et al. (1988)	<i>S. cerevisiae</i> D7, D61.M	51.5, 64.4, 77.3 mM	Mutation	Negative (± S9)	An increase in revertants and induction of mitotic aneuploidy was observed at the highest dose in D61.M, but the data were not considered reliable due to poor survival.
NTP (2002)	Chinese hamster ovary cells	Up to 12,630 µg/mL or cytotoxic dose	Chromosomal aberrations	Negative (± S9)	
Sawada et al. (1987)	Chinese Hamster lung fibroblast cell line	0.25, 0.5, 1.0, 2.0 mg/mL	Chromosomal aberrations	Negative (± S9)	
NTP (2002)	Chinese hamster ovary cells	Up to 12,630 µg/mL or cytotoxic dose	Sister chromatid exchange	Negative (± S9)	

Reference(s)	Test System	Doses and Exposure Conditions	Endpoint	Results	Comment
Sawada et al. (1987)	Chinese Hamster lung fibroblast cell line	0.25, 0.5, 1.0, 2.0 mg/mL	Sister chromatid exchange	Negative (+/- S9)	
Costa and Ivanetich (1984)	Long-Evans rat hepatocytes	4.3 mM (highest non-cytotoxic dose) dissolved in ethanol vehicle	Unscheduled DNA synthesis	Negative	
Onfelt (1987)	V79 Chinese hamster lung cells	6.5, 13, and 26 mM	Aneuploidy	Positive	Increased percentages of cells with >22 chromosomes seen at all exposures but without a dose-response
Positive results are bolded .					

In vivo genotoxicity tests are shown in Table 2-14. Bronzetti et al. (1984) observed *decreases* in mitotic gene conversion and point mutations in *S. cerevisiae* injected into mice that were then exposed to *trans*-1,2-dichloroethylene via oral gavage. *In vivo* studies of micronuclei and sister chromatid exchanges yielded negative results. *trans*-1,2-Dichloroethylene did not alter the frequency of micronuclei in the peripheral blood of mice exposed to up to 8000 mg/kg-day through microcapsules in feed for 14 weeks (NTP, 2002). In mice exposed to single dose of 2000 mg/kg via intraperitoneal administration, the frequency of sister chromatid exchanges in the bone marrow was not different from controls (NTP, 2002).

Table 2-14. *In vivo* Genotoxicity Studies on *trans*-1,2-Dichloroethylene

Reference	Species	Tissue/Cell Type	Dose, Frequency, and Route	Endpoint	Result
Bronzetti et al. (1984)	<i>Saccharomyces cerevisiae</i> injected retro-orbitally prior to dosing in male Swiss-Webster albino mice	Liver, Kidney, Lung	1,300 mg/kg once, or 300 mg/kg-day for 8 days with 600 mg/kg on day 9 for a total of 3,000 mg/kg (gavage in corn oil)	TRP+ convertants 4 hours after final dosing	Decrease in TRP+ convertants in kidney and lung at 1,300 mg/kg
Bronzetti et al. (1984)	<i>Saccharomyces cerevisiae</i> injected retro-orbitally prior to dosing in male Swiss-Webster albino mice	Liver, Kidney, Lung	1,300 mg/kg once, or 300 mg/kg-day for 8 days with 600 mg/kg on day 9 for a total of 3,000 mg/kg (gavage in corn oil)	ILV+ revertants 4 hours after final dosing	Decrease in ILV+ revertants in kidney at 1,300 mg/kg or a total dose of 3,000 mg/kg
NTP (2002)	Male B6C3F1 mice	Bone marrow	2000 mg/kg (single dose, intraperitoneal)	Sister chromatid exchanges 17 hours after dosing	No significant effects on sister chromatid exchange
NTP (2002)	Male and female B6C3F1 mice	Peripheral blood	Up to 8000 mg/kg-day for 14 weeks (through	Micronuclei 17 hours after dosing	No significant effects on micronuclei

Reference	Species	Tissue/ Cell Type	Dose, Frequency, and Route	Endpoint	Result
			microcapsules in feed)		
TRP+ = tryptophan-independent; ILV+ = isoleucine prototrophy					

cis-1,2-Dichloroethylene and Mixtures: Similar results are obtained for the *cis*- isomer, though there are some positive *in vivo* results for gene mutation/conversion in several yeast assays ([ATSDR, 2025](#)). Human peripheral blood lymphocytes were also positive for micronuclei and DNA damage from an unknown isomer mixture *in vitro* using the comet assay both with and without metabolic activation ([Tafazoli and Kirsch-Volders, 1996](#)).

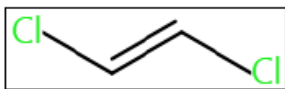
Overall, results are primarily negative for all isomers, but the evidence is more variable for *cis*- and mixed isomers. Interestingly, *in vitro* results were generally the same with and without metabolic activation, suggesting that metabolism may not substantially modulate the toxicity of 1,2-dichloroethylene.

In Silico Evidence

trans-1,2-Dichloroethylene was run through EPA's [OncoLogic™ model version 9.0](#) (accessed December 10, 2025), which applies established toxicological knowledge rules based on expert human judgement and empirical studies to qualitatively estimate the carcinogenicity of a chemical. The model uses structure-activity relationships, expected metabolism, and empirical data to produce a score based on level of concern.

OncoLogic applies one of six “concern levels”: Low, Marginal, Low-Moderate, Moderate, High-Moderate, and High. The OncoLogic report for *trans*-1,2-dichloroethylene assigned a concern level of Marginal. The description for Marginal concern is: “likely to have equivocal carcinogenic activity or may be weakly carcinogenic at doses exceeding maximum tolerated doses.” The report is shown below in Figure 2-2.

OncoLogic Justification Report



The level of concern for this compound, disregarding any highlighted substituents, is MARGINAL. The effect of any highlighted substituents is uncertain.

JUSTIFICATION

Haloalkanes and haloalkenes represent one of the most important classes of synthetic chemicals. Many of these compounds are produced in enormous quantities and are known or suspected carcinogens (e.g., methylene chloride, carbon tetrachloride) with multiple mechanisms involved in their carcinogenic action. Some haloalkanes (e.g., halomethanes) and haloalkenes (e.g., allylic halides) are direct-acting alkylating agents. Others are carcinogenic through biotransformation to highly reactive electrophilic intermediates. Examples of metabolism to reactive intermediates include: (1) conversion of chloroform to phosgene; (2) conversion of polyhalogenated compounds (such as carbon tetrachloride, hexachloroethane) to free radicals; (3) oxidation of haloalkenes to epoxides; and (4) conversion of vic-dihaloethanes to episulfonium ions after conjugation with glutathione.

The chemical reactivity of direct-acting haloalkanes and haloalkenes is dependent on the nature, the number, and the position of the halogen substituents. As the size of the halogen atom increases (in the order: $F < Cl < Br < I$), the bond length increases and the bond energy decreases, thus weakening the C-X (X = halogen) bond and facilitating the leaving of the halogen atom in nucleophilic reactions. In general, the chemical reactivity of direct-acting haloalkanes/haloalkenes follows the order: $I > Br > Cl > F$. However, chemical reactivity decreases with the increase in the degree of halogenation; geminally substituted (with an additional halogen at a carbon atom) halo-compounds are generally less reactive in comparison with those that are monohalo-/vicinally substituted.

The potential of haloalkanes and haloalkenes to alkylate cellular nucleophiles is the basis of concern for their carcinogenicity. However, a number of haloalkanes and haloalkenes appear to be non-genotoxic; their carcinogenic activity is believed to be related to cytotoxicity and various epigenetic mechanisms. The concern level of the compound is determined based on structure-activity relationship analysis as well as mechanistic considerations.

The haloethylene substituted with one chloro on one carbon, and one chloro on the other carbon, with the trans isomer predominating, has a level of concern of MARGINAL.

The final level of concern for this compound is MARGINAL.

Figure 2-2. OncoLogic Report for *trans*-1,2-Dichloroethylene

2.4.5 Mechanistic Studies to Support a Proposed Mode of Action (MOA) for Carcinogenicity

There is insufficient mechanistic information to support any proposed mode of action for cancer. There is an absence of any evidence indicating that *trans*-1,2-dichloroethylene causes cancer and limited mechanistic studies available to evaluate considerations such as key characteristics of cancer (Krewski et al., 2019). The inhibitory effect on oxidative CYP enzymes (Section 2.2.3) indicates that unlike many other chlorinated solvents, *trans*-1,2-dichloroethylene is expected to exhibit time- and dose-dependent kinetic behavior, with a time-dependent decrease in reactive metabolite formation and a nonlinear relationship between dose/duration and target site metabolite exposure, thereby reducing the contribution of reactive oxidative metabolites to its toxicity over time. Oxidative metabolites are therefore unlikely to substantially contribute to toxicity from repeated, chronic-duration exposures.

2.4.6 Weight-of-Scientific-Evidence Conclusions Regarding Carcinogenicity of *trans*-1,2-Dichloroethylene

Due to the limited information available, particularly the absence of chronic bioassays, and limited available evidence on genotoxicity and other mode of action information for *trans*-1,2-dichloroethylene to inform a cancer classification in accordance with EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the Agency instead applied the ReCAAP Framework weight of scientific evidence analysis summarized below. This analysis used on data for *trans*-1,2-dichloroethylene and its isomer to evaluate the extent to which the lack of carcinogenicity studies imparts significant uncertainty on the human health risk assessment. Based on the following findings, has preliminarily determined that there is sufficient evidence for evaluating the carcinogenicity of *trans*-1,2-dichloroethylene based on the reasonably available information, leading to a conclusion that carcinogenic effects from *trans*-1,2-dichloroethylene are not expected as summarized below:

- In the few epidemiological cancer studies available, no statistically significant association with exposure to *trans*-1,2-dichloroethylene or an isomer mixture was identified.
- There are no histopathological indications of pre-cancerous cellular changes such as metaplasia/neoplasia or cellular regeneration for *trans*-1,2-dichloroethylene or the *cis* isomer. Additionally, relatively high doses of at least 175 mg/kg-day or 200 ppm were required for most non-cancer effects, with overall low toxicity across most organ systems below typical limit doses/concentrations.
- Genotoxicity studies demonstrate an overall absence of evidence for DNA damage or mutagenicity from *trans*-1,2-dichloroethylene and the *cis*- isomer or mixtures.
- *In silico* modeling of *trans*-1,2-dichloroethylene assigns only “marginal” concern for carcinogenicity.
- Limited mechanistic information does not support activation of key events or key characteristics of carcinogenicity.
- The self-inhibiting metabolism of *trans*-1,2-dichloroethylene reduces the concern for reactive metabolites that are common to other chlorinated solvents.

Based on the weight of scientific evidence, as stated above, EPA has preliminarily concluded that quantitative cancer risk assessment of *trans*-1,2-dichloroethylene is not warranted and carcinogenic effects from *trans*-1,2-dichloroethylene are not expected. Although there is some remaining uncertainty based on the absence of direct cancer data or chronic toxicity data, the overall weight of scientific evidence is sufficient for making this conclusion and any additional cancer bioassays would be unlikely to provide evidence leading to a different conclusion.

In considering the absence of adequate chronic cancer data alongside all other available evidence used in evaluating carcinogenicity, EPA has slight-to-moderate confidence in this conclusion. This approach is consistent with TSCA requirements for considering the weight of scientific evidence and making conclusions based on the best available science. Data from chronic exposure studies and more directly relevant carcinogenicity data would be required for raising the Agency’s confidence that carcinogenic effects are not expected or in order to make a formal cancer classification in accordance with (U.S. EPA, 2005).

2.5 Consideration of PESS and Aggregate Exposure

2.5.1 Hazard Considerations for Aggregate Exposure

EPA has defined aggregate exposure as “the combined exposures from a chemical substance across multiple routes and across multiple pathways” (40 CFR 702.33). Aggregation across routes could be biologically relevant for oral and dermal routes, which will use the same PODs. However, given the physical-chemical properties of *trans*-1,2-dichloroethylene (see Table 2-1 in (U.S. EPA, 2026b)) and the limited dermal absorption (Section 2.2.3), non-inhalation routes are likely to be very minor contributors to the overall risk for the chemical. The acute inhalation POD is the risk driver for all durations and is specific to the inhalation route; therefore, aggregation across routes is not expected to be relevant except when inhalation exposure is not present.

2.5.2 PESS Based on Greater Susceptibility

In this section, EPA addresses subpopulations expected to be more susceptible to *trans*-1,2-dichloroethylene exposure than other populations. Table 2-15 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 *trans*-1,2-dichloroethylene.

EPA examined sources of biological susceptibility for each of the susceptibility factors in Table 2-15. 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 (<https://www.epa.gov/expobox/exposure-assessment-tools-lifestages-and-populations-highly-exposed-or-other-susceptible>, accessed June 8, 2026).

EPA used the most sensitive effects from rodent assays (including reproductive/developmental toxicity tests) that were supported by the weight of evidence and consistent with use of the best available science for non-cancer dose-response modeling. A 10× 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.

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Table 2-15. PESS Evidence Crosswalk for Biological Susceptibility Considerations

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to <i>trans</i> -1,2-Dichloroethylene		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to <i>trans</i> -1,2-Dichloroethylene		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
Lifestage	Embryos/fetuses/infants	Decreased mean female fetal body weights were observed in rodents following gestational inhalation exposure.	Hurtt et al. (1993)			The most sensitive effects from rodent assays were used for non-cancer dose-response modeling; effects in adult animals identified lower PODs than those identified for developmental effects.
	Pregnancy/lactating status	A dose-related increase in early resorptions was observed in pregnant rodent dams exposed via inhalation.	Hurtt et al. (1993)			The most sensitive effects from rodent assays were used for non-cancer dose-response modeling; there was no evidence of increased susceptibility in pregnant animals.
	Males of reproductive age	No direct evidence identified.		Development and maturation of sperm in males of reproductive age are sensitive to perturbations in the biochemical environment of the male reproductive system.	U.S. EPA (1996)	EPA applied a 10× UF _H .
	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 effects due to age-related reductions in immune response (<i>i.e.</i> , immunosenescence).	Fulop et al. (2016)	EPA applied a 10× UF _H .

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Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to <i>trans</i> -1,2-Dichloroethylene		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to <i>trans</i> -1,2-Dichloroethylene		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
Pre-existing disease or disorder	Health outcome/target organs	No direct evidence identified.		Any pre-existing condition affecting a target organ (e.g., the immune system or glucose homeostasis in the liver) will increase susceptibility to <i>trans</i> -1,2-dichloroethylene toxicity in that organ.	ATSDR (2005)	EPA applied a 10× UF _H . EPA also relied upon the most sensitive endpoint for immunotoxicity from among scientifically supported options.
	Toxicokinetics	Suicide inhibition of CYP enzymes could impact sensitivity to processing of drugs and other xenobiotics, dependent on exposure levels and timing of co-exposure.	Section 2.2.3	Higher rates of metabolism (e.g., by cytochrome P450 isoform 2E1 [CYP2E1]) resulting in increased reactive metabolites will increase susceptibility, especially for liver toxicity (a major site of metabolism).	ATSDR (2025)	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	No direct evidence identified.		Alcohol consumption (which induces CYP2E1) and alcoholism are well-established to be associated with liver disease.	ATSDR (2025) ; Crabb (1993)	No direct evidence available.
	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.

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Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to <i>trans</i> -1,2-Dichloroethylene		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to <i>trans</i> -1,2-Dichloroethylene		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	Description of Interaction	Key Citation(s)	
Sociodemographic	Sex	Health effects in rodents observed following oral or inhalation exposures often demonstrated differential sensitivity across sexes.	Hurtt et al. (1993) ; Shopp et al. (1985)			The most sensitive sex from rodent assays was used for non-cancer dose-response modeling.
Nutrition	Diet	Tissue:air coefficients suggest preferential accumulation in adipose tissue, suggesting that obesity may result in higher body burden for a given exposure.	Gargas et al. (1989) ; Gargas et al. (1988)			Quantitative data for this chemical is 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 <i>trans</i> -1,2-dichloroethylene.	Miller et al. (2001)	No direct evidence available.
	Toxicokinetics	No direct evidence identified.		Higher rates of metabolism (<i>e.g.</i> , by CYP2E1) resulting in increased reactive metabolites will increase susceptibility, especially for liver toxicity (a major site of metabolism).	ATSDR (2025)	No direct evidence available.

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to <i>trans</i> -1,2-Dichloroethylene		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to <i>trans</i> -1,2-Dichloroethylene		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Citations	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	No direct evidence identified.		Exposure to other chemicals that impact the same organ systems could result in additive or synergistic toxicity.	U.S. EPA (2003a, 1986)	No direct evidence available.

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2.6 Human Health Hazard Assessment Conclusions

In this human health assessment of *trans*-1,2-dichloroethylene, EPA derived distinct non-cancer PODs and corresponding UFs for inhalation and oral/dermal routes and for each duration category to be used for risk estimation. The database for *trans*-1,2-dichloroethylene is limited by the absence of any chronic studies, however a variety of study types covering multiple hazard outcomes were available.

Table 2-16 lists the studies and corresponding HECs, HEDs, and UFs that EPA is using for risk characterization following acute, intermediate, and chronic exposure, respectively. Previous sections and systematic review supplemental files ([U.S. EPA, 2026d](#); [U.S. EPA, 2026m](#); [U.S. EPA, 2026n](#); [U.S. EPA, 2026l](#)) provide additional information on key studies.

For consistency across exposure scenarios and with other risk evaluations, all HEDs are expressed as daily doses and most HECs are based on daily, continuous concentrations (24 hours/day, 7 days/week) assuming a breathing rate for individuals at rest. The exception is for ocular irritation, which is independent of duration. The HEC for ocular irritation was not duration-adjusted from the original study. For those PODs that were adjusted to continuous exposure, corresponding adjustments to exposure durations and frequencies and breathing rates are made in the exposure estimates used to calculate risks for individual exposure scenarios. For route-to-route extrapolation, where applicable, EPA applied exposure factors of 0.6125 m³/h (14.7 m³/24 h) breathing rate and 80 kg body weight.

Based on the weight of scientific evidence, EPA has preliminarily concluded that quantitative cancer risk assessment of *trans*-1,2-dichloroethylene is not warranted as carcinogenic effects from *trans*-1,2-dichloroethylene are not expected based on primarily negative results for genotoxicity, no evidence of precancerous lesions in subchronic studies, only “marginal” carcinogenicity concern from *in silico* modeling, and minimal formation of reactive metabolites (Section 2.4.6). Although there is some remaining uncertainty based on the absence of any direct cancer data or chronic toxicity data, the overall weight of scientific evidence is sufficient for making this conclusion and any additional cancer bioassays would be unlikely to provide evidence leading to a different conclusion.

Table 2-16. Non-Cancer Points of Departure and Critical Endpoints Used for Risk Estimates of Each Exposure Scenario

Target Organ System	Species	Duration	Study POD	Effect	HED (mg/kg-day)	HEC (mg/m ³)	Uncertainty Factors	Reference (OQD)	Confidence ^a
Acute Exposure Scenario (inhalation)									
Ocular/Neurological	Rats (Female)	6 hours/day GD 7-16	LOAEC = 7930 mg/m ³	Ocular irritation / CNS depression	N/A	7,930 mg/m ³ (2,000 ppm)	UF _A = 3; UF _H = 3; UF _L = 3; Total UF = 30	(Hurtt et al., 1993) (High)	Moderate-to-Robust
Intermediate Exposure Scenario (all routes)									
Immune	Mouse (Male)	90 days	NOAEL = 17 mg/kg-day	Decreased humoral immune response (AFCs)	BMDL _{1SD} = 21.4 mg/kg-day	116 mg/m ³ (29.4 ppm)	UF _A = 3; UF _H = 10; Total UF = 30	(Shopp et al. (1985)) (High)	Moderate-to-Robust (oral/inhalation); Moderate (dermal)
Chronic Exposure Scenario (oral)									

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Target Organ System	Species	Duration	Study POD	Effect	HED (mg/kg-day)	HEC (mg/m ³)	Uncertainty Factors	Reference (OQD)	Confidence ^a
Immune	Mouse (Male)	90 days	NOAEL = 17 mg/kg-day	Decreased humoral immune response (AFCs)	BMDL _{1SD} = 21.4 mg/kg-day	N/A	UF _A = 3; UF _H = 10; UF _S = 10; <i>Total UF</i> = 300	Shopp et al. (1985) (High)	Moderate
Chronic Exposure Scenario (inhalation/dermal)									
Immune	Mouse (Male)	90 days	Route-to-route extrapolation	Decreased humoral immune response (AFCs)	BMDL _{1SD} = 21.4 mg/kg-day	116 mg/m ³ (29.4 ppm)	UF _A = 3; UF _H = 10; UF _S = 3; <i>Total UF</i> = 100	Shopp et al. (1985) (High)	Moderate (inhalation); Slight-to-Moderate (dermal)
AFCs = antibody forming cells; BMDL _{1SD} = benchmark dose lower 95% confidence limit 1 SD; HEC = human equivalent concentration; HED = human equivalent dose; OQD = overall study quality determination for the individual study that was used; POD = point of departure; UF = uncertainty factor; UF _A = interspecies uncertainty factor; UF _H = intraspecies uncertainty factor; UF _L = LOAEL-to-NOAEL uncertainty factor; UF _S = subchronic-to-chronic uncertainty factor; ^a POD confidence selection is based on an evaluation of the identified POD and the confidence in the alignment of this POD to the assigned route/duration and any uncertainties associated with the POD being used for risk estimates (e.g., route-to-route extrapolation, duration adjustment, etc.).									

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3 ENVIRONMENTAL HAZARD ASSESSMENT

3.1 Approach and Methodology

EPA utilized systematic review processes to search, screen, evaluate, extract, and integrate reasonably available information on adverse environmental effects from *trans*-1,2-dichloroethylene. Following evidence integration, the Agency derived hazard thresholds for aquatic and terrestrial receptor groups as supported by the evidence integration for use in risk characterization. EPA next evaluated the weight of scientific evidence for each aspect of the assessment and determined overall confidence ratings for each critical hazard outcome. The generalized process for conducting environmental assessments under TSCA is presented below in Figure 3-1.

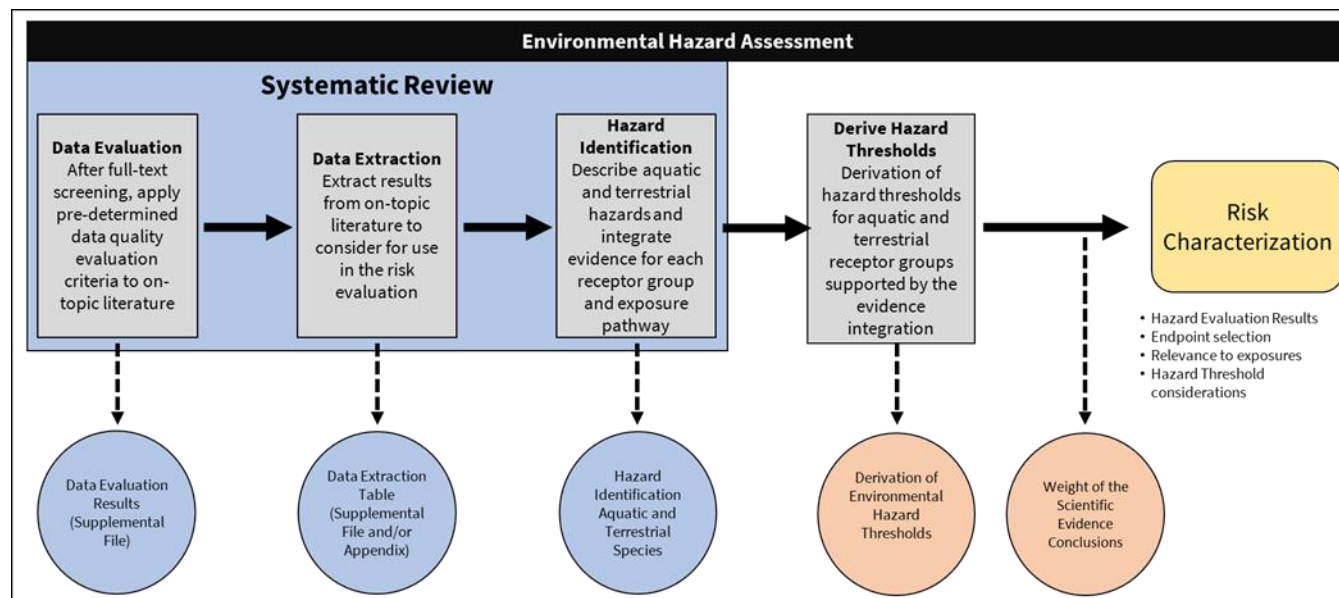


Figure 3-1. Approach to Environmental Hazard Identification and Dose-Response Analysis for *trans*-1,2-Dichloroethylene

During scoping, EPA reviewed potential environmental hazards associated with *trans*-1,2-dichloroethylene and identified sources of environmental hazard data shown in Figure 2-9 of *Final Scope of the Risk Evaluation for trans*-1,2-Dichloroethylene; CASRN 156-60-5 (U.S. EPA, 2020a). An updated literature search was also performed in April 2025. Relevant studies were not identified from the updated search. Results of PECO screening are provided for animal toxicology, epidemiology, and dermal absorption in Appendix G.

EPA completed the review of environmental hazard data 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, 2021). Studies were assigned an overall quality of high, medium, low, or uninformative. Studies that received OQDs of high, medium, or low were considered for use to set quantitative hazard thresholds. Studies with OQDs of high or medium are preferentially used to set quantitative hazard thresholds. In cases where high or medium rated studies are limited or absent, then studies with OQDs of low can be used to set quantitative thresholds. EPA completed the review of environmental hazard data during risk evaluation using the data quality review evaluation metrics and the rating criteria described in the Draft Systematic Review Protocol (U.S. EPA, 2021). Full details for all environmental hazard studies that underwent data evaluation and extraction are available in the *Draft Data Quality Evaluation Information for Environmental Hazard for trans*-1,2-Dichloroethylene and the *Draft Data*

Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for *trans*-1,2-Dichloroethylene ([U.S. EPA, 2026c, e](#)). Full details and screening results for all the identified studies are described in the *Draft Systematic Review Protocol for trans*-1,2-Dichloroethylene ([U.S. EPA, 2026i](#)). With the reasonably available data, EPA used studies rated high, medium, and low for quantitative analysis during data integration. Any study assigned an OQD level of uninformative was not used in setting quantitative hazard thresholds but were used qualitatively in the weight of evidence evaluation.

3.1.1 Identification of Analogs

EPA did not identify any hazard data for chronic exposure durations for *trans*-1,2-dichloroethylene for aquatic invertebrates, vertebrates, vascular plants or terrestrial invertebrates. Additionally, the Agency only identified a single acute aquatic study that reported data for one species of water flea. To fill these data gaps, EPA identified analogs with data that are appropriate for read-across. The process for selection of the analogs and results for *trans*-1,2-dichloroethylene are described in detail in Appendix E. Analogs were identified based on analyses of structural similarity; physical, chemical, and environmental fate similarity; and ecotoxicological similarities. Based on the analyses both *cis*-1,2-dichloroethylene and trichloroethylene and were identified as appropriate analogs for *trans*-1,2-dichloroethylene. While the *cis* isomer of 1,2-dichloroethylene is expected to be the closest analog there were also few data identified for *cis*-1,2-dichloroethylene; therefore, the analog trichloroethylene was also selected to bolster the data. Trichloroethylene is expected to be a conservative analog, in studies where both chemicals were tested, trichloroethylene was repeatedly found to have the most conservative results while remaining relatively close (within order of magnitude). An example of this can be seen in the amphibian study ([Mcdaniel et al., 2004b](#)) where effect concentrations of 50% (EC50s) were calculated for developmental deformities in tadpoles at 92.5 mg/L for *trans*-1,2-dichloroethylene and at 33.6 mg/L for trichloroethylene. This trend was observed across the few studies that looked at both *trans*-1,2-dichloroethylene and trichloroethylene a detailed comparison of *trans*-1,2-dichloroethylene and its analogs can be found in Table_Apx E-4. Selection of appropriate analogs for *trans*-1,2-dichloroethylene was limited to those chemicals that had already undergone the full SR process as described in Section 3.1. The available aquatic environmental hazard data for trichloroethylene were evaluated as part of the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#)).

For trichloroethylene, EPA identified 25 acceptable studies that contained aquatic toxicity data, including data for fish, amphibians, aquatic invertebrates, and algae. For *cis*-1,2-dichloroethylene, the Agency identified two acceptable studies that contained relevant aquatic toxicity data.

3.1.2 Concentrations of Concern (COCs) and Hazard Thresholds

3.1.2.1 Aquatic COCs

For aquatic species, EPA estimates hazard by calculating a COC, which can be identified by either deterministic methods or probabilistic methods. COCs calculated deterministically are divided by a hazard value by an assessment factor (AF) according to EPA methods ([U.S. EPA, 2016b, 2013, 2012c](#)) as shown in Equation 3-1.

Equation 3-1.

$$COC = toxicity\ value \div AF$$

An AF is applied to account for uncertainty in the hazard threshold and varies depending on data availability. EPA applies an AF where appropriate and when data are limited to account for species-to-species differences and extrapolating from laboratory studies to the field ([Zeeman, 1995](#); [Zeeman and](#)

[Gilford, 1993](#)). If data are available for all taxonomic groups (invertebrates, vertebrates, and aquatic plants or algae), an AF of 5 is applied to the acute COC (for deterministic methods) and an AF of 10 is applied to the chronic and aquatic plant and algae COCs as protective for an ecosystem on a national level ([U.S. EPA, 2020e](#); [ECB, 2003](#)). A larger AF may be applied if there is additional uncertainty. For example, if EPA only had fish toxicity data (no invertebrate or aquatic plant data) for a chemical, an AF of 100 could be applied to the fish value to account for the uncertainty of not having multiple taxonomic groups represented in the dataset ([EPA-HQ-OPPT-2019-0500-0111](#)) ([ECB, 2003](#)).

COCs can also be calculated using probabilistic methods. For example, a species sensitivity distribution (SSD) can be used to calculate a hazardous concentration (HC) for 5% of species (HC05). The HC05 is an estimate of the concentration that is expected to be protective for 95% of species and this value will be presented as a COC. The lower-bound of the 95% CI of the HC05 can be used to account for uncertainty and is thus also assigned as a COC rather than dividing by a fixed AF to account for uncertainty. EPA has more confidence in the probabilistic approach as the HC05 is representative of a larger portion of species in the environment. The application of Web-ICE models eliminates the need for AFs by extrapolating toxicity to a diversity of species representing a wide range of aquatic taxa with surrogate species sensitivity ([Awkerman et al., 2014](#)). Raimondo et al ([2025](#)) found that using the lower 95% CI as the COC reduced uncertainty. ([2025](#)) found that using the lower 95% CI as the COC reduced uncertainty.

For chronic aquatic toxicity studies, when possible, EPA calculates chronic values (ChV), which are the geometric mean of a NOEC and LOEC as shown below in Equation 3-2.

Equation 3-2. ChV Calculation

$$ChV = \sqrt{NOEC \times LOEC}$$

3.1.2.2 Terrestrial Hazard Thresholds or Toxicity Reference Values (TRVs)

Mammals and Birds

In lieu of terrestrial mammalian wildlife studies, all mammal studies were from rodents (mice and rats) used as human health model organisms. These mammal studies were used to calculate a mammalian toxicity reference value (TRV). The TRV and hazard value are expressed as a dose in units of mg/kg-bw/day for oral studies and ppm for inhalation studies. A TRV is derived when the minimum dataset requirement is met (as established as part of the Ecological Soil Screening Levels (Eco-SSL) guidance ([U.S. EPA, 2003b](#))). When the minimum TRV dataset requirement (3 results [NOAEL or LOAEL values] for reproduction, growth, or mortality for at least 2 mammalian or avian species) is met, EPA prefers to derive the TRV by calculating the geometric mean of the NOAELs across all results for ecologically relevant endpoints (growth and reproduction), rather than using a single result and endpoint. The TRV method is preferred because the geometric mean of NOAELs across studies, species, and endpoints provides greater representation of environmental hazard to terrestrial mammals and/or birds. The TRV derivation process as described in the Eco-SSL guidance is described further in Section 3.3.1.2. In cases where the minimum dataset is not available and the Eco-SSL TRV process cannot be used, EPA uses an alternative process to identify the hazard threshold for mammals and/or birds. This process identifies the lowest dose with no-observable-adverse effects to behavior, growth, reproduction or survival, which also reports an associated lowest-observed-adverse effect. This would be the most conservative protective hazard threshold.

Terrestrial Plants and Soil Invertebrates

Similarly for terrestrial plants and soil invertebrates, the relevant hazard value is assigned as the hazard threshold after examination of results across all available studies.

3.2 Aquatic Species Hazard

3.2.1 Acute Hazards

3.2.1.1 Acute Hazard Studies

The Agency only identified one paper with two studies for one invertebrate species and no fish species with acceptable data for *trans*-1,2-dichloroethylene. A fish study that was rated low quality was not included because mortality could not be linked to the chemical exposure ([Buccafusco et al., 1981](#)). The dissolved oxygen in the exposure tank crashed to 0.3 mg/L during the exposure. By inclusion of data for the two analogs a total of 28 high- or medium-rated acute aquatic toxicity studies were available as summarized in Table 3-1 and identified as the most relevant for quantitative assessment. EPA assigned OQDs of medium or high for 6 acute aquatic toxicity studies for *trans*-1,2-dichloroethylene and medium or high to eighteen studies for the analog trichloroethylene and medium for 4 studies for the analog *cis*-1,2-dichloroethylene. See Table 3-1 for a listing of the acute hazard studies considered.

Table 3-1. Acute Aquatic Environmental Hazard Studies for *trans*-1,2-Dichloroethylene (and Analogs *cis*-1,2-Dichloroethylene and Trichloroethylene)

Test Organism (Species) (Test Chemical)	Duration/ Endpoint/ Exposures	Hazard Values ^a (mg/L)	Effect Endpoint(s)	Citation (Study Quality)
Invertebrates				
Water flea (<i>Daphnia magna</i>) (<i>trans</i> -1,2- dichloroethylene)	24/48-hour NOEC	>110	Mortality (Immobilization)	Leblanc (1980) (Medium)
Water flea (<i>Daphnia magna</i>) (<i>trans</i> -1,2- dichloroethylene)	24/48-hour LC50	230/220	Mortality (Immobilization)	Leblanc (1980) (Medium)
Mysid shrimp (<i>Mysidopsis bahia</i>) (trichloroethylene)	96-hour LC50 (saltwater)	14 ^d	Mortality	Ward et al. (1986) (Medium)
Water flea (<i>Daphnia magna</i>) (trichloroethylene)	24/48-hour LC50	22 ^d / 18 ^d	Mortality (Immobilization)	Leblanc (1980) (High)
Water flea (<i>Daphnia magna</i>) (trichloroethylene)	48-hour LC50	7.75 ^d	Mortality (Immobilization)	Abernethy et al. (1986) (Medium)
Water flea (<i>Daphnia magna</i>) (trichloroethylene)	24/48/72/96-hour LC50	43.14 ^d / 33.85 ^d / 28.39 ^d / 26.55 ^d	Mortality (Immobilization)	Dobaradaran et al. (2012) (Medium)
Water flea (<i>Ceriodaphnia dubia</i>) (trichloroethylene)	48-hour LC50	17.08 ^d	Mortality (Immobilization)	Niederlehner et al. (1998) (High)
Vertebrates – amphibians				

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Test Organism (Species) (Test Chemical)	Duration/ Endpoint/ Exposures	Hazard Values ^a (mg/L)	Effect Endpoint(s)	Citation (Study Quality)
Green frog (<i>Lithobates clamitans</i>) (<i>trans</i> -1,2-dichloroethylene and trichloroethylene)	96-hour EC50	92.5/33.6 ^d	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
Green frog (<i>Lithobates clamitans</i>) (<i>cis</i> -1,2-dichloroethylene)	96-hour NOEC	>100 ^c	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
American toad (<i>Bufo americanus</i>) (<i>trans</i> -1,2-dichloroethylene, <i>cis</i> -1,2-dichloroethylene and trichloroethylene)	96-hour NOEC	>100 / >100 ^c / >85 ^d	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
Wood Frog (<i>Lithobates sylvaticus</i>) (trichloroethylene)	96-hour EC50	45.7 ^d	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
Wood Frog (<i>Lithobates sylvaticus</i>) (<i>trans</i> -1,2- dichloroethylene)	96-hour NOEC	>100	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
Wood Frog (<i>Lithobates sylvaticus</i>) (<i>cis</i> -1,2-dichloroethylene)	96-hour NOEC	>100 ^c	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
Spotted Salamander (<i>Ambystoma maculatum</i>) (trichloroethylene)	96-hour EC50	60 ^d	Developmental Deformities	Mcdaniel et al. (2004b) (Medium)
African clawed frogs (<i>Xenopus laevis</i>) (trichloroethylene)	96-hour LC50	434 ^d	Mortality	Fort et al. (1993) (High)
African clawed frogs (<i>Xenopus laevis</i>) (trichloroethylene)	96-hour LC50	425 ^d , 443 ^d (434 ^d)	Mortality	Fort et al. (1991) (Medium)
African clawed frogs (<i>Xenopus laevis</i>) (trichloroethylene)	96-hour LC50	412 ^d , 426 ^d , 490 ^d (441 ^d)	Mortality	Fort et al. (2001) (Medium)
Vertebrates – fish				
Fathead minnow (<i>Pimephales promelas</i>) (trichloroethylene)	96-hour LC50	44.1 ^d	Mortality	Geiger et al. (1985) (High)

Test Organism (Species) (Test Chemical)	Duration/ Endpoint/ Exposures	Hazard Values ^a (mg/L)	Effect Endpoint(s)	Citation (Study Quality)
Fathead minnow (<i>Pimephales promelas</i>) (trichloroethylene)	96-hour LC50 Flow through/ Static renewal	40.7 ^d / 66.8 ^d	Mortality	Alexander et al. (1978) (High)
American flagfish (<i>Jordanella floridae</i>) (trichloroethylene)	96-hour LC50 Flow through/ Static renewal	28.28 ^d / 31 ^d	Mortality	Smith et al. (1991) (High)
Fathead minnow (<i>Pimephales promelas</i>) (trichloroethylene)	96-hour LC50	55.2 ^d , 40.5 ^d , 45.7 ^d (46.7^b)	Mortality	Broderius et al. (2005) (High)
Bluegill (<i>Lepomis macrochirus</i>) (trichloroethylene)	96-hour LC50	45 ^d	Mortality	Buccafusco et al. (1981) (Medium)
Sheepshead minnow (<i>Cyprinodon variegatus</i>) (trichloroethylene)	LC50 Initial (m) / LC50 Average (m)	99 ^d / 52^d	Mortality	Ward et al. (1986) (Medium)
Bolded values are used in the Web-Based Interspecies Correlation Estimation (Web-ICE) v4.0 analyses in Table_Apx F-2. EC50 = Concentration where effect was observed in 50% of the population; L=liter; LC50=Concentration lethal to 50% of the test population; LOEC = lowest-observed-effect concentration; (m) =measured; mg=milligram; (n) = nominal; NOEC = no-observed-effect concentration. ^a Hazard values presented as ranges represent the range of all the definitive values in the citations and are presented with the number of significant figures reported by the authors. ^b Geometric mean of definitive values only (<i>i.e.</i>, >100 mg/L was not used in the calculation). Bolded values inside “()” are geometric means. ^c Hazard values represented by analog <i>cis</i>-1,2-dichloroethylene. ^d Hazard values represented by analog trichloroethylene.				

Aquatic Vertebrates – Amphibians

EPA assigned a OQD of medium to one study ([Mcdaniel et al., 2004b](#)) containing *trans*-1,2-dichloroethylene amphibian hazard data resulting from acute exposure. In addition to *trans*-1,2-dichloroethylene, this study included acute amphibian exposures to the isomer and analog *cis*-1,2-dichloroethylene and the analog chemical trichloroethylene as separate individual tests. The study reported the EC50 or Effect Concentration for 50% of organisms with developmental deformities of tadpoles. Freshly harvested (<24-hour) egg masses from three species of amphibians were separately exposed to all three chemicals, American toad (*Bufo americanus*), Green frog (*Lithobates clamitans*), and Wood frog (*Lithobates sylvaticus*). These species were observed for effects on tadpole developmental deformities during the 96-hour exposure. The *cis*-1,2-dichloroethylene EC50 was found to be higher than the maximum exposure concentration of 100 mg/L for all three observed species. The *trans*-1,2-dichloroethylene EC50 was found to be higher than the maximum exposure concentration of 100 mg/L for two of the three observed species (*B. americanus* and *L. sylvaticus*). No LOEC was reported in the study. An EC50 in the species *L. sylvaticus* was calculated to be a nominal concentration of 92.5 mg/L. Exposures to the trichloroethylene resulted in EC50s of 33.6 mg/L, 45.7 mg/L, and 60

mg/L, respectively, for *L. clamitans*, *L. sylvaticus*, and *A. maculatum*, (spotted salamander was only exposed to trichloroethylene) respectively. The maximum dose of 85 mg/L was not sufficient to calculate an EC50 for *B. americanus* ([Mcdaniel et al., 2004b](#)). The studies are summarized in Table 3-1.

Acute data were available for trichloroethylene from three additional amphibian studies with an OQD of high or medium. These focused on the African clawed frogs (*Xenopus laevis*). The studies are summarized in Table 3-1. Developmental effects observed in amphibians exposed to trichloroethylene were irreversible and could result in premature death. Across the all amphibian studies developmental effects described included gut miscoiling and microphthalmia, muscular kinking, severe hypognathia, and edema and dorsal flexure of the tail and notochord in tadpoles ([McDaniel et al., 2004a](#); [Fort et al., 2001](#); [Fort et al., 1993](#); [Fort et al., 1991](#)). As stated previously, ([McDaniel et al., 2004a](#)) reported signs of narcosis in *L. clamitans* and *L. sylvaticas* tadpoles.

Aquatic Vertebrates – Fish

EPA did not identify any acute studies for exposure to fish to *trans*-1,2-dichloroethylene. Acute fish data for trichloroethylene were identified in six studies assigned an OQD of medium or high. Four different species, fathead minnows (*Pimephales promelas*), American flagfish (*Jordanella floridae*), bluegill (*Lepomis macrochirus*), and sheepshead minnow (*Cyprinodon variegatus*) were used in these studies representing both fresh and salt water fish. In these studies the lethal concentrations at which 50% of test organisms die (LC50s) ranged from 28.28 to 66.8 mg/L ([Geiger et al., 1985](#));([Broderius et al., 2005](#); [Smith et al., 1991](#); [Ward et al., 1986](#); [Buccafusco et al., 1981](#); [Alexander et al., 1978](#)) (Table 3-1). Because baseline narcosis is the expected mode of action for trichloroethylene in both freshwater and saltwater fish ([Alexander et al., 1978](#)); ([Ward et al., 1986](#)); ([Broderius et al., 2005](#)), freshwater and saltwater LC50 values were assessed together during data integration. ([Alexander et al., 1978](#))

Aquatic Invertebrates

EPA assigned an OQD of medium to one study ([Leblanc, 1980](#)) containing *trans*-1,2-dichloroethylene aquatic invertebrate hazard data resulting from acute exposure. This study reported 24- and 48-hour LC50 (lethal concentration for 50% of the test population) at 230 and 220 mg/L, respectfully, for the water fleas (*Daphnia magna*) exposed to *trans*-1,2-dichloroethylene. This same study reported that 110 mg/L had no discernable effect on mortality of exposed *D. magna* (Table 3-1).

For trichloroethylene, EPA assigned an OQD of medium or high to five studies for acute exposures for aquatic invertebrates. These studies include three test species, two water fleas (*Daphnia magna*, and *Ceriodaphnia dubia*), and mysid shrimp (*Mysidopsis bahia*). These studies recorded LC50s from a range of exposures including 24, 48, 72, and 96 hours. The reported LC50s range from 7.75 to 43.14 mg/L the studies are summarized in Table 3-1. The lowest LC50 was reported in a daphnid study ([Abernethy et al., 1986](#)) that provide few details on the 48-hour exposure set up. A study on mysids was the only saltwater study of the group ([Ward et al., 1986](#)). It used a 1.6 L glass container to expose the mysis to a known concentration of trichloroethylene diluted in a liter of sea water. This resulted in a LC50 of 14 mg/L after 96 hours. A study that focused on the water flea *C. dubia* used continuous exposure and chemical analysis to verify the concentrations accuracy ([Niederlehner et al., 1998](#)). This study reported an LC50 of 17.08 mg/L. The only study that reported *trans*-1,2-dichloroethylene data also reported an LC50 value for 24- and 48-hour exposures as 18 mg/L and 22 mg/L respectively ([Leblanc, 1980](#)). The highest LC50 was reported from a study that observed LC50s for *D. magna* at 24-, 48-, 72-, and 96-hour exposures ([Dobaradaran et al., 2012](#)).

Predicted Acute Toxicity

The [Web-ICE version 4.0](#) (accessed June 8, 2026) modeling approach can predict acute toxicity values for environmental species that are absent from an empirical dataset and therefore provide a more robust dataset to estimate toxicity thresholds. EPA used predictions for 80 aquatic species from Web-ICE (fish, amphibians, aquatic invertebrates, and benthic invertebrates) based on the acute aquatic empirical hazard data for *trans*-1,2-trichloroethylene and trichloroethylene ([Raimondo, 2010](#)) Details outlining the Web-ICE methods and analyses for *trans*-1,2-dichloroethylene are provided in Appendix F.1.1.1. The Web-ICE application was used to predict LC50 and EC50 (effect concentration at which 50% of test organisms exhibit an effect). The effects modeled are for mortality or immobilization (assumed to be mortality).

3.2.1.2 Acute Aquatic Concentrations of Concern (COC)

EPA derived an acute COC, using a probabilistic method with *trans*-1,2-dichloroethylene hazard data supplemented with acute aquatic toxicity data for trichloroethylene and hazard estimates from the Web-ICE (Version 4.1) modeling (Appendix F.1.1.1). An SSD is a type of probability distribution of toxicity values from multiple species. It can be used to visualize which species are most sensitive to a chemical exposure, and to predict a concentration of the chemical that is hazardous to a percentage of test species. This hazardous concentration is represented as an HC_p, where p is the percent of species. EPA used an HC05 (hazardous concentration threshold for 5% of species) to estimate a concentration that would protect 95% of species. EPA created SSDs using EPA's SSD Toolbox and the acute hazard data for aquatic species, including fish, amphibians, and invertebrates (Figure 3-2) ([Etterson, 2020a](#)). Toxicity data from the test species (n = 8) and predicted species (n = 80) were used to calculate the distribution of species sensitivity to *trans*-1,2-dichloroethylene exposure through the SSD Toolbox as described in Appendix 3.6F.1.1.3 and shown in Figure 3-2 ([Etterson, 2020a](#)). The calculated HC05 from the SSD is 4.44 mg/L and this value will be presented as a COC. The confidence interval of the HC05 can be used to account for uncertainty (95% CI = 3.01–6.51 mg/L) (Figure 3-2) (Appendix F.1.1.3). The lower 95% CI of the HC05 (3.01 mg/L) was also selected as the acute COC to represent hazard to aquatic invertebrates and vertebrates for *trans*-1,2-dichloroethylene.

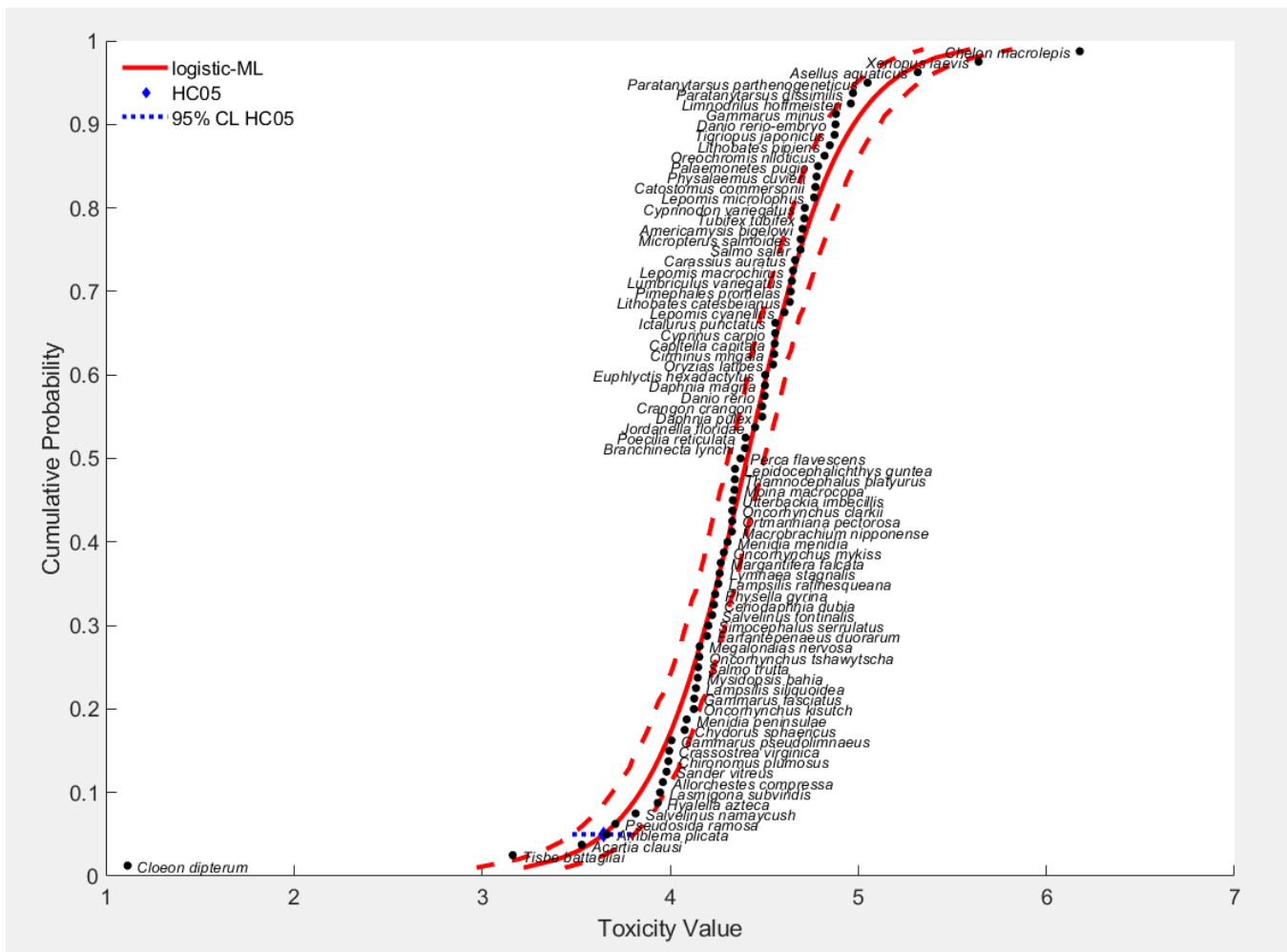


Figure 3-2. Acute Aquatic Data Species Sensitivity Distribution for *trans*-1,2-Dichloroethylene (and Analog Trichloroethylene) (Etterson, 2020a)

3.2.1.3 Weight of Scientific Evidence for Acute Aquatic COC

The weight of evidence indicates that *trans*-1,2-dichloroethylene poses acute hazard to aquatic vertebrates and invertebrates at 4,438 µg/L and also represented by the lower 95% percentile confidence interval 3,005 µg/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. The analogs used in deriving this COC are either one to one or conservative in comparison to *trans*-1,2-dichloroethylene which further bolsters confidence that this COC will be protective, a detailed analog comparison can be found in Table_Apx E-4. For the acute aquatic assessment, the database consisted of 13 studies with OQDs of high or medium for *trans*-1,2-dichloroethylene and the analogs trichloroethene and *cis*-1,2-dichloroethylene with both aquatic invertebrates and vertebrates represented. Data from six empirical studies were supplemented with Web-ICE to obtain additional estimated acute toxicity values and generate a subsequent SSD output; therefore, a robust confidence was assigned to quality of the database. Outcomes in the empirical and predicted data were generally consistent with most toxicity values falling within two log scales of each other.

For the acute aquatic assessment, immobilization and mortality were observed in the empirical data for freshwater and saltwater aquatic invertebrates, freshwater fish, and freshwater amphibians, and mortality was predicted in additional species. Although modeled approaches such as Web-ICE can have more uncertainty than empirical data when determining the hazard, the use of the SSD probabilistic approach within this risk evaluation increases confidence compared to a deterministic approach and the use of the lower 95% CI instead of a fixed assessment factor also increases confidence, as it is a more data-driven way of accounting for uncertainty.

EPA used a probabilistic technique (SSD) to derive a 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 and dependent on the three or four lowest values (Newman et al., 2000). Notwithstanding the limitations of SSD analyses, this method is widely used and accepted in risk assessments. 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 Hazards

3.2.2.1 Chronic Aquatic Hazard Studies

No chronic hazard studies were identified for *trans*-1,2-dichloroethylene or *cis*-1,2-dichloroethylene for aquatic vertebrates, invertebrates or vascular plants. EPA identified four chronic aquatic studies with a OQD of high that were identified for trichloroethylene and evaluated as part of the *Risk Evaluation for Trichloroethylene* (U.S. EPA, 2020d). Chronic studies identified in the risk evaluation for trichloroethane are summarized in Table 3-2. These include an aquatic invert study that looked at the water flea *Ceriodaphnia dubia* (Niederlehner et al., 1998). This study used steady state measured concentrations to verify exposure concentration throughout the exposure. The results found that there was no negative effect on reproduction at the concentration of 7.1 mg/L and the concentration where 50% inhibition of reproduction was reported to be 11 mg/L. The remaining three chronic aquatic trichloroethylene exposure studies each looked at a different species of fish. Fathead minnow growth was observed during a 32-day exposure (Broderius et al., 2005). Measured concentrations were used and the exposure was in a flow through system. An effect on growth was observed in 50% of the exposed minnows (EC50) at 11.8 mg/L and an effect on growth was observed in 20% of the exposed minnows (EC20) at 7.88 mg/L. Flag

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fish fry survival was the subject of another study given a high rating ([Smith et al., 1991](#)). This study looked at effects on fry survival during a 10- and 28-day flow through exposure study. Both the lowest observed effect concentration and the concentration at which no effect was observed for both exposure durations. For the 28-day study those values are 10.568 and 29.915 mg/L respectively; for the 10-day study they are 5.758 and 21.233 mg/L respectively. The final trichloroethylene study with a high confidence rating assessed mortality in a 10-day medaka exposure ([Schell, 1987](#)). A lethal concentration for half of the exposed fish was calculated to be 82 mg/L in that study.

Table 3-2. Chronic Aquatic Species Environmental Hazard Studies for the Analog Trichloroethylene

Test Organism (Species)	Duration/Endpoint/Exposures	Hazard Values ^a (mg/L)	Geometric Mean ^b (mg/L)	Effect Endpoint(s)	Citation (Study Quality)
Invertebrates					
Water flea (<i>Ceriodaphnia dubia</i>)	7-day NOEC/LOEC	7.1 ^c / 12 ^c	9.2 ^c ChV	Reproduction	Niederlehner et al. (1998) (high)
Water flea (<i>Ceriodaphnia dubia</i>)	7-day IC ₅₀	11 ^c		Reproduction	Niederlehner et al. (1998) (high)
Vertebrates – fish					
Fathead minnow (<i>Pimephales promelas</i>)	32-day EC20	7.93 ^c , 7.71 ^c , 7.59 ^c	7.88^c	Growth	Broderius et al. (2005) (High)
Fathead minnow (<i>Pimephales promelas</i>)	32-day EC50	11.9 ^c , 10.5 ^c , 10.8 ^c	11.8 ^c	Growth	Broderius et al. (2005) (High)
Flagfish (<i>Jordanella floridae</i>)	28-day NOEC/LOEC	10.568 ^c / 20.915 ^c	14.87 ^c	Fry Survival	Smith et al. (1991) (High)
Flagfish (<i>Jordanella floridae</i>)	10-day NOEC/LOEC	5.758 ^c / 21.233 ^c	11 ^c	Fry Survival	Smith et al. (1991) (High)
Japanese medaka (<i>Oryzias latipes</i>)	10-day LC50	82 ^c		Mortality	Schell (1987) (High)

IC50 = The concentration of a substance that causes a 50% inhibition of a specific biological function or endpoint. EC50 = Concentration where effect was observed in 50% of the population; EC20 = concentration where effect was observed in 20% of the test population; LOEC = lowest-observed-effect concentration; (n) = nominal, NOEC = no-observed-effect concentration

^a Hazard values presented as ranges represent the range of all the definitive values in the citations and are presented with the number of significant figures reported by the authors.

^b Geometric mean of definitive values only (*i.e.*, >100 mg/L was not used in the calculation).

^c Hazard values represented by analog trichloroethylene.

Bolded value = identified aquatic chronic COC.

3.2.2.2 Chronic Aquatic Concentrations of Concern

No chronic studies were identified for *trans*-1,2-dichloroethylene or *cis*-1,2-dichloroethylene for aquatic vertebrates, invertebrates, benthic invertebrates or vascular aquatic plants. Chronic aquatic toxicity data are available for trichloroethylene. The Agency used the aquatic chronic COC of 788 µg/L identified for trichloroethylene in Section 3.5.1 of the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#)). EPA is using read-across from this chronic COC identified for the analog trichloroethylene as the Aquatic Chronic COC for *trans*-1,2-dichloroethylene.

3.2.2.3 Weight of Scientific Evidence for Aquatic Chronic COC

The weight of evidence suggests that *trans*-1,2-dichloroethylene poses chronic hazard to aquatic vertebrates at 788 µg/L. For the chronic aquatic assessment, the database consisted of studies only for trichloroethylene used as read-across for the chronic toxicity of *trans*-1,2-dichloroethylene. EPA has moderate confidence in this hazard threshold to be protective of chronic aquatic. The Agency has confidence in the identification of trichloroethylene as an appropriate analog based on the examination structural, physical/chemical and ecotoxicological similarities, EPA has moderate confidence in the quality of the database for the analog. These studies examined numerous apical endpoints including mortality, reproduction, and development/growth. Therefore, consistent effects were observed among the studies, which all maintained a reasonable dose-response design using measured concentrations. Therefore, EPA has moderate confidence in consistency, strength and precision, dose-response, and relevance in the chronic invertebrate hazard assessment.

3.2.3 Aquatic Plants

3.2.3.1 Algal Hazard Data

For aquatic plants hazard studies, algae are the common test species. Algae are cellular organisms which will cycle through several generations in hours to days; therefore, the data for algae was assessed together regardless of duration rather than being categorized as acute or chronic. No data were identified for *trans*-1,2-dichloroethylene for aquatic plants (algae). However, there were six acceptable studies (high or medium quality) identified for trichloroethylene.

The reported data for trichloroethylene are for 11 species of algae, including fresh and saltwater species, cyanobacteria and eukaryotes. There was a wide range of toxicity values reported in the literature for algae exposed to trichloroethylene. EC50s measuring growth represent nine species and range from 26.24 to 820 mg/L ([Lukavsky et al., 2011](#); [Labra et al., 2010](#); [Tsai and Chen, 2007](#); [Ando et al., 2003](#); [Brack and Rottler, 1994](#); [Ward et al., 1986](#)). Ward et al. (1986) reported results on the only saltwater species found in the acceptable studies, *Skeletonema costatum*, with an EC50 of 95 mg/L. This value is within the range of values for freshwater species, so saltwater and freshwater species were integrated together. EPA derived a geometric mean of 242 mg/L from the high and medium quality EC50s. A 72-hour EC10 of 12.3 mg/L was also established by Brack and Rottler (1994) measuring biomass (a measure of growth) in *Chlamydomonas reinhardtii*, a freshwater eukaryotic green algae. Additionally, several NOECs and LOECs were established. Labra et al. (2010) found a 72-hour NOEC of 0.02 mg/L and a LOEC of 0.05 mg/L for cell count (a measure of growth) in *Raphidocelis subcapitata*. This study also assessed the integrity of algal cell membranes and found a dose-dependent increase in membrane damage starting at 0.05 mg/L. EPA used the above mentioned algae data quantitatively (as excerpted from page 217 and 218 of the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#))).

([Ando et al., 2003](#)) measured relative absorbance of chlorophyll a (an indirect measure of algal growth) in three species of algae, *Selenastrum capricornutum*, *Chlorella vulgaris*, and *Volvox steinii*. They found no significant change in the relative absorbance of chlorophyll a for *S. capricornutum* or *C.*

vulgaris during the 10-day test; however, they established a 10-day LOEC of 0.003 mg/L for *V. steinii*, a flagellar alga. The authors attributed the variation in algal species sensitivity to trichloroethylene to *V. steinii*'s high metabolism. These data were considered less biologically relevant than values from other studies and were not used quantitatively during data integration (as excerpted from page 217 and 218 of the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#))).

3.2.3.2 Aquatic Plant (Algae) Concentrations of Concern

EPA derived an acute COC for aquatic plants (all algae), using a probabilistic method for *trans*-1,2-dichloroethylene based on the empirical data available for the analog trichloroethylene. An SSD for algae for trichloroethylene was produced as part of the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#))). That SSD is slightly revised here, two distribution methods that were dropped that were not good fits with the maximum likelihood method, Burr and Gumbel. Additionally, the lower 95% lower confidence intervals for the HC05 were also included as a COC along with the HC05 instead of using an AF on the HC05. The analyses are provided as Appendix F.1.1.2.

Because there was no obvious distribution that was the best fit using the available metrics of goodness-of-fit, standard error, and Akaike's Information Criterion "corrected" for sample-size (AICc), EPA used all four distributions to calculate an HC05 (Figure 3-3). Using the normal, logistic, triangular, and Weibull distributions, EPA calculated a modeled average HC05 of 93.36 mg/L. A modeled average lower confidence interval of the HC05 was calculated to be 51.47 mg/L. The modeled average lower 95% CI of the HC05 (51.47 mg/L) was selected as the acute COC to represent hazard to aquatic plants (algae) for *trans*-1,2-dichloroethylene using data for trichloroethylene.

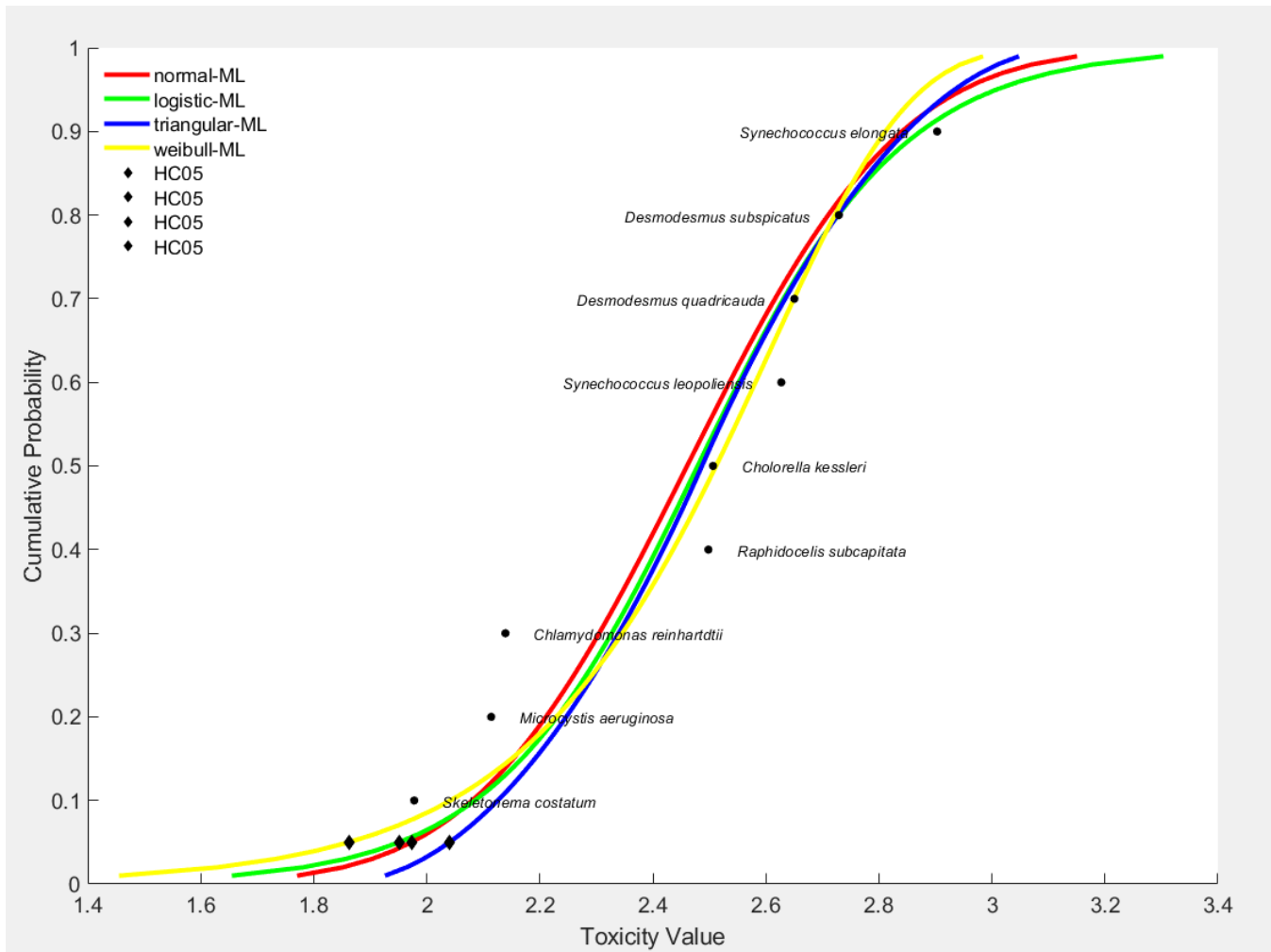


Figure 3-3. Species Sensitivity Distribution (SSD) for Algae Species Using EC50s for the Analog Trichloroethylene (Etterson, 2020a)

(reproduced from Page 260 of the *Risk Evaluation for Trichloroethylene* (U.S. EPA, 2020d))

3.2.3.3 Weight of Scientific Evidence for Aquatic Plant COC

The weight of evidence suggests that *trans*-1,2-dichloroethylene poses hazard to algae species at 39.34 mg/L. For the aquatic plant and algal assessment, the database consisted of studies for trichloroethylene. Aquatic plant data were not identified for *trans*-1,2-dichloroethylene. EPA has confidence in the identification of trichloroethylene as an appropriate analog based on the examination structural, physical/chemical and ecotoxicological similarities. EPA has robust confidence in the quality of the database for the analog.

EPA used a probabilistic technique (SSD) to derive a COC that is protective of 95% of the aquatic plants (algae) by incorporating hazard values across species and habitats. The use of the SSD probabilistic approach within this risk evaluation increases confidence compared to a deterministic approach and the use of the lower 95% CI instead of a fixed AF also increases confidence, as it is a more data-driven way of accounting for uncertainty. EPA has robust confidence in the quality of the database, consistency, strength and precision, dose-response, and relevance in algal hazard assessment. The Agency has moderate-to-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.

3.2.4 Benthic (Sediment-Dwelling Invertebrates)

There were no sediment-dwelling invertebrate studies identified for *trans*-1,2-dichloroethylene. Under the authority of TSCA section 4(a)(2), EPA ordered environmental hazard toxicity tests for *trans*-1,2-dichloroethylene (CASRN 156-60-5) (Docket: [EPA-HQ-OPPT-2018-0465-0065](#)) signed on June 21, 2022, and modified on August 5, 2022. The Order included the evaluation of toxicity to chironomids with acute exposure (OECD 219) and chronic exposure (OECD 233) in spiked water. The consortia submitted initial study plans to evaluate the feasibility of the toxicity tests. The initial feasibility study plans were approved following EPA review and subsequent revision, after which the test sponsor commenced preliminary feasibility testing. Included in the feasibility study plan was a comparison of measured exposure concentrations achieved and maintained for 28-days following the addition of the test substance *trans*-1,2-Dichloroethylene.

In July 2024, EPA received a study report for the preliminary feasibility test titled “An Evaluation of Dosing Methods in Support of Sediment-Water Chironomid Toxicity Testing with *trans*-1,2-Dichloroethylene” that is summarized in a memorandum extinguishing the Test Order ([U.S. EPA, 2024b](#)).

In the preliminary feasibility trial, nominal concentration (100 and 400 mg/L), selected by conducting a visual dispersibility trial, were added to the overlying water of test vessels either daily or on test day 0 only. Half of the test vessels were aerated, and half were not aerated. The feasibility trials did not involve exposure to sediment-dwelling organisms. Although measurement of *trans*-1,2-dichloroethylene in water was achieved, results from the preliminary feasibility trial demonstrate testing would not be successful for multiple reasons. First, retention of *trans*-1,2-dichloroethylene in the overlying water ranged from less than the limit of detection to 65% and concentrations varied an order of magnitude over the study period with a mean retention of 15%, which is significantly below standard guidelines. Measured concentrations of *trans*-1,2-dichloroethylene in pore water and sediment were also variable and generally low, ranging from less than 1% to 78% of nominal concentrations with an overall mean of 15% of nominal for pore water, and ranging from less than the limit of detection to 6.5% of nominal concentrations with an overall mean of 1% of nominal in sediment. Second, retention of *trans*-1,2-dichloroethylene in overlying water in the preliminary trial was highest with daily spiking and no aeration, though aeration of vessels is required to maintain acceptable oxygen concentrations for the test organisms. Third, daily re-spiking of the overlying water can result in oversaturation of the overlying water and phase separation, which was observed during the preliminary feasibility trial. Finally, the purity of the test substance was observed to substantially decline from the start to the termination of the feasibility trial, which further decreases the ability to accurately dose overlying water daily.

During the preliminary feasibility trial, a sediment-spiked dosing method was also tested using nominal concentrations of 100 and 1,000 mg/kg dry weight (dw). In the sediment-spiked trial, retention of *trans*-1,2-dichloroethylene in the overlying water, pore water, and sediment was lower than the overlying water-spiked trial. Retention of *trans*-1,2-dichloroethylene in sediment ranged from less than the limit of detection to 6.7% and concentrations varied up to three orders of magnitude over the study period with a mean retention of 0.28%, which is significantly below standard guidelines. Measured concentrations in overlying water and pore water were also variable and low, ranging from less than the limit of detection to 7% with an overall mean of 0.41% of nominal in overlying water, and ranging from less than the limit of detection to 11% with an overall mean of 0.61% of nominal in pore water. Therefore, dosing sediment instead of overlying water was not a viable alternative approach.

Following review of this study, the Agency concluded that the OECD 219 and OECD 233 tests would not yield relevant exposures due to the volatile and non-adsorptive nature of the test substance, and that

these testing requirements should therefore be extinguished. The preliminary feasibility trials measuring concentrations of *trans*-1,2-dichloroethylene in water and sediment matrices at multiple time points were not successful. EPA determined that the *trans*-1,2-dichloroethylene study is not feasible because the test substance was shown to be unstable in water and sediment matrices based on analytical measurements of the exposure concentrations at applicable time points, and an alternative approach to conduct the testing and fill the data need identified in the test order is unavailable.

EPA issued a modification that extinguished the requirement to conduct OECD 219 and OECD 233 and all other requirements in the Order that flow from that testing requirement ([U.S. EPA, 2024b](#)). The modification did not alter any other provisions of the Order as previously issued and modified. The July 2024 report titled “An Evaluation of Dosing Methods in Support of Sediment-Water Chironomid Toxicity Testing with *trans*-1,2-Dichloroethylene,” is available in the public docket ([EPA-HQ-OPPT-2018-0465-0072](#)).

Based on the results of the preliminary testing as described that resulted in the extinguishing of the sediment toxicity testing Test Order, the Agency is not evaluating risks for sediment-dwelling (benthic) invertebrates as exposures to *trans*-1,2-trichloroethylene in sediments are not expected to occur based on the observed instability in water and sediment matrices in the preliminary studies from the test order. EPA considered the use of analog data to fill the data gap (trichloroethylene) but deemed relying on the test order conclusions was more scientifically sound considering the that the volatility of *trans*-1,2-dichloroethylene is higher than trichloroethylene.

3.3 Terrestrial Species Hazard

3.3.1 Mammalian and Avian Hazard Data

3.3.1.1 Terrestrial Vertebrate Hazard Data

EPA did not identify any reasonably available terrestrial vertebrate studies with mammalian or avian wildlife species for either *trans*-1,2-dichloroethylene or its analog *cis*-1,2-dichloroethylene. The Agency identified 31 chronic toxicity studies for human health animal model laboratory rodents with ecologically relevant effects (*e.g.*, behavior, reproduction, growth, survival) for use in deriving mammalian and avian hazard thresholds. From these, eight studies assigned an OQD of high or medium were included in the environmental hazard data that focused on the relevant endpoints: behavior, reproduction, growth and mortality. Five of these studies focused on oral hazard and are summarized in Table 3-3. The remaining three studies focused on inhalation hazard and are summarized in Table 3-4. The Agency did not use the analog trichloroethylene for terrestrial vertebrate hazard as the animal model dataset for *trans*-1,2-dichloroethylene was robust and did not require the addition of analog data to fill data gaps. EPA did use available animal toxicity data for *cis*-1,2-dichloroethylene as it is an isomer of *trans*-1,2-dichloroethylene and some animal studies represent exposures for mixtures of the two isomers. Avian data was not identified for either *trans*-1,2-dichloroethylene or either analog (*cis*-1,2-dichloroethylene or trichloroethylene).

Terrestrial Vertebrates – Oral Exposures for Mammals and Birds

Mammals: Ecologically relevant effects (those that could result in adverse effects on wildlife populations) were observed in thirty-one mammalian animal studies as summarized in Table 3-3. The doses are plotted by effect group (behavior, reproduction, growth and survival) in Figure 3-4. For additional details on these studies, see *Draft Mammalian TRV Calculator for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026g](#)). Five oral exposure studies were selected to be included in the environmental hazard data. These studies covered two species and two chemicals. Four of these studies included only *trans*-

1,2-dichloroethylene data, the remaining one included only the isomer *cis*-1,2-dichloroethylene. The two species covered in these exposures were rats (*Rattus norvegicus*) and mice (*Mus musculus*). Two of these are 14-day gavage studies. One of these exposed rats to *cis*-1,2-dichloroethylene and reported results for the endpoints behavior, reproduction and growth ([McCauley et al., 1995](#)). The other 14-day gavage study reported on the endpoints of behavior and reproduction in both rats and mice after an exposure to *trans*-1,2-dichloroethylene ([NTP, 2002](#)). The remaining three studies included in the oral hazard data all were 90-day drinking water exposures to *trans*-1,2-dichloroethylene. Drinking water studies are difficult to quantify the precise concentration of the chemical due to its volatile nature and therefore the concentrations are considered nominal unless otherwise stated as measured. One reported on the endpoints of behavior, reproduction, growth, and mortality in rats ([Hayes et al., 1987](#)). Another used mouse exposure and reported the endpoints behavior, reproduction and growth ([Barnes et al., 1985](#)). The final study included was a mouse mortality study ([Shopp et al., 1985](#)). Additional details on the data from these studies can be found in Table 3-3.

Birds: EPA did not identify any avian oral toxicity data for *trans*-1,2-dichloroethylene, *cis*-1,2-dichloroethylene, or trichloroethylene.

Table 3-3. Mammalian Oral Hazard Data Used for Mammalian Wildlife TRV (Hazard Threshold)

Number	Study Duration Exposure Route (Test Chemical)	Test Organism	Endpoint(s)	Hazard Values (mg/kg- bw/day)	Effect(s)	Citation (Data Evaluation Rating)
1	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) CD-1	NOAEL/ LOAEL	175/ 387	Behavior: Water consumption	Barnes et al. (1985) (Medium)
2	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	LOAEL	353	Behavior: Water Consumption	Hayes et al. (1987) (Medium)
3	14 weeks Oral Gavage	Rat (<i>Rattus norvegicus</i>) SD	NOAEL/ LOAEL	969 ^a / 1,939a	Behavior: Activity	McCauley et al. (1995) (Medium)
4	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL	3,210	Behavior: Food Consumption	NTP (2002) (High)
5	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL	3,245	Behavior: Food Consumption	NTP (2002) (High)
6	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL	8,065	Behavior: Food Consumption	NTP (2002) (High)
7	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL	7,925	Behavior: Food Consumption	NTP (2002) (High)

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Number	Study Duration Exposure Route (Test Chemical)	Test Organism	Endpoint(s)	Hazard Values (mg/kg- bw/day)	Effect(s)	Citation (Data Evaluation Rating)
8	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) CD-1	NOAEL	387	Reproduction: Testes Weight	Barnes et al. (1985) (Medium)
9	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	NOAEL	3,114	Reproduction: Testes Weight	Hayes et al. (1987) (High)
10	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	NOAEL	2,809	Reproduction: Organ Weight	Hayes et al. (1987) (High)
11	14 weeks Oral Gavage (<i>cis</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	NOAEL/ LOAEL	969 ^a / 1,939 ^a	Reproduction: Testes Weight	McCauley et al. (1995) (Medium)
12	14 weeks Oral Gavage (<i>cis</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	NOAEL	1,939 ^a	Reproduction: Reproductive Organ Weight	(McCauley et al., 1995) (Medium)
13	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL	3,210	Reproduction: Reproductive Organ Histology	NTP (2002) (High)
14	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL	3,245	Reproduction: Reproductive Organ Histology	NTP (2002) (High)
15	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL	8,065	Reproduction: Reproductive Organ Histology	NTP (2002) (High)
16	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL	7,925	Reproduction: Reproductive Organ Histology	NTP (2002) (High)
17	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) CD-1	NOAEL	387	Growth: Body Weight	Barnes et al. (1985) (Medium)
18	90 days Drinking Water (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) CD-1	NOAEL	452	Growth: Body Weight	Barnes et al. (1985) (Medium)
19	90 days Drinking Water	Rat	NOAEL	3,114	Growth: Body Weight	Hayes et al. (1987) (High)

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Number	Study Duration Exposure Route (Test Chemical)	Test Organism	Endpoint(s)	Hazard Values (mg/kg- bw/day)	Effect(s)	Citation (Data Evaluation Rating)
	(<i>trans</i> -1,2-dichloroethylene)	(<i>Rattus norvegicus</i>) SD				
20	90 days Drinking Water (<i>trans</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	NOAEL	2,809	Growth: Body Weight	Hayes et al. (1987) (High)
21	14 weeks Oral Gavage (<i>cis</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD	NOAEL/ LOAEL	969 ^a / 1,939 ^a	Growth: Body Weight	McCauley et al. (1995) (Medium)
22	14 weeks Food (<i>trans</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL/ LOAEL	1,540/ 3,210	Growth: Body Weight	NTP (2002) (High)
23	14 weeks Food (<i>trans</i> -1,2-dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL/ LOAEL	915/ 1,830	Growth: Body Weight	NTP (2002) (High)
24	90 days Drinking Water (<i>trans</i> -1,2-dichloroethylene)	Mouse (<i>Mus musculus</i>) CD-1	NOAEL	387	Mortality	Shopp et al. (1985) (High)
25	90 days Drinking Water (<i>trans</i> -1,2-dichloroethylene)	Mouse (<i>Mus musculus</i>) CD-1	NOAEL	452	Mortality	Shopp et al. (1985) (High)
26	90 days Drinking Water (<i>trans</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD males	NOAEL	3,114	Mortality	Hayes et al. (1987) (High)
27	90 days Drinking Water (<i>trans</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) SD females	NOAEL	2,809	Mortality	Hayes et al. (1987) (High)
28	14 weeks Food (<i>trans</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL	3,210	Mortality	NTP (2002) (High)
29	14 weeks Food (<i>trans</i> -1,2-dichloroethylene)	Rat (<i>Rattus norvegicus</i>) F344/N	NOAEL	3,245	Mortality	NTP (2002) (High)
30	14 weeks Food (<i>trans</i> -1,2-dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL	8,065	Mortality	NTP (2002) (High)

Number	Study Duration Exposure Route (Test Chemical)	Test Organism	Endpoint(s)	Hazard Values (mg/kg- bw/day)	Effect(s)	Citation (Data Evaluation Rating)
31	14 weeks Food (<i>trans</i> -1,2- dichloroethylene)	Mouse (<i>Mus musculus</i>) B6C3F1	NOAEL	7,925	Mortality	NTP (2002) (High)

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SD = Sprague-Dawley; TRV = toxicity reference value
^a *cis*-1,2-dichloroethylene data

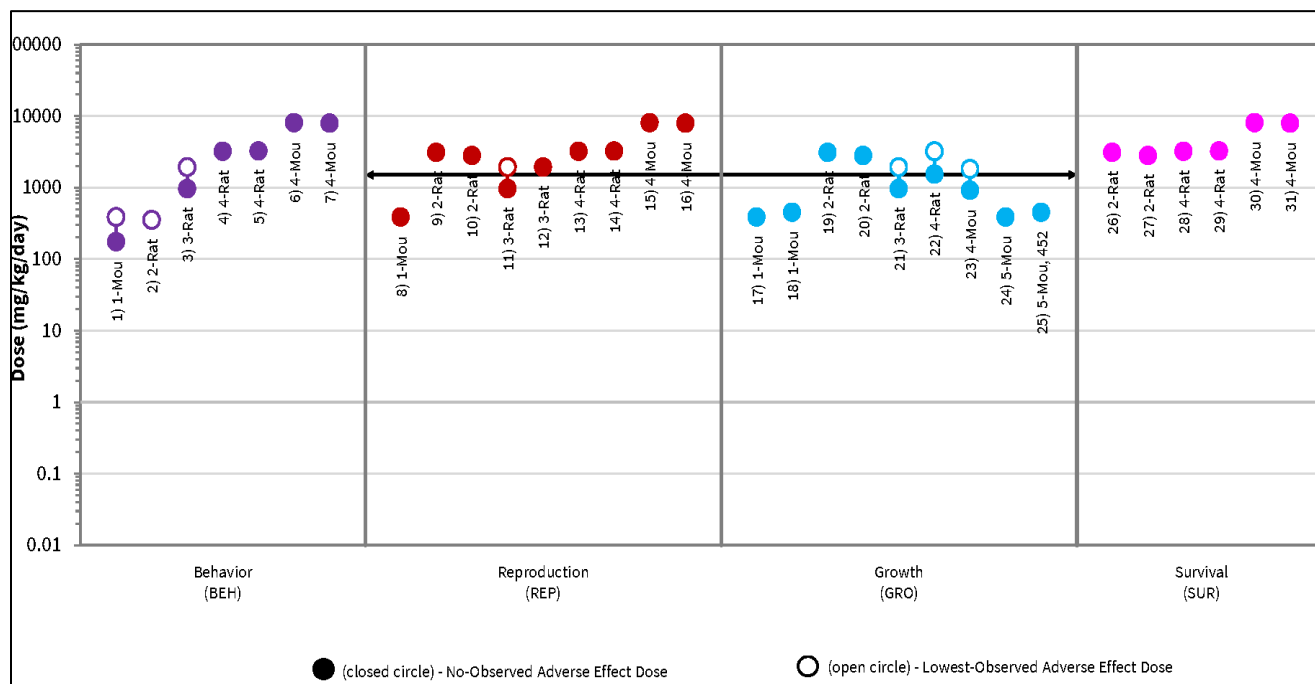


Figure 3-4. Oral Doses (mg/kg-bw/day) of *trans*-1,2-Dichloroethylene for Effects on Mammalian Wildlife Used for Derivation of Wildlife Toxicity Reference Value (TRV)

Terrestrial Vertebrates – Inhalation Exposures for Mammals and Birds

Mammals: Ecologically relevant effects that could result in adverse effects on wildlife populations (effects to behavior, reproduction, growth and survival) were observed in three mammalian inhalation studies. These three inhalation studies identified by EPA received high confidence ratings that reported the hazard of *trans*-1,2-dichloroethylene on these ecologically relevant endpoints. The relevant results from these studies are compiled in Table 3-4. All studies used rats as the test species and *trans*-1,2-dichloroethylene in the exposure. One 90-day study ([DuPont Haskell Lab, 1998](#)) looked at both behavioral effects in the form of food consumption along with mortality. Both endpoints were found to be unaffected by the studies highest dose of 4,000 ppm. A gestational exposure study from days 7 to 16 found no effect at the concentration of 6,000 ppm ([Hurtt et al., 1993](#)). The lowest observed effect level on reproduction in this study was found to be 12,000 ppm. The final inhalation study was a 4-hour exposure that looked at rat mortality ([\[Redacted\], 1999](#)). There was no observed effect at 12,300 ppm and the lowest observed effect was reported at 22,500 ppm.

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Birds: EPA did not identify any avian inhalation toxicity data for *trans*-1,2-dichloroethylene.

Table 3-4. Mammalian Inhalation Environmental Toxicity Studies for *trans*-1,2-Dichloroethylene

Study Duration/ Exposure Type/ Doses (ppm)	Test Organism	Endpoint(s)	Hazard Values (ppm)	Effect(s)	Citation (Data Evaluation Rating)
90-day, 5-day-week, 6hr-day/ inhalation/ 0, 200, 1,000, 4,000	SD rat Crl:CD BR (<i>Rattus norvegicus</i>)	NOAEL	4,000	Behavior Food Consumption	DuPont Haskell Lab (1998) High
Gestation Days 7-16/ inhalation/ 0, 2000, 6,000 or 12,000	Female SD rat Crl:CD BR (<i>Rattus norvegicus</i>)	NOAEL/ LOAEL	6,000 / 12,000	Reproductive	Hurtt et al. (1993) High
4hr/ inhalation/ 0, 12,300, 22,500, 28,100, 34,100 ppm	SD rat Crl:CD BR (<i>Rattus norvegicus</i>)	NOAEL/ LOAEL	12,300/ 22,500	Mortality	[Redacted] (1999) High
90-day, 5-day-week, 6 h-day/ inhalation/ 0, 200, 1,000, 4,000	SD rat Crl:CD BR (<i>Rattus norvegicus</i>)	NOAEL	4,000	Mortality	DuPont Haskell Lab (1998) High
LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect-level; SD = Sprague-Dawley Bolded value = hazard threshold					

3.3.1.2 Terrestrial Vertebrate Thresholds

Thresholds for terrestrial vertebrates (mammals and birds) are discussed for each of two exposure routes: oral and inhalation.

Terrestrial Vertebrate Oral Threshold

EPA used Eco-SSL methods ([U.S. EPA, 2007](#)) as a starting point to establish a TRV-derivation process for use in risk evaluations of chemicals evaluated under TSCA. For terrestrial mammals exposed to *trans*-1,2-dichloroethylene, EPA estimated hazard by calculating an oral TRV using the process as described in the Eco-SSL Guidance ([U.S. EPA, 2007](#)). For terrestrial mammals, the oral TRV is expressed as doses in units mg/kg-bw/day. The flowchart in Figure 3-5 was used to select the to calculate the TRV using NOAEL and/or LOAEL values that are plotted in Figure 3-4. The movement through the flowchart used to calculate the TRV for *trans*-1,2-dichloroethylene is described below. The complete details on the derivation of the oral TRV are provided in *Draft Mammalian Reference Value (TRV) Calculator for trans-1,2-Dichloroethylene* supplemental file ([U.S. EPA, 2026g](#)).

Step 1: The minimum dataset required to derive a TRV consists of three results (NOAEL or LOAEL values) for reproduction, growth, or mortality for at least two mammalian or avian species. This minimum dataset is met. Move to Step 2.

Step 2: Calculation of a geometric mean requires at least three NOAEL results from the reproduction or growth effect groups. There are at least three NOAEL results.

Move from Step 2 to Step 4: Calculate a geometric mean of the NOAELs for reproduction and growth. The geometric mean is 1,504 mg/kg-bw/day. Is this number lower than the lowest bounded LOAEL for reproduction, growth, and mortality? Yes, this number is lower than the lowest bounded LOAEL for reproduction, growth and mortality which is 1,830 mg/kg-bw/day. Is the mechanism of toxicity addressed? Yes, the mechanism of toxicity is addressed. The oral TRV for *trans*-1,2-dichloroethylene is 1,504 mg/kg-bw/day.

Terrestrial Vertebrate Inhalation Threshold

For terrestrial mammals, the inhalation TRV is expressed as doses in units of ppm. The flowchart in Figure 3-5 was used to select the data to calculate the TRV with NOAEL and/or LOAEL data as presented in Table 3-4.

Step 1: The minimum dataset required to derive a TRV consists of three results (NOAEL or LOAEL values) for reproduction, growth, or mortality for at least two mammalian or avian species.

Stop: The minimum data set required is not met for derivation of a TRV using the Eco-SSL process as data are only available for one test species.

As an alternative, EPA identified an inhalation threshold or hazard value for mammalian wildlife by selecting to lowest bounded NOAEL of 6,000 ppm for reproductive effects reported from ([Hurtt et al., 1993](#)).

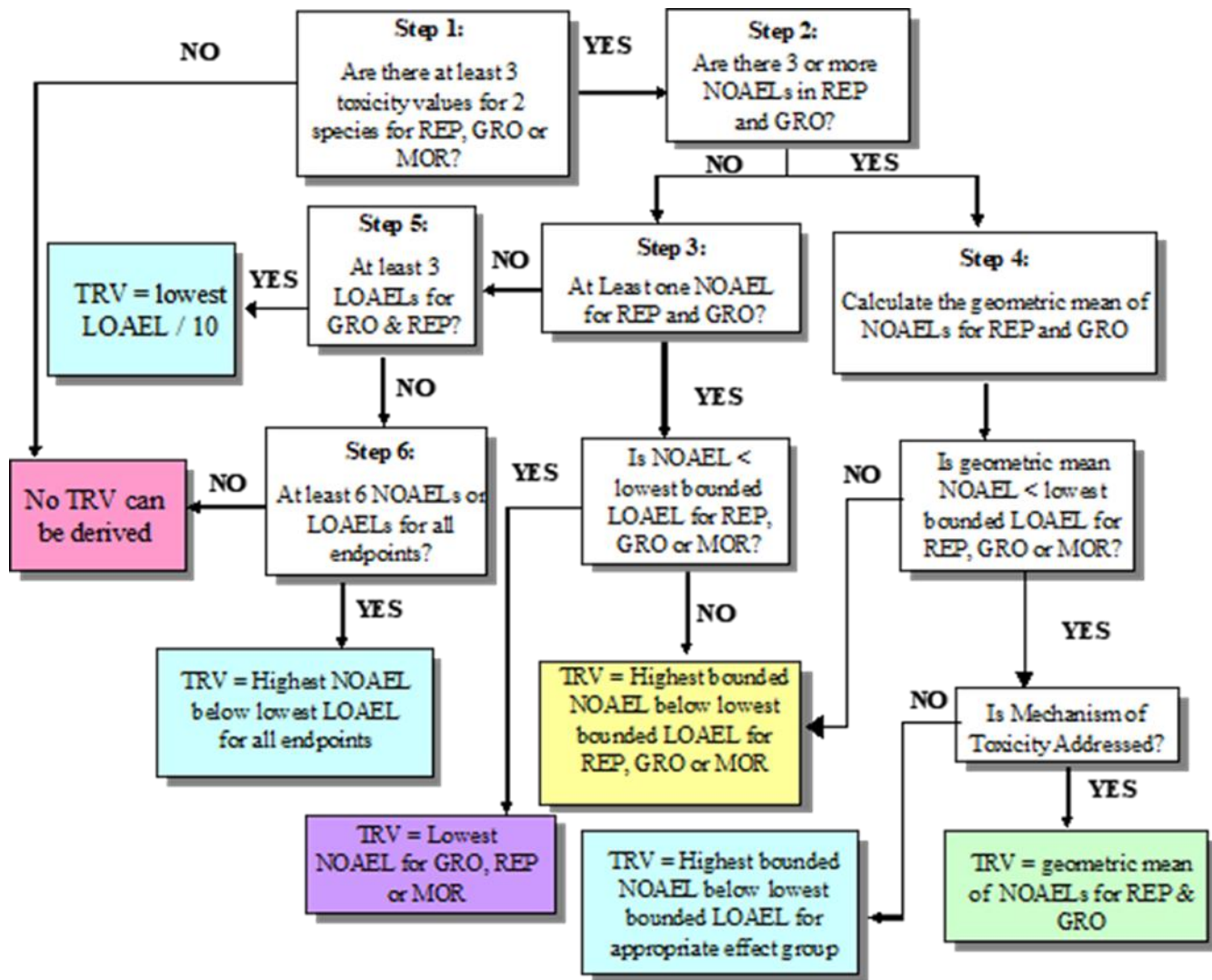


Figure 3-5. Eco-SSL TRV Selection Process Flowchart

Avian Threshold

Avian data were not available for *trans*-1,2-dichloroethylene or the analogs.

3.3.1.3 Weight of Scientific Evidence for Mammalian Thresholds

Mammalian Oral TRV

The weight of evidence indicates that *trans*-1,2-dichloroethylene poses chronic hazard to mammalian wildlife at oral doses exceeding 1,508 mg/kg-bw/day. EPA has robust confidence in this hazard threshold. EPA also has robust confidence that this threshold is protective of behavioral, reproductive, growth and survival effects based on the strength of the hazard database for animal toxicity of 31 studies. That hazard data shows consistent concordance of NOAEL/LOAEL doses within a narrow range across multiple studies. This is especially the case for exposures that report effects on reproductive and growth effects.

Mammalian Inhalation Threshold

The weight of evidence indicates that *trans*-1,2-dichloroethylene poses chronic hazard to mammalian wildlife at inhalation doses above 6,000 ppm. Overall EPA has moderate confidence in this hazard threshold. The Agency has moderate confidence that this threshold is protective of behavior,

reproduction, and survival, but low confidence based on the limitations of the hazard database to one species only (rats).

3.3.2 Terrestrial Invertebrates

3.3.2.1 Terrestrial Invertebrate Hazard Data

EPA assigned an OQD of high to one terrestrial invertebrate (soil-dwelling) study ([Neuhauser et al., 1985](#)) for the earthworm (*Eisenia fetida*) exposed to *trans*-1,2-dichloroethylene. The study ([Neuhauser et al., 1985](#)) tested both *trans*-1,2-dichloroethylene and trichloroethylene using a filter paper contact test to calculate the concentration that was lethal to half the exposed organisms (LC50). The LC50 of *trans*-1,2-dichloroethylene in the 48-hour filter paper contact was calculated as 286 mg/kg. The LC50 of trichloroethene in the 48-hour filter paper contact was calculated as 105 mg/kg (Table 3-5).

EPA completed a search of the [Ecotoxicology \(ECOTOX\) Knowledgebase](#) (accessed June 6, 2026) for data on soil-dwelling invertebrates and exposures to the analogs trichloroethylene and *cis*-1,2-dichloroethylene. The Agency identified three papers ([Lau et al., 1997](#); [Fuller et al., 1997](#); [Wang et al., 2021](#)) with eight studies for trichloroethylene. These studies were evaluated as part of the systematic review for *trans*-1,2-dichloroethylene and were assigned OQDs of high or medium. The terrestrial invertebrate (soil-dwelling) studies are summarized in Table 3-5.

Lau ([1997](#)) exposed the bacterial feeding nematode (*Cruzema tripartitum*) to 0, 1, and 30 µg/mL trichloroethylene solution added to 50 g of soil in a closed capped glass soil system for 48 hours. Declined respiration of *C. tripartitum* was observed at the 1 µg/mL solution addition exposure (Table 3-5).

In a study reporting soil arthropod activity after trichloroethylene exposure, activity was measured in closed capped glass soil systems for 10 days after the addition of 0, 1, 30 and 60 µg/mL trichloroethylene solution added to 100 grams of soil. Arthropod activity was measured by inspection of the bottles periodically for evidence of visible burrows in the soil. The number of burrows was significantly reduced in the 30 µg/mL trichloroethylene solution addition compared to control and the 1 µg/mL trichloroethylene solution addition. Burrows were not observed in the 60 µg/mL trichloroethylene solution ([Fuller et al., 1997](#) and Table 3-5).

([Fuller et al., 1997](#)) also investigated trichloroethylene's effect on nematode abundance and community diversity. This portion of the study consisted of a 28-day exposure of two different sediments, Yolo soil from an agricultural field and riparian soil collected from an adjacent creek. The Yolo soil was dried before 100 grams were weighed into three bottles per concentration. Once in the bottle the soil was brought to 16% moisture. The riparian soil was weighed wet into 50 grams per bottle with four bottles per concentration. All bottles were sealed to contain the volatile test chemical. After the 28-day exposure the chemical was purged from the bottles and inverts were extracted from the soil via a wet-sieving-sugar-centrifugation method. Results from this study were described in both total abundance and community diversity. Total abundance was reported as number of nematodes present per 100 g of soil and a significant decrease was found at the 30 µg/L concentration while no effect was seen at the 1 µg/L concentration (Table 3-5).

The community diversity aspect of this study ([Fuller et al., 1997](#)) was represented with a maturity index (MI). This is an ecological indicator that captures the successional status and disturbance sensitivity of the nematode community. MI weights the community by each taxon's colonizer–persister (c–p) value (from 1 = enrichment-type colonizers to 5 = disturbance-sensitive persisters) and reflects shifts toward

tolerant vs. sensitive groups under stress. In this paper, c-p class 1 was deliberately excluded because its presence tends to indicate nutrient enrichment rather than chemical stress. The nematodes were broken down by their trophic type (bacteria feeder, fungal feeder, herbivore, and predator), identified to the taxonomic level of family, and assigned a c-p value. The original trophic break-down and c-p values for Yolo and riparian soil were then compared to the post exposure values. The initial community composition of the two soils was very different, which had an impact on the results. The riparian soil had a more mature assemblage with a greater share of higher c-p taxa, so exposure reduced these more sensitive groups and lowered its MI noticeably at a concentration of 30 ug/L. In contrast, the Yolo soil was dominated by low c-p taxa, so changes from exposure were harder to detect and MI stayed about the same even at a concentration of 60 ug/L.

[Wang et al. \(2021\)](#) exposed *E. fetida* to trichloroethylene in three studies including an acute lethal toxicity test, a growth inhibition test and an avoidance test. The acute lethal toxicity test and growth inhibition test were performed in a closed soil microcosm for 48 hours where *E. fetida* were exposed to nominal concentrations of 0 (control), 4,000, 5,000, 6,000, 7,000 and 8,000 mg/kg soil. After 24 and 48 hours of exposure ([Wang et al., 2021](#)) reported LC50s of 5,332.36 and 4,522.41 mg/kg, respectively. The biomass of each tested earthworm was recorded after 12, 24, 35 and 48 hours to evaluate growth inhibition effects. Growth inhibition was observed at the lowest concentration tested at 4,000 mg/kg. All tested concentrations inhibited the growth of *E. fetida* with the inhibitory effect significantly increasing with increasing concentrations tested ([Wang et al., 2021](#)) (Table 3-5).

In a separate avoidance behavior test, *E. fetida* were exposed to trichloroethylene at nominal concentrations 0, 1,000, 2,000, 3,000, 4,000 and 5,000 mg/kg soil in a closed microcosm system that allowed worms to escape from exposure. Avoidant behavior was observed in earthworms at a concentration of 5,000 mg/kg ([Wang et al., 2021](#)) (Table 3-5).

Table 3-5. Soil-Dwelling Invertebrate Hazard Studies for *trans*-1,2-Dichloroethylene (and the Analog Trichloroethylene)

Test Organism (Genus/Species) (test chemical)	Duration/ Endpoint/ (Exposures)	Hazard Values ^a (Units)	Hazard Threshold	Effect	Citation (Study Quality)
Earthworm (<i>Eisenia fetida</i>) Filter paper (<i>trans</i> -1,2- dichloroethylene and trichloroethylene)	48-hour LC50 Filter paper	286/105 ^c (µg/cm ²)	NA	Mortality	Neuhauser et al. (1985) (High)
Bacterial Feeding Nematode (<i>Cruzinema tripartitum</i>) Capped Glass Soil System (trichloroethylene)	48-hour LOEC (0/1/30 µg/mL) Soil solution	1 ^c (mg/L=ppm soil)	NA	Declined respiration rates	Lau et al. (1997) (Medium)
Soil Arthropods (Yolo soil) Capped Glass Soil System (trichloroethylene)	10-day NOEC/LOEC (0/1/30/60 µg/mL)	1 ^c /30 ^c (mg/L = ppm soil solution)	5.48 ^c (geometric mean of NOEC/LOEC)	Soil arthropod activity as evidenced by observed burrowing.	Fuller et al. (1997) (Medium)

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Test Organism (Genus/Species) (test chemical)	Duration/ Endpoint/ (Exposures)	Hazard Values ^a (Units)	Hazard Threshold	Effect	Citation (Study Quality)
				Decreased compared to control.	
Nematodes (Yolo soil) Capped Glass Soil System (trichloroethylene)	28-day NOEC/LOEC (0/1/30/60 mg/L)	1°/30° (mg/L soil solution)	5.48° (geometric mean of NOEC/LOEC)	Total abundance	Fuller et al. (1997) (Medium)
Nematodes (Riparian soil) Capped Glass Soil System (trichloroethylene)	28-day NOEC/LOEC (0/1/30 µg/mL)	1°/30° (mg/L soil solution)	5.48° (geometric mean of NOEC/LOEC)	Total abundance	Fuller et al. (1997) (Medium)
Nematodes (Yolo soil) Capped Glass Soil System (trichloroethylene)	28-day NOEC (0/1/30/60 µg/mL)	60° (mg/L soil solution)	60°	Community diversity: Maturity index	Fuller et al. (1997) (Medium)
Nematodes (Riparian soil) Capped Glass Soil System (trichloroethylene)	28-day NOEC/LOEC (0/1/30 µg/mL)	1°/30° (mg/L soil solution)	5.48° (geometric mean of NOEC/LOEC)	Community diversity: Maturity index (decreased)	Fuller et al. (1997) (Medium)
Earthworm (<i>Eisenia fetida</i>) Closed microcosm system Acute lethality test (trichloroethylene)	24/48-hour LC50 (0/4,000/5,000/6,000/7, 0000/8,000 mg/kg soil)	5,332.36°/4,522. 41° (mg/kg soil)		Mortality	Wang et al. (2021) (High)
Earthworm (<i>Eisenia fetida</i>) Closed microcosm system Growth inhibition test (trichloroethylene)	48-hour LOEC (0/4,000/5,000/6,000/7, 0000/8,000) mg/kg soil	4,000° (mg/kg soil)	Acute =4,000/10 AF= 40	Developme nt: Growth inhibition	Wang et al. (2021) (High)
Earthworm (<i>Eisenia fetida</i>) Closed microcosm system divided to allow for avoidance Avoidance test (trichloroethylene)	48-hour LOEC (0/1,000/2,000/3,000/4, 0000/5,000) mg/kg soil	1,000° (mg/kg soil)	Acute =1,000/10 AF= 100	Behavior: Avoidance	Wang et al. (2021) (High)
LC50 = test concentration lethal to 50% of the test population; NOEC = no observed effect concentration; LOEC = lowest observed effect concentration					
^a Hazard values presented as ranges represent the range of all the definitive values in the citations and are presented with the number of significant figures reported by the authors.					
^b Geometric mean of definitive values only (<i>i.e.</i> , >100 mg/L was not used in the calculation).					

Test Organism (Genus/Species) (test chemical)	Duration/ Endpoint/ (Exposures)	Hazard Values ^a (Units)	Hazard Threshold	Effect	Citation (Study Quality)
^c Hazard values represented for trichloroethylene. Assessment Factor (AF) of 10 was applied for LOEC to NOEC.					

3.3.2.2 Terrestrial Invertebrate Toxicity Threshold

The 48-hour filter paper contact exposure of earthworms to *trans*-1,2-dichloroethylene applied to filter paper reported an LC50 of 286 µg/cm² ([Neuhauser et al., 1985](#)). However, because the filter paper contact test is not considered a relevant exposure pathway for soil invertebrates due to the absorbed amount of chemical to earthworm via dermal contact being uncertain, EPA did not use this study in establishing a hazard threshold for terrestrial invertebrates (soil-dwelling organisms).

The available data for the hazard of *trans*-1,2-dichloroethylene and the analogs *cis*-1,2-dichloroethylene and trichloroethylene to soil-dwelling invertebrates are for both acute (24–48 hours) and chronic exposures (10 or 28 days). Hazard values are reported for different exposures including filter paper ([Neuhauser et al., 1985](#)), closed capped glass or other glass systems (microcosms) with soil and test chemicals added to the systems in small amounts of solution (*i.e.*, 1 mL) ([Fuller et al., 1997](#); [Wang et al., 2021](#); [Lau et al., 1997](#)). Reported adverse effects to soil-dwelling invertebrates associated with *trans*-1,2-dichloroethylene and analog exposures include avoidance, mortality, growth inhibition, reduced respiration rates, decreases in community diversity and decreases in abundance.

EPA identified two hazard thresholds for *trans*-1,2-dichloroethylene for two types of soil exposures for soil-dwelling invertebrates including one for mg/L soil solution and one for mg/kg soil. The hazard thresholds were identified based on a review of hazard data as summarized in Table 3-5.

A hazard threshold of 5.48 mg/L soil solution was derived based on geometric means of NOECs and LOECs reported in four studies with trichloroethylene from ([Fuller et al., 1997](#)) associated with reduced soil arthropod activity, reduced abundance and impairment of community diversity. A lower exposure of 1 mg/L to trichloroethylene is reported by ([Lau et al., 1997](#)) for a decline in respiration rates. This effect was not used by EPA to identify a hazard threshold as the endpoint is not ecologically relevant compared to the 5.8 mg/L threshold, which is associated with reductions in abundance and community diversity.

A hazard threshold of 10 mg/kg soil was derived from the studies reported by ([Wang et al., 2021](#)) for the analog trichloroethylene. In these studies, a 48-hour LC50 of 4,522 was reported for mortality and 48-hour LOECs of 4,000 and 1,000 mg/kg were reported for growth inhibition and avoidance, respectively. EPA derived a hazard threshold based on these effects reported at 1,000 mg/kg and higher using an application factor (AF) for LOEC to NOEC converting $1,000 \div \text{AF (10)} = 100 \text{ mg/kg soil}$.

3.3.2.3 Weight of Scientific Evidence for Terrestrial Invertebrate Toxicity Threshold

The weight of evidence suggests that *trans*-1,2-dichloroethylene poses hazard to terrestrial invertebrate species at 100 mg/kg soil and 5.88 mg/L soil solution. For the terrestrial soil-dwelling invertebrate, the database consisted of 10 studies, including 1 for *trans*-1,2-dichloroethylene and 9 for trichloroethylene. The one study that included data for both chemicals ([Neuhauser et al., 1985](#)) showed that trichloroethylene was a conservative analog with a hazard value close to the 0.3 found in the comparison table from Table_Apx E-4. This increases confidence that trichloroethylene invertebrate exposure study results will be protective for *trans*-1,2-dichloroethylene. Across studies the adverse effects were

consistent in reporting decreases in abundance, diversity, and mortality. The adverse effects observed are ecologically relevance in that the reduction in abundance, (growth) diversity and survival are related to the short term and long-term viability of terrestrial soil invertebrate populations and the communities of animals that are dependent on these receptors. Therefore, the Agency assigned moderate-to-robust confidence to the terrestrial soil-dwelling invertebrate hazard threshold.

3.3.3 Terrestrial Plants

3.3.3.1 Terrestrial Plant Hazard Data

For terrestrial plant species, EPA identified two *trans*-1,2-dichloroethylene hazard studies assigned a OQD of medium. One study ([Dietz and Schnoor, 2001](#)) exposed 8-inch cuttings of the Canadian poplar (*Populus deltoides*) to *trans*-1,2-dichloroethylene. The cuttings were placed in sealed flasks with 200 mL of a nutrient solution. The authors describe the test system as “sealed bioreactors” with two ports (1 for dosing and 1 for sampling). The plant cuttings were exposed to 0, 175, 291, 427, and 727 mg/L of *trans*-1,2-dichloroethylene mixed into nutrient solution and replaced every 2 days to ensure a consistent dose to the cuttings. After 14 days of exposure the study found that *trans*-1,2-dichloroethylene begins to slow the growth of the *P. deltoides* cuttings at the lowest exposure concentration of 175 mg/L. A zero growth concentration was calculated at 465 mg/L. The study also calculated a 50% reduced transpiration of the *P. deltoides* cuttings at 349 mg/L. Results are also reported for exposures of the two analogs *cis*-1,2-dichloroethylene and trichloroethylene to *P. deltoides* using the same exposure regime. The study results are summarized in Table 3-6. The purpose of this study was to examine the use of the plant species for phytoremediation of waste sites.

The other study ([Schubert et al., 1995](#)) exposed the pollen of tobacco (*Nicotiana tabacum*) to *trans*-1,2-dichloroethylene for 2 hours. The pollen was exposed to concentrations of 0, 10, 40, 60, 100, and 200 mg/dm³ of *trans*-1,2-dichloroethylene as a gas injected into a sealed glass trough containing the germinating tobacco pollen in petri dishes; the air in the sealed trough was water saturated. The study authors noted that the short exposure period was necessary to avoid stimulation of pollen germination in the closed test vessel due to an increase in CO₂ partial pressure ([Schubert et al., 1995](#)). The measured germination rate was then compared to the control. The calculated 50% effective dose (ED50) and 25% effective dose (ED25) for *trans*-1,2-dichloroethylene were 64 mg/L (15,890 ppm in air) and 41.7 mg/L (10,350 in air), respectively. The study by ([Schubert et al., 1995](#)) is relevant for the hazard evaluation for *trans*-1,2-dichloroethylene because it is a volatile chemical where releases to air are expected and the exposures in the study are related to adverse effects when the plant pollen was exposed to *trans*-1,2-dichloroethylene in air.

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3100**Table 3-6. Terrestrial Plant Hazard Studies for *trans*-1,2-Dichloroethylene (and Analogs Trichloroethylene and *cis*-1,2-Dichloroethylene)**

Test Organism (Genus/ Species) Test Chemical	Duration/ Endpoint/ (Exposures) (Units)	Hazard Values (Units)	Effect	Citation (Study Quality)
Poplar (<i>Populus deltoides</i>) <i>trans</i> -1,2- dichloroethylene	14 day/LOEC/Concn _{zo} (0/175 ^a / 291 ^a / 427 ^a / 727 ^a) (mg/L)	175/465 (mg/L in soil solution)	Growth: reduction wet weight and no growth	Dietz and Schnoor (2001) (Medium)
Poplar (<i>Populus deltoides</i>) <i>cis</i> -1,2- dichloroethylene	14 day LOEC/Concn _{zo} (0,136 ^{a b} /262 ^{a b} /359 ^{a b} /543 ^{a b}) (mg/L)	136 ^{a b} / 582 ^b (mg/L in soil solution)	Growth: reduction wet weight and no growth	Dietz and Schnoor (2001) (Medium)
Poplar (<i>Populus deltoides</i>) trichloroethylene	14 day/ LOEC/Concn _{zo} (0,79 ^{a c} ,155 ^{a c} ,237 ^{a c} ,263 ^{a c}) (mg/L)	79 ^{a c} /118 ^c (mg/L in soil solution)	Growth: reduction wet weight and no growth	Dietz and Schnoor (2001) (Medium)
Poplar (<i>Populus deltoides</i>) <i>trans</i> -1,2- dichloroethylene	14 day/ Concn _{50%T}	349 (mg/L in soil solution)	Growth: transpiration reduced by 50%	Dietz and Schnoor (2001) (Medium)
Poplar (<i>Populus deltoides</i>) <i>cis</i> -1,2- dichloroethylene	14 day/ Concn _{50%T}	494 ^b (mg/L in soil solution)	Growth: transpiration reduced by 50%	Dietz and Schnoor (2001) (Medium)
Poplar (<i>Populus deltoides</i>) trichloroethylene	14 day/ Concn _{50%T}	131 ^c (mg/L in soil solution)	Growth: transpiration reduced by 50%	Dietz and Schnoor (2001) (Medium)
Tobacco (<i>Nicotiana tabacum</i>) <i>trans</i> -1,2- dichloroethylene	2-hour/ ED50/ ED25 (0/2,482/4,964/9,928/14,892/24,820/49,640) (ppm)	15,890/ 10,350 (ppm in air)	Development: Germination Inhibition	Schubert et al. (1995) (Medium)
Tobacco (<i>Nicotiana tabacum</i>) trichloroethylene	2-hour/ ED50/ ED25 (0/183 ^c / 366 ^c / 732 ^c / 1,099 ^c / 1,465 ^c / 1,831 ^c /3,662 ^c / 7,324 ^c / 10,986 ^c) (ppm)	5800 ^c / <730 ^c (ppm in air)	Development: Germination	Schubert et al. (1995) (Medium)

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Test Organism (Genus/ Species) Test Chemical	Duration/ Endpoint/ (Exposures) (Units)	Hazard Values (Units)	Effect	Citation (Study Quality)
Concn_{zo} = concentration where 0 growth was measured over exposure; Concn_{50%T} = concentration where transpiration rate was 50% that of the control; ED50 = effective dose to 50% of the test population; ED25 = effective dose to 25% of the test population; LOEC = lowest observable effect concentration; ^a Hazard value converted from mM published in study to mg/L ^b Hazard values represented by <i>cis</i>-1,2-dichloroethylene. ^c Hazard values represented by trichloroethylene. Bolded values are equal to the identified hazard threshold.				

3.3.3.2 Terrestrial Plant Hazard Thresholds

The terrestrial plant hazard threshold for *trans*-1,2-dichloroethylene was based on the examination of the data available for the target chemical and for the two analogs (trichloroethylene and *cis*-1,2-dichloroethylene). Hazard thresholds for plants were identified for both soil solution exposures and air exposures. For soil solution exposures, all chemicals (target and analogs) significantly reduced growth and transpiration at all concentrations tested. The lowest concentrations tested for *trans*-1,2-dichloroethylene, *cis*-1,2-trichloroethylene and trichloroethylene were 175, 136, and 79 mg/L respectively. As these values are LOECs and do not represent a threshold for no adverse effects, the lowest of these values (79 mg/L) was identified as the hazard threshold for *trans*-1,2-dichloroethylene in soil solution. The reported Conc_{50%} (or EC₅₀) values reported and expressed as mg/L soil solution from the same paper (([Dietz and Schnoor, 2001](#))) for reduced transpiration were less sensitive compared the growth measurements and were not used to identify a terrestrial plant hazard threshold (Table 3-6).

From the testing reported ([Schubert et al., 1995](#)), it was possible to identify a terrestrial plant hazard threshold for ambient air exposure. The most sensitive hazard value was based on the 2-hour ED25 (effective dose of a test material that reduces tissue viability by 25% in toxicity testing) reported for *trans*-1,2-dichloroethylene at 10,350 ppm in air for *N. tabacum* representing reduced germination effects for pollen ([Schubert et al., 1995](#)).

3.3.3.3 Weight of Scientific Evidence for Terrestrial Plants

The weight of evidence suggests that *trans*-1,2-dichloroethylene poses hazard to terrestrial invertebrate species at 79 mg/L in soil solution and 10,350 ppm in air. The terrestrial plant database consisted of eight studies in two citations including three for *trans*-1,2-dichloroethylene and five for either the analog *cis*-trichloroethylene or trichloroethylene. Across studies the adverse effects were consistent in reporting decreases in growth (biomass), transpiration (survival) and germination (reproduction) The adverse effects observed are ecologically relevance in that the reduction in growth, survival and reproduction are related to the short-term and long-term viability of terrestrial soil invertebrate populations and the communities of animals that are dependent on these receptors. Therefore, the Agency assigned moderate-to-robust confidence to the terrestrial plant hazard thresholds.

3.4 Summary of Environmental Thresholds

Table 3-7 provides a summary of the environmental toxicity thresholds for aquatic and terrestrial species for both acute and chronic exposures. The environmental toxicity threshold for aquatic plants (algae) is one value.

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Table 3-7. Summary of Environmental Toxicity Thresholds

Environmental Toxicity Thresholds	Analog	Hazard Value	Assessment Factor (AF)	COC/TRV/ Threshold	Assessment Medium	Overall Confidence
Aquatic species COCs						
Acute aquatic exposure: Lower 95th Confidence Interval of the HC05 and the HC05 from SSD.	Trichloroethylene	3,005 (µg/L)	N/A	3,005 (µg/L)	Water column	Robust
		4,438 (µg/L)	N/A	4,438 (µg/L)		Robust
Chronic aquatic exposure:	Trichloroethylene (read across)	7,880 (µg/L)	10	788 (µg/L)	Water column	Moderate
Chronic sediment dwelling organism:	Not derived (see Section 3.2.4)				Sediment pore water	NA
Aquatic plant exposure: Lower 95th Confidence Interval of the HC05 and the HC05 from empirical SSD.	Trichloroethylene	51,467 (µg/L)	N/A	51,467 (µg/L)	Water column	Moderate-to-Robust
		93,364 (µg/L)	N/A	93,364 (µg/L)	Water column	Moderate-to-Robust
Terrestrial species thresholds						
Terrestrial Plants	N/A	10,350 (ppm in air)	N/A	10,350 (ppm in air)	Outdoor Ambient Air	Moderate-to-Robust
Terrestrial Plants	Trichloroethylene	79 (mg/L in soil solution)	N/A	79 (mg/L in soil solution)	Soil Pore water	Moderate-to-Robust
Terrestrial Soil-Dwelling Invertebrates	Trichloroethylene	1,000 (mg/kg soil)	10	100 (mg/kg soil)	Soil	Moderate-to-Robust
Terrestrial Soil-Dwelling Invertebrates	Trichloroethylene	5.48 (mg/L in soil solution)	N/A	5.48 (mg/L in soil solution)	Soil Pore water	Moderate-to-Robust
Chronic toxicity reference value (TRV) for mammals for oral (mg/kg-bw/day)	N/A	1,504 mg/kg-bw/day	N/A	1,504 mg/kg-bw/day	Diet, drinking water, incidental ingestion of soils, sediments.	Robust
Chronic toxicity threshold for mammals for inhalation (mg/cm³)	N/A	6,000 ppm 23,789 mg/m³	N/A	6,000 pm 23,789 mg/m³	Outdoor Ambient Air	Moderate
bw = body weight; SSD=species sensitivity distribution						

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3.5 Weight of Scientific Evidence Conclusions for Environmental Hazard Assessment

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After calculating the hazard thresholds that will be carried forward to characterize risk in the Draft *Risk Evaluation for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026h](#)), EPA considers the weight of scientific

evidence for the hazard thresholds. See Appendix F.1.2 for more information on the method the Agency used to weigh the scientific evidence.

3.6 Environmental Hazard Assessment Conclusions

EPA considered all reasonably available information identified through the systematic review process and the TSCA section 4 Test Order process under TSCA to characterize environmental hazard endpoints for *trans*-1,2-dichloroethylene. The following summarizes the hazard values and overall hazard confidence:

- EPA found a limited number of quality exposure studies for *trans*-1,2-dichloroethylene, so the isomer *cis*-1,2-dichloroethylene and the analog trichloroethylene were selected to supplement the areas lacking empirical *trans*-1,2-dichloroethylene data.
- Aquatic species:
 - LC50 and EC50 values from eight exposures to *trans*-1,2-dichloroethylene in aquatic invertebrates, amphibians, and fish and immobilization EC50 values from exposure to *cis*-1,2-trichloroethylene and trichloroethylene were used alongside Web-ICE derived hazard estimates to develop an acute aquatic SSD. The HC05 of 4.44 mg/L was used as a COC along with the lower confidence interval of the HC05 of 3.01 mg/L. This range was used to account for uncertainty and indicated that acute aquatic toxicity occurs between 3.01 and 4.44 mg/L.
 - Chronic aquatic studies were not identified for *trans*-1,2-dichloroethylene or its analog *cis*-1,2-dichloroethylene. Therefore, chronic aquatic studies from trichloroethylene were used to determine the chronic aquatic COC. A 32-day exposure study on fathead minnow growth was selected as the most relevant choice for the COC with a value of 788 mg/L
 - Trichloroethylene algal exposure studies were selected as an analog for *trans*-1,2-dichloroethylene that lacked relevant studies. The empirical data from four trichloroethylene algal exposure studies was used to create an algal SSD. The HC05 of 93.36 mg/L was used as a COC along with the lower confidence interval of the HC05 of 51.47 mg/L. This range was used to account for uncertainty and indicated that algal toxicity occurs between 51.47 and 93.36 mg/L.
- Benthic species:
 - EPA did not identify any existing sediment-dwelling invertebrate studies for *trans*-1,2-dichloroethylene, so a TSCA section 4 Test Order required acute and chronic chironomid toxicity tests. However, preliminary feasibility testing demonstrated that *trans*-1,2-dichloroethylene could not be maintained at stable or measurable concentrations in overlying water, pore water, or sediment due to extreme volatility, rapid loss, and inconsistent retention—even under multiple dosing and aeration conditions. Both water-spiked and sediment-spiked methods failed, with measured concentrations often below detection limits or representing only a small fraction of nominal levels. Because reliable exposures could not be achieved and no viable alternative method existed, EPA extinguished the sediment toxicity testing requirements. As a result, the Agency concluded that meaningful sediment exposures are unlikely to occur in the environment and did not evaluate risks to sediment-dwelling invertebrates.
- Terrestrial species:
 - Terrestrial vertebrate effects of *trans*-1,2-dichloroethylene were characterized using rodent studies, as no wildlife mammalian or avian studies were available. Across multiple

subchronic oral and inhalation studies in rats and mice, *trans*-1,2-dichloroethylene produced only limited effects at relatively high doses, involving changes in food or water consumption, activity, reproductive organ metrics, and body weight. Using these ecologically relevant endpoints, EPA derived a mammalian oral toxicity reference value (TRV) of 1,504 mg/kg-bw/day. The Agency identified an inhalation threshold or hazard value for mammalian wildlife by selecting to lowest bounded NOAEL of 6,000 ppm for reproductive effects.

- Terrestrial invertebrate hazard data for *trans*-1,2-dichloroethylene are limited, with only one acceptable study directly testing the chemical and additional studies available for *cis*-1,2-dichloroethylene and trichloroethylene. The single high-quality *trans*-1,2-dichloroethylene study reported a 48-hour earthworm LC50 of 286 mg/kg in a filter-paper contact test, but this exposure route is not considered environmentally relevant. Read-across studies with trichloroethylene showed effects such as reduced respiration in nematodes, decreased arthropod activity, altered nematode community structure, mortality, growth inhibition, and avoidance at relatively high soil concentrations. When integrating this data, EPA identified two terrestrial invertebrate hazard thresholds including one for *trans*-1,2-dichloroethylene at 5.48 mg/L for soil solution and one at 100 mg/kg in soil.
- EPA selected two terrestrial plant exposure studies for *trans*-1,2-dichloroethylene, both studies also contained data for trichloroethylene and one study contained data for both analogs. A pore water exposure study measured the chemical's effect on the growth and transpiration of Poplar cuttings during a 14-day exposure. Hazard thresholds for plants were identified for both soil solution exposures and air exposures. For soil solution exposures, all chemicals (target and analogs) significantly reduced growth and transpiration at all concentrations tested. The lowest concentrations tested for *trans*-1,2-dichloroethylene, *cis*-1,2-trichloroethylene and trichloroethylene were 175 mg/L, 136 mg/L and 79 mg/L, respectively. As these values are LOECs and do not represent a threshold for no adverse effects, the lowest of these values (79 mg/L) was identified as the hazard threshold for *trans*-1,2-dichloroethylene in soil solution. The reported Conc50% (or EC50) values reported and expressed as mg/L soil solution from the same paper for reduced transpiration were less sensitive compared to the growth measurements and were not used to identify a terrestrial plant hazard threshold. From the testing reported it was possible to identify a terrestrial plant hazard threshold for ambient air exposure. The most sensitive hazard value was based on the 2-hour ED25 reported for *trans*-1,2-dichloroethylene at 10,350 ppm in air for *N. tabacum* representing reduced germination effects for pollen.

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Appendix A BENCHMARK DOSE MODELING RESULTS FOR CRITICAL ENDPOINTS

EPA performed benchmark dose (BMD) modeling using EPA's BMD modeling software (BMDS Version BMDS Online 25.1) for selected critical non-cancer human health outcomes (immunological/hematological toxicity and sensory irritation) identified in the *trans*-1,2-dichloroethylene non-cancer hazard assessment (see Section 2.3). EPA conducted BMD modeling in a manner consistent with EPA's *Benchmark Dose (BMD) Technical Guidance* ([U.S. EPA, 2012b](#)). The BMDS-generated MS Word reports for the datasets discussed below are provided in the BMDS output supplemental file ([U.S. EPA, 2026a](#)). The supplemental file includes the input data, BMDS results, and plots of the selected models. All doses and concentrations from toxicity studies were adjusted to HECs or HEDs prior to modeling to allow easier comparison of results for POD selection.

Non-cancer endpoints selected for modeling were based on either dichotomous or continuous data. The default model selection settings in BMDS were used for all BMD modeling runs, unless otherwise stated. For dichotomous data, the default model settings include the restricted Dichotomous Hill, Gamma, Log Logistic, Multistage, and Weibull models and the unrestricted Logistic, Log Probit, Probit, and Quantal Linear models. For continuous data, the default model settings include the restricted Exponential, Hill, Polynomial, and Power models and the unrestricted Linear model.

Dichotomous models were fit employing a benchmark response (BMR) of 10% extra risk (ER). Adequacy of model fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit.

Continuous models were fit employing a BMR of 1 standard deviation (SD). An adequate fit was judged based on the chi-square goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (*i.e.*, Test 2; p -value > 0.05), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (p -value < 0.05), the dataset was run again while modeling the variance as a power function of the mean to account for nonconstant variance. If this nonconstant variance model also did not adequately fit the data (*i.e.*, Test 3; p -value < 0.05), the dataset was considered unsuitable for BMD modeling.

For both dichotomous and continuous data, the lowest benchmark dose lower confidence level (BMDL) from all models providing adequate fit was selected if the BMDLs estimated from different models varied >3 -fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected.

A.1 Humoral Immune Response to Sheep Red Blood Cells ([Shopp et al., 1985](#))

Continuous data for decreased humoral immune response to sheep red blood cells (sRBC) (AFC/10⁶ cells) in male CD-1 mice administered *trans*-1,2-dichloroethylene in drinking water for 90 days were modeled using a BMR of 1 SD consistent with EPA's *Benchmark Dose (BMD) Technical Guidance* ([U.S. EPA, 2012b](#)). Analysis was performed using time-weighted average (TWA) doses reported in the study. Table_Apx A-1 presents the dose and response data used for modeling.

Table_Apx A-1. Humoral Immune Response Dataset Used for BMD Modeling ([Shopp et al., 1985](#))

TWA Doses (mg/kg-day) ^a	Number of Animals	Mean (AFC/10 ⁶ cells)	SD
0	12	2,200	433
2.21	8	2,048	430
22.8	8	1,625	385
50.3	8	1,618	639

^a TWA doses as reported in [Shopp et al. \(1985\)](#).

The BMD modeling results are summarized in Table_Apx B-1. Based on the poor visual fit for the BMD model on the full dataset and large residual near the BMD (see ([U.S. EPA, 2026a](#))), EPA additionally modeled the dataset with the highest dose dropped because the dose-response appeared to be flat between the two highest doses. These results are included in Table_Apx A-2 for comparison with the full dataset; however, EPA determined that it was not appropriate to use BMD results for the truncated dataset because viable models were available using the full dataset.

Table_Apx A-2. Summary of BMD Modeling Results for Humoral Immune Response in Male Mice Administered *trans*-1,2-Dichloroethylene in Drinking Water ([Shopp et al., 1985](#)) Using the Constant Variance Model^a

Model	BMDL 1 SD (mg/kg-day)	BMD 1 SD (mg/kg-day)	AIC	Scaled Residual Near BMD	Fit ^b	Model Selection Notes
Full dataset						The constant variance model provided adequate fit to the variance data (Test 2 p-value > 0.05). Using the full dataset, the Exponential 3, Polynomial 2, Power, and Linear models provided adequate fit to the means (Test 4 p-value > 0.1).
Exponential 3	21.4	36.9	550.15	0.65	S	
Polynomial 2	25.4	40.2	550.53	0.60	V	
Power	25.3	40.2	550.53	0.60	V	
Linear	25.3	40.2	550.53	0.60	V	
Exponential 5, Hill, Polynomial 3	Degrees of freedom = 0; saturated model				Q	
Highest dose excluded ^c						
Exponential 3	9.33	15.9	420.70	0.05	S	
Polynomial 2	10.8	16.7	420.75	0.04	V	
Power	10.7	16.7	420.75	0.04	V	
Linear	10.7	16.7	420.75	0.04	V	
Exponential 5, Hill	Degrees of freedom = 0; saturated model				Q	The BMDLs of the viable models were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected.

The model results for the truncated dataset are included for comparison.

^a Data are shown only for models that were considered viable.

^b Model fit: S = selected viable model; V = viable model (bold indicates the model being considered for POD derivation); Q = questionable model. Green shading indicates viable models. Gray shading indicates questionable models.

^c Results for the truncated dataset are shown only for comparison to the full dataset.

BMDs package version and timestamps: U.S. Environmental Protection Agency. (2025). BMDs Online (25.1; pybmds 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed February 13, 2026.



Figure_Apx A-1. BMD Modeling Graph for Exponential 3 Model of Humoral Immune Response in Male Mice



Figure_Apx A-2. BMD Modeling Graph for Exponential 3 Model of Humoral Immune Response in Male Mice (Trimmed Dataset Excluding the Highest Dose)

A.2 Sensory Irritation ([Hurtt et al., 1993](#))

Dichotomous data for increased incidences of lacrimation and periocular (brown) staining in female Crl:CD (SD) BR rats exposed to *trans*-1,2-dichloroethylene via inhalation on gestational days (GDs) 7 to 16 (6 hours/day) were modeled using a BMR of 10% ER consistent with EPA's *Benchmark Dose (BMD) Technical Guidance* ([U.S. EPA, 2012b](#)). Analyses were performed after exposure concentrations in ppm were converted to mg/m³; duration was not adjusted from 6 hours/day to a continuous duration based on the assumption that effects are concentration-dependent, not duration-dependent. Table_Apx A-3 presents the exposure concentrations and response data used for modeling.

Table_Apx A-3. Sensory Irritation Datasets Used for BMD Modeling ([Hurtt et al., 1993](#))

Concentration (mg/m ³)	Number of Animals	Incidence of Lacrimation	Incidence of Periocular (Brown) Staining
0	24	0	1
7,930	24	13	3
23,800	24	22	18
47,580	24	24	22

The BMD modeling results for increased incidence of lacrimation and periocular staining are summarized in Table_Apx A-4 and Table_Apx A-5, respectively. For the lacrimation effects, there are limited data to inform the shape of the curve in the region of interest (10% ER) due to the concentration spacing of the study design, resulting in some uncertainty in the BMD/BMDL values.

Table_Apx A-4. Summary of BMD Modeling Results for Lacrimation in Female Rats Exposed to *trans*-1,2-Dichloroethylene via Inhalation ([Hurtt et al., 1993](#))^a

Model	BMDL 10% ER (mg/m ³)	BMD 10% ER (mg/m ³)	AIC	Scaled Residual Near BMD	Fit ^b	Model Selection Notes
Log Probit ^{c,d}	914	2,770	51.38	-6.05E-4	S	The Log Probit, Hill, and Log Logistic models provided adequate fit to the data (chi-square p-value > 0.1) and were considered viable.
Hill ^c	1,020	2,930	51.67	-6.05E-4	V	
Log Logistic ^c	1,020	2,930	51.67	-6.05E-4	V	
Gamma, Multistage 1-, 2-, and 3-degree, Weibull, Quantal linear	Lowest dose/BMDL ratio > 10.0				Q	The BMDLs of the viable models were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected. The result was flagged with a warning because the BMDL is more than 3-fold below the lowest dose tested and the BMD:BMDL ratio is > 3.
Logistic, Probit	Goodness-of-fit p-value < 0.1					

^a Data are shown only for models that were considered viable.

^b Model fit: S = selected viable model; V = viable model (bold indicates the model being considered for POD derivation); Q = questionable model. Green shading indicates viable models. Gray shading indicates questionable models.

^c Lowest dose/BMDL ratio >3.0.

^d BMD/BMDL ratio >3.0.

BMDS package version and timestamps: U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmds 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed August 19, 2025.

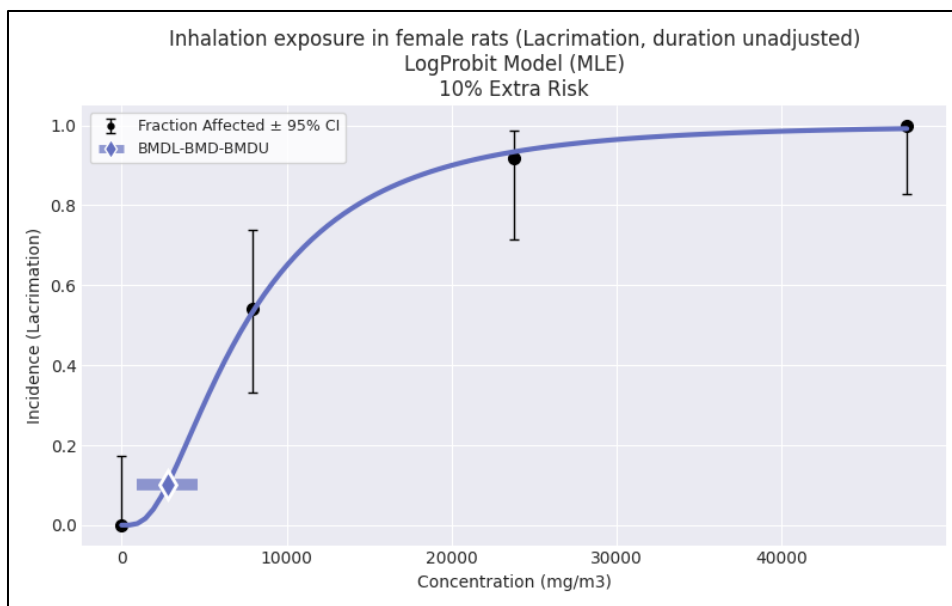


Figure Apx A-3. BMD Modeling Graph for LogProbit Model of Lacrimation in Female Rats

Table Apx A-5. Summary of BMD Modeling Results for Periocular (Brown) Staining in Female Rats Exposed to *trans*-1,2-Dichloroethylene via Inhalation (Hurt et al., 1993) ^a

Model	BMDL 10% ER (mg/m ³)	BMD 10% ER (mg/m ³)	AIC	Scaled Residual Near BMD	Fit ^b	Model Selection Notes
Log Logistic	4,440	7,610	73.61	−0.26	S	The Log Logistic, Gamma, Multistage 2- and 3-degree, Weibull, and Log Probit models provided adequate fit to the data (chi-square p-value > 0.1).
Gamma	3,150	6,740	74.90	−0.55	V	
Multistage 2-degree ^c	2,250	5,210	74.43	−0.88	V	
Multistage 3-degree ^c	2,240	5,210	74.43	−0.88	V	
Weibull ^c	2,640	5,630	73.67	−0.85	V	
Log Probit	4,560	7,550	73.83	−0.31	V	
Hill	Zero degrees of freedom; saturated model				Q	The BMDLs of the viable models were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected.
Multistage 1-degree, Quantal Linear, Logistic, Probit	Goodness-of-fit p-value < 0.1					

^a Data are shown only for models that were considered viable.

^b Model fit: S = selected viable model; V = viable model (**bold** indicates the model being considered for POD derivation); Q = questionable model. Green shading indicates viable models. Gray shading indicates questionable models.

^c Lowest dose/BMDL ratio >3.0.

BMDS package version and timestamps: U.S. Environmental Protection Agency. (2025). BMDS Online (25.1; pybmds 25.1; bmdscore 25.1) [Software]. Available from <https://bmdsonline.epa.gov>. Accessed August 19, 2025.

Appendix B HUMAN HEALTH HAZARD CONFIDENCE SUMMARY

Table_Apx B-1 summarizes the confidence ratings for each factor for the critical human health hazard endpoints and associated hazard values considered for acute, intermediate, and chronic non-cancer scenarios, and cancer lifetime exposure scenarios. The bolded rows in the table are the most robust and sensitive health effect for each exposure scenario and will be used to calculate risks for *trans*-1,2-dichloroethylene. “Slight” is indicated by a single +, moderate by ++, and robust by +++.

Table_Apx B-1. Confidence Summary for Human Health Hazard Assessment

Hazard Domain	Evidence Integration Conclusion	Selection of Most Critical Endpoint and Study	Relevance to Exposure Scenarios	Dose-Response Considerations	PESS Sensitivity	Overall Hazard Confidence
Acute inhalation non-cancer						
Sensory Irritation/ Neurotoxicity	++	++	+++	++	++	Moderate-to-Robust
Intermediate oral/inhalation non-cancer						
Immunological	++	+++	+++ (oral) ++ (inhalation)	+ / ++	++	Moderate-to-Robust
Intermediate dermal non-cancer						
Immunological	++	+++	++	+	++	Moderate
Chronic oral/inhalation non-cancer						
Immunological	++	+++	++ (oral) + (inhalation)	+ / ++	++	Moderate
Chronic dermal non-cancer						
Immunological	++	+++	+	+	++	Slight-to-Moderate
Lifetime cancer						
Cancer	Quantitative cancer risk assessment is not needed					Slight-to-Moderate
+++ Robust confidence suggests thorough understanding of the scientific evidence and uncertainties. The supporting WOSE outweighs the uncertainties to the point where it is unlikely that the uncertainties could have a significant effect on the hazard estimate.						
++ Moderate confidence suggests some understanding of the scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize hazard estimates.						
+ Slight confidence is assigned when the weight of the scientific evidence may not be adequate to characterize the scenario, and when the assessor is making the best scientific assessment possible in the absence of complete information. There are additional uncertainties that may need to be considered.						

Appendix C INTERPRETATION OF DERMAL ABSORPTION TEST ORDER DATA

Background

In order to inform the dermal exposure assessment of *trans*-1,2-dichloroethylene, EPA issued a test order (Docket: [EPA-HQ-2018-0465-0045](#)) in accordance with TSCA Section 4(a)(2). The test order included examination of dermal absorption of *trans*-1,2-dichloroethylene for both finite doses (*i.e.*, ≤ 10 uL/cm²) and infinite doses (*i.e.*, ≥ 100 uL/cm²). In the study ([TDCE Consortium, 2023](#)), finite doses were applied to human skin samples as a neat material, 10% solution, 1% solution, and 0.1% solution. Solutions were prepared with both IPM and toluene to compare the effect of mixture components on absorption of *trans*-1,2-dichloroethylene. Absorption was measured for 24 hours post application, and skin samples were washed at the 8-hour timepoint. Finite dose experiments yielded values of fractional absorption for use in occupational and consumer exposure scenarios. Infinite doses were applied to human skin samples as a neat material, 50% solution, and 10% solution. Solutions were prepared with both IPM and receptor fluid (phosphate buffered saline) to compare the effect of mixture components on absorption of *trans*-1,2-dichloroethylene. Absorption was measured for 24 hours post application, and results yielded values of steady-state flux and permeability coefficient (K_p).

Finite Doses and Fractional Absorption

For determining the fractional absorption from finite dose scenarios, EPA considered the potentially absorbable dose which is comprised of the cumulative chemical reaching the receptor fluid, the amount remaining in the skin and stratum corneum, and the amount in tape strips 3 to 20. Percent absorption results ranged from 0.4 to 1.4% without a clear relationship between test preparation concentration and fraction absorbed, but test preparations with toluene generally led to higher levels of absorption than test preparations with IPM. The mass balance recoveries were less than 80% for all test preparations, and the coefficients of variation were greater than 25% for several, but not all, test preparations. The values of fractional absorption from finite dose experiments were not adjusted for missing mass since the chemical is highly volatile and it was assumed that missing mass was due to volatilization. However, fractional absorption values were adjusted for high variability among measured results. EPA used the multiplication factor approach outlined in the [EFSA Guidance on Dermal Absorption](#) to derive an upper confidence interval based on the number of experimental replicates. Specifically, the EFSA guidance indicates that the sample mean plus the product of the sample standard deviation and multiplication factor results in the upper confidence value. Individual outliers were excluded from analysis based on Dixon's Outlier Test at 10% significance level in ProUCL 5.2. Fractional absorption values from finite dose testing were used to estimate exposure to all occupational and consumer exposure scenarios. Statistical adjustments performed by EPA are provided in *Draft Dermal Absorption Calculations for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026f](#)).

Occupational Exposures: For occupational exposure scenarios, all COUs involve handling *trans*-1,2-dichloroethylene in a concentration greater than 10%. The results of the 10% test preparation in IPM (when adjusted for outliers) showed mean absorption of 1.2%, and after the application of the EFSA upper confidence adjustment, percent absorbed ranged from 0.7 to 1.7%. Therefore, EPA employed a Monte Carlo model of occupational dermal exposure with a triangular distribution for percent absorbed ranging from 0.7 to 1.7% with a peak at 1.2%.

Consumer Exposures: For consumer exposure scenarios, the exposure durations may be less than the occupational exposure durations. Consequently, EPA considered the average absorption of *trans*-1,2-dichloroethylene in receptor fluid across all test preparations at both the 4- and 24-hour timepoints, resulting in percent absorbed values of 0.6 and 1.2%, respectively, for consumer exposure

scenarios. The 24-hour value is the same mean value applied for occupational scenarios after adjusting for outliers, while the 4-hour value is intended to better approximate the shorter exposure duration of consumer scenarios.

Infinite Doses and Permeability

For determining permeability and K_p among infinite dose test preparations, EPA considered steady-state flux for linear portions of the absorption curves. In some cases the study report ([TDCE Consortium, 2023](#)) calculated flux and K_p from non-linear portions of the absorption curve, and EPA reduced such intervals to ensure linearity. Statistical adjustments performed by EPA are provided in *Draft Dermal Absorption Calculations for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026f](#)).

Results of infinite dose testing showed an inverse relationship between K_p values and concentration, and test preparations with receptor fluid resulted in higher values of K_p than test preparations with IPM. For the 50% test preparation in receptor fluid, it was determined that *trans*-1,2-dichloroethylene was dissociating in receptor fluid post-dosing and these data were excluded from the final analysis.

General Population: Permeability data from infinite dose experiments were used to estimate general population exposure from incidental contact by the general population which may occur during swimming. Specifically, the value of K_p determined for a 10% test preparation with receptor fluid (*i.e.*, $K_p = 9.16 \times 10^3$ cm/hour) was used to estimate dermal flux from an aqueous solution while swimming in an impacted body of water. It is unlikely that environmental surface water concentrations would approach several orders of magnitude of a 10% concentration, however that is the lowest aqueous concentration available in the test order dataset. EPA acknowledges the uncertainty applying K_p from this concentration to extrapolate to much more dilute real-world scenarios.

Data quality evaluation results for dermal absorption is provided in *Data Quality Evaluation Information for Dermal Absorption for trans-1,2-Dichloroethylene* ([U.S. EPA, 2026l](#)).

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Appendix D HAZARD VALUES USED IN OTHER HUMAN HEALTH ASSESSMENTS

Table_Apx D-1. Hazard Reference Values and Cancer Classifications Used in Other Human Health Assessment

Agency	Hazard Value ^a (UF)			Cancer Classification
	Acute	Intermediate	Chronic	
ATSDR MRL (2025)	3 ppm based on lacrimation in female rats (10× UF _A , 10× UF _H) ^a	0.2 mg/kg-day based on decreased humoral immunity in male mice (10× UF _A , 10× UF _H) ^b	Not derived	Cancer not evaluated
EPA IRIS RfD/C (2010)	N/A – IRIS program did not evaluate acute hazard values	Not derived	0.02 mg/kg-day based on decreased humoral immunity in male mice (10× UF _A , 10× UF _H , 10× UF _S , 3× UF _D) ^b	Inadequate information to assess carcinogenic potential
EPA PPRTV RfD/C (2020b)	Not derived	0.4 mg/m ³ screening p-RFC based on decreased lymphocyte counts (3× UF _A , 10× UF _H , 10× UF _D) ^d	0.04 mg/m ³ screening p-RFC based on decreased lymphocyte counts (3× UF _A , 10× UF _H , 10× UF _S , 10× UF _D) ^d	Not derived
CalEPA/OEHHA (2018)	Not derived	Not derived	0.0048 mg/kg-day based on decreased humoral immunity in male mice (10× UF _A , 30× UF _H , 3× UF _S , 3× UF _D) ^b	Not listed on the Proposition 65 List
UF = uncertainty factor; UF _A = extrapolation from animal to human (interspecies); UF _H = potential variation in sensitivity among members of the human population (intraspecies); UF _S = subchronic-to-chronic duration extrapolation; UF _D = deficiencies and uncertainties in the database ^a These hazard values incorporate (the above) uncertainty factors ^b Based on (Hurt et al., 1993). ^c Based on (Shopp et al., 1985). ^d Based on (DuPont Haskell Lab, 1998).				

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) was established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals. AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels, AEGL-1, AEGL-2 and AEGL-3 (summarized in Table_Apx D-2), are developed for each of five exposure periods (10 and 30 minutes and 1, 4, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

- AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m³]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain

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asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

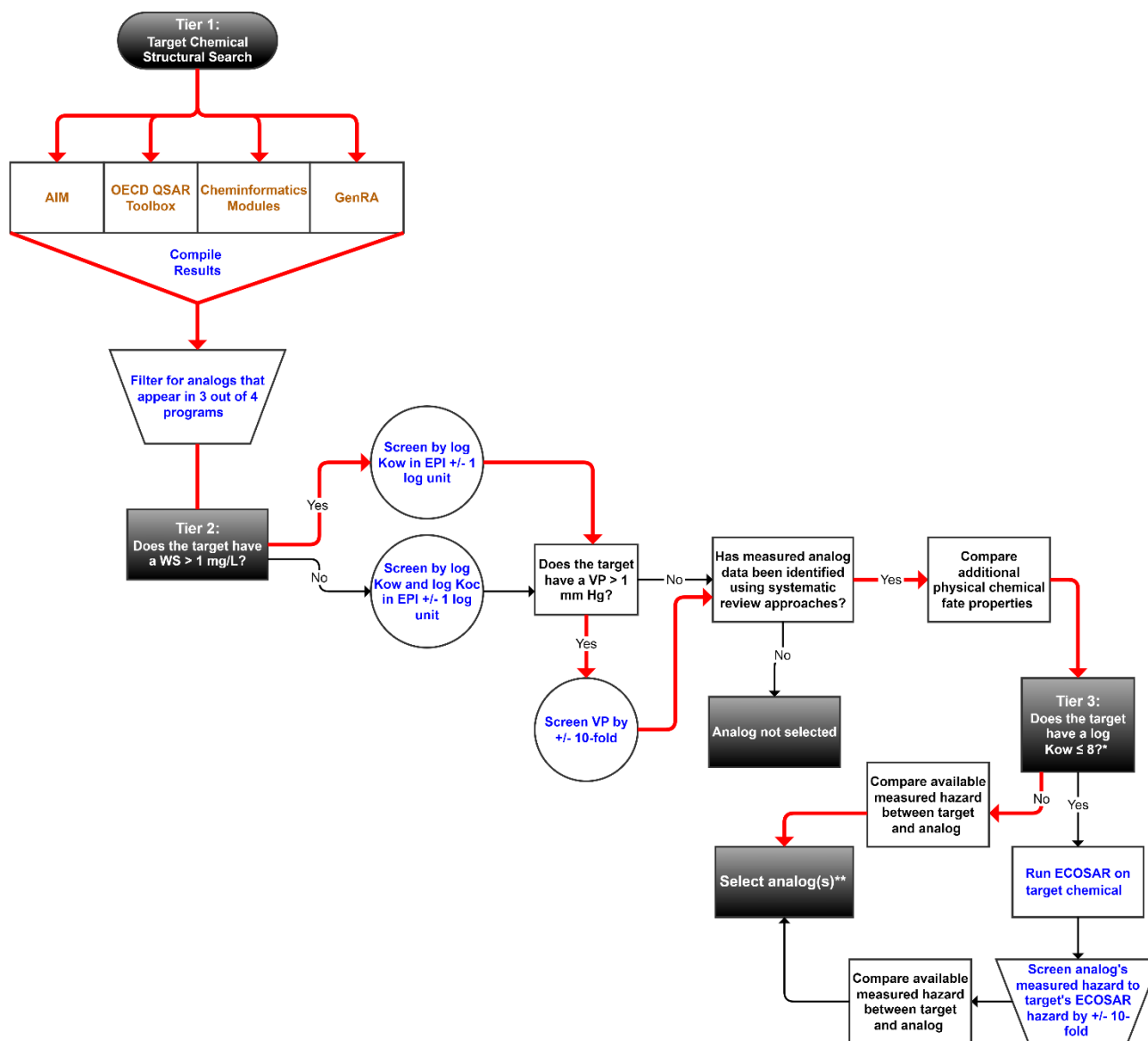
- AEGL-2 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
- AEGL-3 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Table_Apx D-2. Summary of Acute Exposure Guideline Levels (AEGLs) Values for trans-1,2-Dichloroethene [ppm(mg/m³)]

Classification	10 Minutes	30 Minutes	1 Hour	4 Hours	8 Hours	Endpoint (Reference)
AEGL-1 ^a	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)	280 (1,109)	Ocular irritation in humans (Lehmann and Schmidt-Kehl, 1936)
AEGL-2 ^b	1,000 (3,960)	1,000 (3,960)	1,000 (3,960)	690 (2,724)	450 (1,782)	Narcosis in rats:4- & 8-h (Hurtt et al., 1993); Anesthetic effects in humans (Lehmann and Schmidt-Kehl, 1936)
AEGL-3 ^c	1,700 (6,732)	1,700 (6,732)	1,700 (6,732)	1,200 (4,752)	620 (2,455)	No death in rats: 4- & 8-h ([Redacted], 1999); Nausea, intracranial pressure, and dizziness in humans:10, 30, & 60 min (Lehmann and Schmidt-Kehl, 1936)
Source: (U.S. EPA, 2022) ^a Airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. Effects are not disabling and are transient and reversible upon cessation of exposure. ^b Airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. ^c Airborne concentration it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.						

Appendix E SELECTION OF ENVIRONMENTAL ANALOGS

Few data were identified for *trans*-1,2-dichloroethylene for aquatic species (vertebrates, invertebrates or plants) and terrestrial species (soil-dwelling invertebrates and plants). Using a tiered approach with multiple lines of evidence (structural similarity, physical chemical, environmental fate and transport similarity, readily available measured benthic hazard data, and ecotoxicological similarity), analog selection was conducted to identify appropriate analogs to read-across to *trans*-1,2-dichloroethylene. (Figure_Apx E-1). *cis*-1,2-Dichloroethylene and trichloroethylene were selected as analogs for read-across of aquatic hazard and terrestrial hazard data to supplement the *trans*-1,2-dichloroethylene environmental hazard data. The *cis* isomer of 1,2-dichloroethylene is the closest analog; however, a lack of data identified for *cis*-1,2-dichloroethylene required the use of the analog trichloroethylene as well. As stated in 3.1.1 trichloroethylene is expected to be a conservative analog for *trans*-1,2-dichloroethylene which is supported by results from the few studies that tested both chemicals. A detailed comparison between *trans*-1,2-dichloroethylene and the selected analogs can be found in Table_Apx E-4. The analog selection process including evaluating similarities between *trans*-1,2-dichloroethylene and *cis*-1,2-dichloroethylene and trichloroethylene are described in the following subsections. Details are provided in the *Draft Tool Settings and Analog List for Environmental Hazard Assessment for trans-1,2-Dichloroethylene* supplemental file ([U.S. EPA, 2026j](#)).



Figure_Apx E-1. Framework for *trans*-1,2-Dichloroethylene Environmental Hazard Analog Selection

* Target chemicals without aquatic hazard data gaps may also bypass the ECOSAR toxicity comparisons.

** Weight of scientific evidence and professional judgement involved in finalizing selection.

E.1 Structural Similarity

Structural similarity between *trans*-1,2-dichloroethylene and candidate analogs was assessed using two TSCA NAMs (the Analog Identification Methodology (AIM) program and the Organisation of Economic Cooperative Development Quantitative Structure Activity Relationship [OECD QSAR] Toolbox) and two additional EPA products (Generalized Read-Across [GenRA] and the Search Module within the Cheminformatics Modules, both accessed June 8, 2026) as shown in Table_Apx E-1 and Figure_Apx E-1. These four programs provide complementary methods of assessing structural similarity. There are several different methods for determining structural similarity. A fragment-based

approach (e.g., as implemented by AIM) searches for compounds with similar structural moieties or functional groups. EPA's TSCA New Chemicals Program utilizes the Confidential Business Information (CBI) version of AIM to identify analogs with data (including analogs with CBI; however, no analogs with CBI were included in the environmental hazard analog selection for *trans*-1,2-dichloroethylene). Analogues with CBI are not found in the public-facing version of AIM in order to protect business confidentiality, and CBI-AIM has undergone updates not found in the public-facing version of AIM. Therefore CBI-AIM can provide a more robust list of analogs, including analogs without CBI. A structural identifier approach (e.g., the Tanimoto coefficient) calculates a similarity coefficient based on molecular fingerprinting (Belford, 2023). Molecular fingerprinting approaches assess similarity in atomic pathway radius between the analog and target chemical substance (e.g., Morgan fingerprint in GenRA that calculates a Jaccard similarity index). Some fingerprints might be better suited for certain characteristics and chemical classes. For example, substructure fingerprints such as PubChem fingerprints perform best for small molecules like drugs, while atom-pair fingerprints—which assigns values for each atom within a molecule and thus computes atom pairs based on these values—are preferable for large molecules. Some tools (e.g., OECD QSAR Toolbox, Cheminformatics, GenRA) implement multiple methods for determining similarity. Regarding programs that generate indices, it has been noted that because the similarity value is dependent on the method applied these values should form a line of evidence rather than be utilized definitively (Pestana et al., 2021; Mellor et al., 2019).

Analogues identified via AIM analysis were described as 1st or 2nd pass, with 1st pass using more stringent search criteria than 2nd pass (only analogs not considered CBI are included in Appendix E). Tanimoto-based PubChem fingerprints were obtained in the OECD QSAR Toolbox (v4.8.2) using the "Structure Similarity" option. Chemical Morgan Fingerprint scores were obtained in GenRA (v3.1) (limit of 100 analogs, no ToxRef filter). Tanimoto scores were obtained in the Cheminformatics Search Module using Similar analysis. AIM 1st and 2nd pass analogs were compiled with the top 100 analogs with indices greater than 0.5 generated from the OECD QSAR Toolbox and the Cheminformatics Search Module and indices greater than 0.1 generated from GenRA. These filtering criteria are displayed in Table_Apx E-1. Analogues that appeared in three out of four programs were identified as potential analogue candidates (Figure_Apx E-1). Using these parameters, 9 analogs were identified as potentially suitable analogue candidates for *trans*-1,2-dichloroethylene based on structural similarity. Of these identified analogue candidates, 2 had undergone and completed the SR data evaluation and extraction as part of the SR process and were considered further in the analogue selection process. The results for structural comparison of *trans*-1,2-dichloroethylene to *cis*-1,2-dichloroethylene (CASRN 156-59-2) and trichloroethylene (CASRN 79-01-6) were further described below due to those analogue candidates having completed data evaluation and extraction. There were two studies identified examining exposure to 1,2-dichloroethylene of unspecified isomer, however these studies scored low or uninformative and were not further considered (U.S. EPA, 2026c, e). The full list of analogs identified from these tools, including those that met filtering criteria in only one or two of the tools, can be viewed in the *Tool Settings and Analogue List for Environmental Hazard Assessment for trans-1,2-Dichloroethylene* supplemental file (U.S. EPA, 2026j).

cis-1,2-Dichloroethylene (CASRN 156-59-2) and trichloroethylene were indicated as structurally similar to *trans*-1,2-dichloroethylene in AIM (1st pass), OECD QSAR Toolbox (PubChem features = 85.7–100%), and the Cheminformatics Search Module (Tanimoto coefficient =0.67–1.0) (Table_Apx E-2). The structural similarity of *trans*-1,2-dichloroethylene to its analogs indicated in these tools supported the read-across to *trans*-1,2-dichloroethylene environmental hazard. *cis*-1,2-Dichloroethylene and trichloroethylene were ultimately selected for read-across of aquatic toxicity data, including data for fish, amphibians, aquatic invertebrates, and algae hazard to *trans*-1,2-dichloroethylene based on the additional lines of evidence (physical, chemical, and environmental fate and transport similarity, readily

available measured benthic hazard data, and ecotoxicological similarity).

Table_Apx E-1. Structure Program Filtering Criteria

Program	Index ^a	Filtering Parameters ^a
Analog Identification Methodology (AIM)	Fragment-based	1st or 2nd pass
OECD QSAR Toolbox	Tanimoto-based PubChem fingerprints	Top 100 analogs ≥ 0.5
Cheminformatics Search Module	Similarity-type: Tanimoto	Top 100 analogs with index ≥ 0.5
GenRA	Morgan Fingerprints	Top 100 analogs with index ≥ 0.1 (ToxRef data filter off)
^a Additional settings used in each tool can be viewed in the <i>Tool Settings and Analog List for Environmental Hazard Assessment for trans-1,2-Dichloroethylene</i> supplemental file (U.S. EPA, 2026j).		

Table_Apx E-2. Structural Similarity Between trans-1,2-Dichloroethylene and Analog Candidates That Met Filtering Criteria in at Least 3 of 4 Structure Programs ^a

Chlorinated Solvent	CASRN	AIM pass	OECD QSAR Toolbox % Similarity	Cheminformatics	GenRA	Count
<i>trans</i> -1,2-Dichloroethylene (target)	156-60-5	Exact match	100	1.00	1.00	4
cis-1,2-Dichloroethylene ^b	156-59-2	Exact match/1st	100	1.00	1.00	4
1,2-Dichloroethylene (mixture/unspecified)	540-59-0	Exact match/1st	100	1.00	1.00	4
Vinyl chloride	75-01-4	2nd	92.3	0.83	0.38	4
Trichloroethylene ^b	79-01-6	1st	85.7	0.67	0.30	4
1,1-Dichloroethylene	75-35-4	2nd	71.4	0.63	—	3
1-Chloropropene	590-21-6	2nd	—	0.56	0.44	3
1,2-Dichloroprop-1-ene	563-54-2	2nd	66.7	0.5	—	3
(1E)-1-Chloroprop-1-ene	16136-85-9	2nd	—	0.56	0.44	3
(1Z)-1-Chloroprop-1-ene	16136-84-8	2nd	—	0.56	0.44	3
AIM = Analog Identification Methodology; CASRN = Chemical Abstracts Service Registry Number; GenRA = Generalized Read-Across; OECD = Organisation of Economic Cooperative Development; QSAR = quantitative structure-activity relationship; “—” = value not identified with structure similarity tool						
^a The full list of analogs identified from these tools, including those that met filtering criteria in only 1 or 2 of the tools, can be viewed in the <i>Draft Tool Settings and Analog List for Environmental Hazard Assessment for trans-1,2-Dichloroethylene</i> supplemental file (U.S. EPA, 2026j).						
^b Analogs that have completed data evaluation and extraction are bolded.						

E.2 Physical, Chemical, and Environmental Fate and Transport Similarity

trans-1,2-Dichloroethylene analog candidates from the structural similarity analysis were preliminarily screened based on similarity in log octanol-water partition coefficient (log K_{OW}) and vapor pressure obtained using EPI Suite™ (Figure_Apx E-1). Measured values were used when available. For this screening step, *trans*-1,2-dichloroethylene, *cis*-1,2-dichloroethylene, and trichloroethylene physical chemistry parameters were obtained from the *Draft Chemistry, Fate, Release, and Exposure Assessment for trans-1,2-Dichloroethylene* (U.S. EPA, 2026b), the *Toxicological Review of cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* (U.S. EPA, 2010) and the *Risk Evaluation for Trichloroethylene* (U.S. EPA, 2020d). Analog candidates with log K_{OW} and vapor pressure within one log unit relative to *trans*-1,2-dichloroethylene were considered potentially suitable analog candidates for *trans*-1,2-dichloroethylene (Figure_Apx E-1). Two of these chlorinated solvent analogs (*cis*-1,2-dichloroethylene (CASRN 156-59-2) and trichloroethylene (CASRN 79-01-6)) had aquatic hazard data with completed data evaluation and extraction, therefore a more expansive analysis of physical, chemical, environmental fate and transport similarities between *trans*-1,2-dichloroethylene and candidate analogs *cis*-1,2-dichloroethylene and trichloroethylene was conducted (see Figure_Apx E-1 and Table_Apx E-3).

Because the candidate analog aquatic hazard data consisted of exposures in water and in sediment, physical, chemical, and environmental fate and transport similarities between *trans*-1,2-dichloroethylene and its analog candidates *cis*-1,2-dichloroethylene and trichloroethylene were assessed based on additional properties relevant to the aquatic compartments (Table_Apx E-3). Physical, chemical, and environmental fate and transport values for *trans*-1,2-dichloroethylene, *cis*-1,2-dichloroethylene, and trichloroethylene are specified in the *Draft Chemistry, Fate, Release, and Exposure Assessment for trans-1,2-Dichloroethylene* (U.S. EPA, 2026b), the *Toxicological Review of cis-1,2-Dichloroethylene and trans-1,2-Dichloroethylene* (U.S. EPA, 2010) and the *Risk Evaluation for Trichloroethylene* (U.S. EPA, 2020d). Similar values are observed for *trans*-1,2-dichloroethylene and its candidate analogs *cis*-1,2-dichloroethylene and trichloroethylene for water solubility (1,280–6,410 mg/L), log K_{OW} (1.23–2.42), and log K_{OC} (1.69–2.1)—indicating all three solvents are highly water soluble with low affinity for sediment (Table_Apx E-3). All three chlorinated solvents also have relatively similar bioconcentration factors (BCF, 8.7–18.4 L/kg) and bioaccumulation factors (BAF, 9.3–24 L/kg), indicating low bioaccumulation potential in aquatic and terrestrial environments. Although hydrolysis half-lives are relatively long for all three solvents—particularly for *trans*-1,2-dichloroethylene—other properties indicate that these chemicals will likely volatilize before hydrolyzing in aqueous environments.

All three chlorinated solvents are highly volatile (Henry's Law constants 4.08×10^{-3} to 9.8×10^{-3} atm·m³/mol and vapor pressures 73.72–331 mm Hg), indicating volatilization from water will occur. The vapor pressures indicate some difference in volatility between the three chlorinated solvents—particularly for trichloroethylene that has a lower vapor pressure at 73.72 mm Hg, suggesting it is less readily volatile than *trans*-1,2-dichloroethylene with vapor pressure 331 mm Hg. However, potential impacts of volatility differences on read-across to *trans*-1,2-dichloroethylene for environmental hazard can be addressed by factoring in experimental design considerations in the analog hazard dataset such as chemical measurement of the substance in the test medium, regular renewal with chemical solution, capping of test vessels, and/or use of flow-through/dilutor systems. *trans*-1,2-Dichloroethylene and candidate analogs *cis*-1,2-dichloroethylene and trichloroethylene exist as a colorless liquid at room temperature and have similar low molecular weights (Table_Apx E-3). In summary, the similarity of the physical, chemical, fate, and environmental transport behavior of *trans*-1,2-dichloroethylene and candidate analogs *cis*-1,2-dichloroethylene and trichloroethylene in aquatic environments supports the ability to read-across aquatic hazard to *trans*-1,2-dichloroethylene.

Table_Apx E-3. Comparison of *trans*-1,2-Dichloroethylene and Analog Candidates *cis*-1,2-Dichloroethylene and Trichloroethylene for Several Physical and Chemical and Environmental Fate Properties Relevant to Water

Property	<i>trans</i> -1,2-Dichloroethylene (Target)	<i>cis</i> -1,2-Dichloroethylene	Trichloroethylene
Water solubility	4,520 mg/L	6,410 mg/L	1,280 mg/L
Log K _{OW}	1.93	1.86	2.42
Log K _{OC}	1.23	1.69	1.8–2.1
BCF	8.7 L/kg ^a	7.77 L/kg ^a	17–18.4 L/kg
BAF	9.3 L/kg ^a	14.1 L/kg ^a	24 L/kg
Henry's Law constant (atm·m ³ /mol)	7.51E–03	4.08E–03	9.85E–03
Vapor pressure (mmHg)	331	200	73.72
Molecular weight	96.94 g/mol	96.95 g/mol	131.39 g/mol
Physical state of the chemical	Colorless liquid	Colorless liquid	Colorless liquid
^a Estimated using EPI Suite™ (U.S. EPA, 2012d)			

E.3 Ecotoxicological Similarities

A comparison of empirical hazard evidence of aquatic invertebrates exposed in water for was conducted for *trans*-1,2-dichloroethylene and its analogs *cis*-1,2-dichloroethylene and trichloroethylene (Table 3-1). A single acute study in aquatic invertebrates (*Daphnia magna*) was available for *trans*-1,2-dichloroethylene, which showed lower toxicity (>100–230 mg/L) than similar studies in trichloroethylene (7.75–33.85 mg/L). Studies of aquatic vertebrates (amphibians) showed similar toxicity between *trans*-1,2-dichloroethylene and its analog *cis*-1,2-dichloroethylene; hazard values for aquatic vertebrates (amphibians) were within an order of magnitude for *trans*-1,2-dichloroethylene (>100 mg/L) and trichloroethylene (45–434 mg/L). A terrestrial invertebrate study in earthworm (*Eisenia fetida*) ([Neuhauser et al., 1985](#)) tested both *trans*-1,2-dichloroethylene and trichloroethylene using a filter paper contact test to calculate the concentration that was lethal to half the exposed organisms (LC50); the LC50 the 48-hour filter paper contact was calculated as 286 mg/kg for *trans*-1,2-dichloroethylene and 105 mg/kg for trichloroethylene (Table 3-5). No other studies were identified in *trans*-1,2-dichloroethylene to compare with analog data from *cis*-1,2-dichloroethylene and trichloroethylene.

Ecotoxicological similarity for aquatic vertebrates, chronic hazard, aquatic plants and algae, as well as terrestrial vertebrates, invertebrates, and plants, read-across is inferred by the aquatic invertebrate and vertebrate, as well as terrestrial invertebrate, toxicity comparisons made between *trans*-1,2-dichloroethylene and its analogs (Table_Apx E-4), similar to the environmental hazard read-across approach used for phthalates ([U.S. EPA, 2025b, 2024a](#)) and 1,2-dichloroethane ([U.S. EPA, 2026o](#)). Due to *cis*-1,2-dichloroethylene and trichloroethylene similarity to *trans*-1,2-dichloroethylene using multiple lines of evidence (structure, physical chemical, and ecotoxicological) and analog availability of empirical aquatic hazard data, *cis*-1,2-dichloroethylene and trichloroethylene are appropriate analogs for hazard read-across to *trans*-1,2-dichloroethylene.

Table_Apx E-4. Comparison of Measured *trans*-1,2 Dichloroethylene and *cis*-1,2-Dichloroethylene and Trichloroethylene Analog Hazard Values for Aquatic Invertebrates, Aquatic Vertebrates, and Terrestrial Invertebrates

Terrestrial Invertebrates							
Species	Outcome	Endpoint	<i>trans</i> -1,2-Dichloro-ethylene	<i>cis</i> -1,2-Dichloroethylene		Trichloroethylene	
			Measured Hazard (mg/L)	Measured Hazard (mg/L)	Ratio to <i>trans</i> -1,2-Dichloro-ethylene Toxicity	Measured Hazard (mg/L)	Ratio to <i>trans</i> -1,2-Dichloro-ethylene Toxicity
Water flea (<i>Daphnia magna</i>)	24-hour LC50	Mortality (Immobilization)	230 ^a mg/L	NA	NA	22 ^a mg/L	0.10
Water flea (<i>Daphnia magna</i>)	48-hour LC50	Mortality (Immobilization)	220 ^a mg/L	NA	NA	18 ^a mg/L 7.75 ^b mg/L	0.08 0.03
Green frog (<i>Lithobates clamitans</i>)	96-hour EC50/NOEC	Developmental Deformities	EC50 92.5 ^c mg/L	NOEC >100 ^c mg/L	NA	EC50 33.6 ^c mg/L	0.36
American toad (<i>Bufo americanus</i>)	96-hour NOEC	Developmental Deformities	>100 ^c mg/L	>100 ^c mg/L	1	>85 ^c mg/L	0.85
Wood Frog (<i>Lithobates sylvaticus</i>)	96-hour EC50/NOEC	Developmental Deformities	NOEC >100 ^c mg/L	NOEC >100 ^c mg/L	1	EC50 45.7 ^c mg/L	NA
Earthworm (<i>Eisenia fetida</i>)	48-hour LC50	Mortality	286 mg/kg	NA	NA	105 mg/kg	0.36
Average ratio of hazard value for analogs compared to <i>trans</i> -1,2-dichloroethylene:				1 ± 0		0.30 ± 0.31	
^a Taken from Leblanc (1980) (Medium) ^b Taken from Abernethy et al. (1986) (Medium) ^c Taken from Mcdaniel et al. (2004b) (Medium) Taken from (Neuhauser et al., 1985).The study is a filter paper contact test to calculate the concentration that was lethal to half the exposed organisms (LC50), which does not meet PECO for the hazard assessment, but does inform read-across between trans-1,2-dichloroethylene and trichloroethylene							

E.4 Read Across Weight of Scientific Evidence and Summary

In order to address gaps from a limited environmental hazard dataset for *trans*-1,2-dichloroethylene, EPA evaluated candidate analogs for read-across of hazard for aquatic and terrestrial species. Ultimately, *cis*-1,2-dichloroethylene and trichloroethylene were selected as appropriate analogs due to similarities in structure, physical chemical properties and environmental fate. A comparison of aquatic hazard in acute studies of aquatic invertebrates and vertebrates showed similar toxicological profiles between *trans*-1,2-dichloroethylene and *cis*-1,2-dichloroethylene. In contrast, trichloroethylene shows increased toxicity over *trans*-1,2-dichloroethylene (Table_Apx E-4), which indicates that hazard values from trichloroethylene represent a conservative estimate of risk for *trans*-1,2-dichloroethylene.

4211 Therefore, read-across from environmental hazard studies of *cis*-1,2-dichloroethylene, and
4212 trichloroethylene was used to inform the selection of hazard values for *trans*-1,2-dichloroethylene within
4213 this assessment.

Appendix F ENVIRONMENTAL HAZARD IDENTIFICATION

F.1 Hazard Identification

F.1.1 Aquatic Hazard Data

F.1.1.1 Web-Based Interspecies Correlation Estimation (Web-ICE) v4.0

Results from the systematic review process assigned an overall quality level of high or medium to two acute aquatic toxicity study for *trans*-1,2-dichloroethylene. One of these studies was excluded from the web-based interspecies correlation estimation (Web-ICE) because it did not provide LC50 data. Due to the lack of available studies for *trans*-1,2-dichloroethylene, 13 studies that were assigned high or medium quality levels for the analog trichloroethylene selected to be used. The 14 acute aquatic toxicity studies EPA identified as the most relevant for quantitative assessment are displayed in Table_Apx F-1. For further details on these studies, see Section 3.2.1.1. To supplement the empirical data, EPA used a modeling approach, Web-ICE. Web-ICE predicts toxicity values for environmental species that are absent from a dataset and can provide a more robust dataset to estimate toxicity thresholds. Specifically, EPA used Web-ICE to quantitatively supplement empirical data for aquatic organisms for acute exposure durations.

Table_Apx F-1. Empirical Species Hazard Data and Web-ICE Predicted Species That Met Model Selection Criteria

Genus	Species	LC50/ EC50 (mg/L)	Source (Quality Rating)	Used in SSD
<i>trans</i> -1,2-dichloroethylene				
<i>Daphnia</i>	<i>magna</i>	220	(Leblanc, 1980) (High)	Yes
<i>Lithobates</i>	<i>clamitans</i>	92.5	(Mcdaniel et al., 2004b) (high)	No, because study measured EC50 of development not LC50
Trichloroethylene				
<i>Daphnia</i>	<i>magna</i>	18	(Leblanc, 1980) (High)	Yes
<i>Daphnia</i>	<i>magna</i>	22	(Leblanc, 1980) (High)	No, because a 48-hour value was available in the same paper
<i>Daphnia</i>	<i>magna</i>	7.75	(Abernethy et al., 1986) (Medium)	Yes
<i>Daphnia</i>	<i>magna</i>	33.85	(Dobaradaran et al., 2012) (Medium)	Yes
<i>Daphnia</i>	<i>magna</i>	43.14	(Dobaradaran et al., 2012) (Medium)	No, because a 48-hour value was available in the same paper
<i>Daphnia</i>	<i>magna</i>	28.39	(Dobaradaran et al., 2012) (Medium)	No, because a 48-hour value was available in the same paper
<i>Daphnia</i>	<i>magna</i>	26.55	(Dobaradaran et al., 2012) (Medium)	No, because a 48-hour value was available in the same paper
<i>Mysidopsis</i>	<i>bahia</i>	14	(Ward et al., 1986) (Medium)	Yes
<i>Ceriodaphnia</i>	<i>dubia</i>	17.08	(Niederlehner et al., 1998) (High)	Yes
<i>Xenopus</i>	<i>laevis</i>	434	(Fort et al., 1993) (High)	Yes

Genus	Species	LC50/ EC50 (mg/L)	Source (Quality Rating)	Used in SSD
<i>Xenopus</i>	<i>laevis</i>	434	(Fort et al., 1991) (Medium)	Yes, geometric mean of two LC50 values
<i>Xenopus</i>	<i>laevis</i>	441	(Fort et al., 2001) (Medium)	Yes, geometric mean of three LC50 values
<i>Pimephales</i>	<i>promelas</i>	44.1	(Geiger et al., 1985) (High)	Yes
<i>Pimephales</i>	<i>promelas</i>	40.7	(Alexander et al., 1978) (High)	Yes
<i>Pimephales</i>	<i>promelas</i>	66.8	(Alexander et al., 1978) (Medium)	No, because this value from a static study was rated medium for quality and a high-quality flow through value from the same study was available.
<i>Jordanella</i>	<i>floridae</i>	28.28	(Smith et al., 1991) (High)	Yes
<i>Jordanella</i>	<i>floridae</i>	31	(Smith et al., 1991 95201) (Medium)	No, because this value from a static study was rated medium for quality and a high-quality flow through value from the same study was available.
<i>Pimephales</i>	<i>promelas</i>	46.7	(Broderius et al., 2005) (High)	Yes, used a geometric mean of three values for LC50's in the study
<i>Lepomis</i>	<i>macrochirus</i>	45	(Buccafusco et al., 1981) (Medium)	Yes
<i>Cyprinodon</i>	<i>variegatus</i>	52	(Ward et al., 1986) (Medium)	Yes
<i>Cyprinodon</i>	<i>variegatus</i>	99	(Ward et al., 1986) (Medium)	No, because this LC50 measured initial trichloroethylene concentrations and the average concentrations were available in the same study.
LC50 = lethal concentration 50%; EC50 = half maximal effective concentration; SSD = species sensitivity distribution				

The Web-ICE application was developed by EPA and collaborators to provide interspecies extrapolation models for acute toxicity ([Raimondo, 2010](#)). Web-ICE models estimate the acute toxicity (EC50/LC50) of a chemical to a species, genus, or family with no test data (the predicted taxon) from the known toxicity of the chemical to a species with test data (the commonly tested surrogate species).

Web-ICE models are log-linear least square regressions of the relationship between surrogate and predicted taxon based on a database of acute toxicity values. It returns median effect or lethal water concentrations for aquatic species (EC50/LC50). Separate acute toxicity databases are maintained for aquatic animals (vertebrates and invertebrates), aquatic plants (algae), and wildlife (birds and mammals), with 2,286 models for aquatic animals, 58 models for algae, and 560 models for terrestrial wildlife taxa in Web-ICE v4.0 ([U.S. EPA, 2024c](#)). Open-ended toxicity values (*i.e.*, >100 mg/kg or <100 mg/kg) and duplicate records among multiple sources are not included in any of the databases.

While the models for aquatic animals and algae have been expanded (increased) and validated since Web-ICE v1.1 was released in July 2007, the models for Wildlife have remained limited and outdated. The wildlife database for 560 species is limited only to acute studies of pesticides and herbicides from one literature search completed in 2007. This dataset requires more work on validation and updates prior to use by EPA OPPT.

The aquatic animal database within Web-ICE is composed of 48 or 96-hour EC50/LC50 values based on immobility or mortality. This database is described in detail in the Aquatic Database Documentation found on the [Download Model Data](#) (accessed June 8, 2026) page of Web-ICE and describes the data sources, normalization, and quality and standardization criteria (*e.g.*, data filters) for data used in the models. Data used in model development adhered to standard acute toxicity test condition requirements of the American Society of Testing and Materials (ASTM) International ([ASTM, 2014](#)) and EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) ([U.S. EPA, 2016a](#)).

EPA used *trans*-1,2-dichloroethylene and trichloroethylene 48-hour LC50 and EC50 data for aquatic invertebrates *D. magna*, *C. dubia* and *A. bahia* and 96-hour LC50 data for vertebrates African clawed frog (*X. laevis*), American flagfish (*J. floridae*), bluegill (*L. macrochirus*), sheepshead minnow (*C. variegatus*), and fathead minnow (*P. promelas*) as surrogate species to predict LC50 toxicity values using the Web-ICE application ([Raimondo, 2010](#)). The Web-ICE model estimated toxicity values for 140 species. These toxicity predictions were then screened by the following quality standards to ensure confidence in the model predictions. If a predicted species did not meet all the quality criteria below, the species was eliminated from the dataset ([U.S. EPA, 2024c](#)).

- High R^2 (≥ 0.6)
 - The proportion of the data variance that is explained by the model. The closer the R^2 value is to 1, the more robust the model is in describing the relationship between the predicted and surrogate taxa.
- Low mean square error (MSE; ≤ 0.95)
 - An unbiased estimator of the variance of the regression line.
- High slope (≥ 0.6)
 - The regression coefficient represents the change in log10 value of the predicted taxon toxicity for every change in log10 value of the surrogate species toxicity.
- No more than an order of magnitude of difference between the upper- and lower-bounds of the confidence interval of the predicted toxicity.

After screening, the acute toxicity values for 70 additional aquatic organisms (fish, amphibians, and aquatic invertebrates) were added to the empirical data summarized in Table_Apx F-2. Including both empirical and predicted toxicity values with a confidence interval difference of one or less, there were 134 data points across 77 species. This dataset was then used to calculate the distribution of species sensitivity through the SSD Toolbox ([Etterson, 2020a](#)) as shown in Table_Apx F-2 and described in Section F.1.1.3.

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4286 **Table_Apx F-2. Empirical Species Hazard Data and Web-ICE Predicted Species That Met Model**
 4287 **Selection Criteria**

Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Measured data									
African clawed frog	<i>Xenopus</i>	<i>laevis</i>	N/A	4.34E05	N/A				
African clawed frog	<i>Xenopus</i>	<i>laevis</i>		4.34E05					
African clawed frog	<i>Xenopus</i>	<i>laevis</i>		4.41E05					
Fathead minnow	<i>Pimephales</i>	<i>promelas</i>		4.41E04					
Fathead minnow	<i>Pimephales</i>	<i>promelas</i>		4.07E04					
Fathead minnow	<i>Pimephales</i>	<i>promelas</i>		4.67E04					
Water flea	<i>Daphnia</i>	<i>magna</i>		1.80E04					
Water flea	<i>Daphnia</i>	<i>magna</i>		7750					
Water flea	<i>Daphnia</i>	<i>magna</i>		3.39E04					
Water flea	<i>Daphnia</i>	<i>magna</i>		2.20E05					
Flagfish	<i>Jordanella</i>	<i>floridae</i>		2.83E04					
Bluegill	<i>Lepomis</i>	<i>macrochirus</i>		4.50E04					
Sheepshead minnow	<i>Cyprinodon</i>	<i>variegatus</i>		5.20E04					
Mysid	<i>Mysidopsis</i>	<i>bahia</i>		1.40E04					
Waterflea	<i>Ceriodaphnia</i>	<i>dubia</i>	1.71E04						
Modeled data									
Redear sunfish	<i>Lepomis</i>	<i>microlophus</i>	Bluegill (<i>Lepomis macrochirus</i>)	5.82E04	5.00E04 to 6.78E04	0	0.99	0	1.03
Daphnid	<i>Daphnia</i>	<i>pulex</i>	Daphnid (<i>Daphnia magna</i>)	2.46E04	1.59E04 to 3.81E04	0	0.95	0.14	1.01
Zebrafish	<i>Danio</i>	<i>rerio</i>	Fathead minnow (<i>Pimephales promelas</i>)	3.41E04	1.51E04 to 7.71E04	0	0.97	0.04	0.9
Daphnid	<i>Daphnia</i>	<i>pulex</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	3.87E04	1.86E04 to 8.05E04	0	0.95	0.15	1.04
Goldfish	<i>Carassius</i>	<i>auratus</i>	Fathead minnow (<i>Pimephales promelas</i>)	5.30E04	3.52E04 to 7.99E04	0	0.94	0.14	0.97
Largemouth bass	<i>Micropterus</i>	<i>salmoides</i>	Bluegill (<i>Lepomis macrochirus</i>)	4.94E04	2.76E04 to 8.84E04	0	0.93	0.12	1.03
Zebrafish-embryo	<i>Danio</i>	<i>rerio-embryo</i>	Fathead minnow	5.02E04	3.65E04 to 6.90E04	0	0.93	0.2	0.93

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Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
			(<i>Pimephales promelas</i>)						
Common carp	<i>Cyprinus</i>	<i>carpio</i>	Fathead minnow (<i>Pimephales promelas</i>)	4.56E04	2.15E04 to 9.67E04	0	0.84	0.2	0.99
Nile tilapia	<i>Oreochromis</i>	<i>niloticus</i>	Bluegill (<i>Lepomis macrochirus</i>)	6.63E04	5.60E04 to 7.84E04	0	0.99	0	1.04
Guppy	<i>Poecilia</i>	<i>reticulata</i>	Flagfish (<i>Jordanella floridae</i>)	3.85E04	1.77E04 to 8.42E04	0	0.97	0.07	0.92
Yellow perch	<i>Perca</i>	<i>flavescens</i>	Bluegill (<i>Lepomis macrochirus</i>)	2.69E04	1.11E04 to 6.52E04	0	0.91	0.15	0.97
Zebrafish	<i>Danio</i>	<i>rerio</i>	Flagfish (<i>Jordanella floridae</i>)	1.95E04	1.24E04 to 3.06E04	0	0.99	0	0.81
Vernal pool fairy shrimp	<i>Branchinecta</i>	<i>lynchi</i>	Daphnid (<i>Daphnia magna</i>)	2.32E04	1.21E04 to 4.44E04	0	0.98	0.07	0.94
Medaka	<i>Oryzias</i>	<i>latipes</i>	Fathead minnow (<i>Pimephales promelas</i>)	3.89E04	2.46E04 to 6.17E04	0	0.98	0.04	0.85
Beaver-tail fairy shrimp	<i>Thamnocephalus</i>	<i>platyurus</i>	Daphnid (<i>Daphnia magna</i>)	2.14E04	1.38E04 to 3.33E04	0	0.97	0.12	0.91
Beaver-tail fairy shrimp	<i>Thamnocephalus</i>	<i>platyurus</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	2.27E04	1.26E04 to 4.11E04	0	0.97	0.14	0.87
Medaka	<i>Oryzias</i>	<i>latipes</i>	Flagfish (<i>Jordanella floridae</i>)	3.19E04	1.42E04 to 7.16E04	0	0.96	0.02	0.61
Rainbow trout	<i>Oncorhynchus</i>	<i>mykiss</i>	Bluegill (<i>Lepomis macrochirus</i>)	2.86E04	2.38E04 to 3.44E04	0	0.89	0.22	0.95
Channel catfish	<i>Ictalurus</i>	<i>punctatus</i>	Fathead minnow (<i>Pimephales promelas</i>)	3.96E04	2.52E04 to 6.22E04	0	0.87	0.3	0.97
Rainbow trout	<i>Oncorhynchus</i>	<i>mykiss</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.99E04	1.54E04 to 2.59E04	0	0.87	0.28	0.97
Brook trout	<i>Salvelinus</i>	<i>fontinalis</i>	Bluegill (<i>Lepomis macrochirus</i>)	2.83E04	1.09E04 to 7.37E04	0	0.86	0.27	0.97
Cutthroat trout	<i>Oncorhynchus</i>	<i>clarkii</i>	Bluegill (<i>Lepomis macrochirus</i>)	3.24E04	1.41E04 to 7.48E04	0	0.79	0.35	0.87
Rainbow trout	<i>Oncorhynchus</i>	<i>mykiss</i>	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	2.11E04	1.32E04 to 3.39E04	0	0.77	0.35	0.96

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Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Channel catfish	<i>Ictalurus</i>	<i>punctatus</i>	Bluegill (<i>Lepomis macrochirus</i>)	3.31E04	1.96E04 to 5.61E04	0	0.76	0.43	0.81
Indian bullfrog	<i>Euphylyctis</i>	<i>hexadactylus</i>	Flagfish (<i>Jordanella floridae</i>)	3.20E04	1.66E04 to 6.19E04	0	0.99	0	0.7
Cuvier's foam froglet	<i>Physalaemus</i>	<i>cuvieri</i>	Bluegill (<i>Lepomis macrochirus</i>)	6.00E04	3.77E04 to 9.57E04	0	0.99	0	0.63
Bullfrog	<i>Lithobates</i>	<i>catesbeianus</i>	Fathead minnow (<i>Pimephales promelas</i>)	4.52E04	2.44E04 to 8.40E04	0	0.98	0.09	0.97
Bullfrog	<i>Lithobates</i>	<i>catesbeianus</i>	Bluegill (<i>Lepomis macrochirus</i>)	4.13E04	1.76E04 to 9.69E04	0	0.98	0.08	0.88
Common shrimp	<i>Crangon</i>	<i>crangon</i>	Fathead minnow (<i>Pimephales promelas</i>)	3.09E04	1.62E04 to 5.88E04	0	0.99	0	0.97
Paper pondshell	<i>Utterbackia</i>	<i>imbecillis</i>	Daphnid (<i>Daphnia magna</i>)	1.89E04	1.25E04 to 2.87E04	0	0.97	0.08	0.88
Western pearlshell	<i>Margaritifera</i>	<i>falcata</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	2.01E04	1.16E04 to 3.48E04	0	0.97	0.1	0.87
Swamp lymnaea	<i>Lymnaea</i>	<i>stagnalis</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	3.76E04	1.55E04 to 9.11E04	0	0.96	0.17	0.98
Tadpole physa	<i>Physella</i>	<i>gyrina</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	3.07E04	1.60E04 to 5.88E04	0	0.96	0.14	0.98
Tadpole physa	<i>Physella</i>	<i>gyrina</i>	Daphnid (<i>Daphnia magna</i>)	2.77E04	1.29E04 to 5.95E04	0	0.95	0.19	0.96
Swamp lymnaea	<i>Lymnaea</i>	<i>stagnalis</i>	Daphnid (<i>Daphnia magna</i>)	2.82E04	1.04E04 to 7.67E04	0	0.95	0.22	0.94
Fatmucket	<i>Lampsilis</i>	<i>siliquoidea</i>	Daphnid (<i>Daphnia magna</i>)	2.02E04	1.21E04 to 3.38E04	0	0.94	0.18	0.9
Zebrafish-embryo	<i>Danio</i>	<i>rerio-embryo</i>	Daphnid (<i>Daphnia magna</i>)	4.84E04	2.39E04 to 9.81E04	0	0.66	0.86	0.65
Rainbow trout	<i>Oncorhynchus</i>	<i>mykiss</i>	Daphnid (<i>Daphnia magna</i>)	1.77E04	1.31E04 to 2.38E04	0	0.62	0.84	0.71
Mysid	<i>Americamysis</i>	<i>bigelowi</i>	Mysid (<i>Americamysis bahia</i>)	5.06E04	2.54E04 to 1.01E05	1	0.99	0	1.29
Green sunfish	<i>Lepomis</i>	<i>cyanellus</i>	Bluegill (<i>Lepomis macrochirus</i>)	4.05E04	1.63E04 to 1.01E05	1	0.91	0.14	0.85

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Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Mrigal carp	<i>Cirrhinus</i>	<i>mrigala</i>	Fathead minnow (<i>Pimephales promelas</i>)	3.57E04	1.19E04 to 1.07E05	1	0.98	0.01	1.1
Daphnid	<i>Simocephalus</i>	<i>serrulatus</i>	Daphnid (<i>Daphnia magna</i>)	1.60E04	3,953 to 6.44E04	1	0.85	0.28	0.93
Peppered loach	<i>Lepidocephalichthys</i>	<i>guntea</i>	Fathead minnow (<i>Pimephales promelas</i>)	2.21E04	6,319 to 7.75E04	1	0.99	0	0.78
Water flea	<i>Chydorus</i>	<i>sphaericus</i>	Daphnid (<i>Daphnia magna</i>)	1.20E04	7,789 to 1.83E04	1	0.98	0.05	0.94
Water flea	<i>Pseudosida</i>	<i>ramosa</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	5,120	1,167 to 2.25E04	1	0.96	0.19	0.98
Water flea	<i>Moina</i>	<i>macrocopa</i>	Daphnid (<i>Daphnia magna</i>)	2.20E04	5,176 to 9.33E04	1	0.96	0.1	0.72
White sucker	<i>Catostomus</i>	<i>commersonii</i>	Fathead minnow (<i>Pimephales promelas</i>)	9.18E04	1.64E04 to 5.13E05	1	0.92	0.2	1.14
Walleye	<i>Sander</i>	<i>vitreus</i>	Bluegill (<i>Lepomis macrochirus</i>)	9,570	1,247 to 7.34E04	1	0.77	0.21	0.73
Yellow perch	<i>Perca</i>	<i>flavescens</i>	Flagfish (<i>Jordanella floridae</i>)	5.24E04	1.36E04 to 2.02E05	1	0.99	0	1.22
Tidewater silverside	<i>Menidia</i>	<i>peninsulae</i>	Bluegill (<i>Lepomis macrochirus</i>)	1.22E04	1,862 to 8.04E04	1	0.97	0.06	0.9
Vernal pool fairy shrimp	<i>Branchinecta</i>	<i>lynchi</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	2.69E04	8,422 to 8.62E04	1	0.95	0.23	0.91
Amphipod	<i>Allorchestes</i>	<i>compressa</i>	Mysid (<i>Americamysis bahia</i>)	1.74E04	4,326 to 6.99E04	1	0.95	0.03	0.66
Atlantic salmon	<i>Salmo</i>	<i>salar</i>	Bluegill (<i>Lepomis macrochirus</i>)	4.93E04	2.14E04 to 1.14E05	1	0.94	0.13	1.14
Daggerblade grass shrimp	<i>Palaemonetes</i>	<i>pugio</i>	Mysid (<i>Americamysis bahia</i>)	6.11E04	2.09E04 to 1.79E05	1	0.92	0.25	1.09
White sucker	<i>Catostomus</i>	<i>commersonii</i>	Bluegill (<i>Lepomis macrochirus</i>)	3.81E04	1.08E04 to 1.35E05	1	0.92	0.17	1.05
Amphipod	<i>Hyalella</i>	<i>azteca</i>	Mysid (<i>Americamysis bahia</i>)	1.52E04	4,635 to 4.97E04	1	0.88	0.68	1.03
Atlantic silverside	<i>Menidia</i>	<i>menidia</i>	Bluegill (<i>Lepomis macrochirus</i>)	2.02E04	4,139 to 9.85E04	1	0.87	0.29	0.91

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Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Common carp	<i>Cyprinus</i>	<i>carpio</i>	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	2.53E04	9,257 to 6.90E04	1	0.83	0.35	0.88
Cutthroat trout	<i>Oncorhynchus</i>	<i>clarkii</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.41E04	5,277 to 3.78E04	1	0.82	0.34	0.99
Pink shrimp	<i>Farfantepenaeus</i>	<i>duorarum</i>	Mysid (<i>Americamysis bahia</i>)	1.57E04	2,590 to 9.50E04	1	0.81	0.61	0.98
Amphipod	<i>Gammarus</i>	<i>pseudolimnaeus</i>	Mysid (<i>Americamysis bahia</i>)	4,400	1,034 to 1.87E04	1	0.8	0.55	0.82
Coho salmon	<i>Oncorhynchus</i>	<i>kisutch</i>	Bluegill (<i>Lepomis macrochirus</i>)	1.76E04	6,320 to 4.91E04	1	0.79	0.47	0.9
Common carp	<i>Cyprinus</i>	<i>carpio</i>	Bluegill (<i>Lepomis macrochirus</i>)	4.11E04	1.62E04 to 1.04E05	1	0.78	0.46	0.86
Guppy	<i>Poecilia</i>	<i>reticulata</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.99E04	9,189 to 4.31E04	1	0.78	0.38	0.84
Guppy	<i>Poecilia</i>	<i>reticulata</i>	Bluegill (<i>Lepomis macrochirus</i>)	2.08E04	7,138 to 6.06E04	1	0.75	0.39	0.7
Yellow perch	<i>Perca</i>	<i>flavescens</i>	Fathead minnow (<i>Pimephales promelas</i>)	9,380	1,459 to 6.04E04	1	0.73	0.54	0.93
Brown trout	<i>Salmo</i>	<i>trutta</i>	Bluegill (<i>Lepomis macrochirus</i>)	1.41E04	2,867 to 6.93E04	1	0.72	0.68	0.91
Lake trout	<i>Salvelinus</i>	<i>namaycush</i>	Bluegill (<i>Lepomis macrochirus</i>)	1.04E04	3,935 to 2.75E04	1	0.72	0.27	0.69
Goldfish	<i>Carassius</i>	<i>auratus</i>	Bluegill (<i>Lepomis macrochirus</i>)	4.01E04	1.53E04 to 1.06E05	1	0.71	0.51	0.77
Brook trout	<i>Salvelinus</i>	<i>fontinalis</i>	Fathead minnow (<i>Pimephales promelas</i>)	9,870	2,306 to 4.22E04	1	0.7	0.74	0.95
Chinook salmon	<i>Oncorhynchus</i>	<i>tshawytscha</i>	Bluegill (<i>Lepomis macrochirus</i>)	1.43E04	2,433 to 8.39E04	1	0.65	0.95	0.91
Lake trout	<i>Salvelinus</i>	<i>namaycush</i>	Fathead minnow (<i>Pimephales promelas</i>)	4,130	1,126 to 1.51E04	1	0.65	0.33	0.76
Coho salmon	<i>Oncorhynchus</i>	<i>kisutch</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.01E04	2,079 to 4.94E04	1	0.64	0.69	0.91

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Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Northern leopard frog	<i>Lithobates</i>	<i>pipiens</i>	Bluegill (<i>Lepomis macrochirus</i>)	7.06E04	1.07E04 to 4.67E05	1	0.99	0.01	0.79
Oriental river shrimp	<i>Macrobrachium</i>	<i>nipponense</i>	Daphnid (<i>Daphnia magna</i>)	2.13E04	8,912 to 5.09E04	1	0.98	0.05	1.14
Midge	<i>Paratanytarsus</i>	<i>parthenogeneticus</i>	Daphnid (<i>Daphnia magna</i>)	8.84E04	4.00E04 to 1.95E05	1	0.98	0.05	0.97
Isopod	<i>Asellus</i>	<i>aquaticus</i>	Daphnid (<i>Daphnia magna</i>)	5.48E05	1.14E05 to 2.64E06	1	0.91	0.31	0.85
Midge	<i>Chironomus</i>	<i>plumosus</i>	Mysid (<i>Americamysis bahia</i>)	9,790	2,111 to 4.54E04	1	0.77	0.66	0.73
Amphipod	<i>Gammarus</i>	<i>fasciatus</i>	Daphnid (<i>Daphnia magna</i>)	1.34E04	5,443 to 3.31E04	1	0.75	0.75	0.81
Amphipod	<i>Gammarus</i>	<i>pseudolimnaeus</i>	Daphnid (<i>Daphnia magna</i>)	2.34E04	5,994 to 9.17E04	1	0.74	0.75	0.91
Paper pondshell	<i>Utterbackia</i>	<i>imbecillis</i>	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	9.43E04	3.61E04 to 2.46E05	1	0.99	0	1.03
Bigscale mullet	<i>Chelon</i>	<i>macrolepis</i>	Daphnid (<i>Daphnia magna</i>)	1.50E06	5.24E05 to 4.32E06	1	0.99	0	0.9
Neosho mucket	<i>Lampsilis</i>	<i>rafinesqueana</i>	Daphnid (<i>Daphnia magna</i>)	1.80E04	6,027 to 5.40E04	1	0.99	0.02	0.89
Copepod	<i>Tisbe</i>	<i>battagliai</i>	Bluegill (<i>Lepomis macrochirus</i>)	1,450	867 to 2,441	1	0.99	0	0.78
Mayfly	<i>Cloeon</i>	<i>dipterum</i>	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	13.1	9.14 to 18.63	1	0.99	0	0.68
Midge	<i>Paratanytarsus</i>	<i>parthenogeneticus</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.42E05	3.15E04 to 6.40E05	1	0.98	0.09	0.98
Threeridge	<i>Amblema</i>	<i>plicata</i>	Fathead minnow (<i>Pimephales promelas</i>)	1,780	548 to 5,785	1	0.97	0.12	1.3
Washboard	<i>Megaloniais</i>	<i>nervosa</i>	Daphnid (<i>Daphnia magna</i>)	1.29E04	7,372 to 2.25E04	1	0.97	0.12	0.96
Pheasantshell	<i>Ortmanniana</i>	<i>pectorosa</i>	Daphnid (<i>Daphnia magna</i>)	2.14E04	6,148 to 7.43E04	1	0.97	0.11	0.96
Polychaete	<i>Capitella</i>	<i>capitata</i>	Mysid (<i>Americamysis bahia</i>)	3.59E04	1.05E04 to 1.23E05	1	0.97	0.04	0.95

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Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Threeridge	<i>Amblema</i>	<i>plicata</i>	Daphnid (<i>Daphnia magna</i>)	6,990	2,600 to 1.88E04	1	0.97	0.13	0.94
Washboard	<i>Megalonaias</i>	<i>nervosa</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	1.60E04	8,971 to 2.85E04	1	0.96	0.13	0.96
Amphipod	<i>Allorchestes</i>	<i>compressa</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.21E04	4,430 to 3.30E04	1	0.96	0.02	0.84
Green floater	<i>Lasmigona</i>	<i>subviridis</i>	Daphnid (<i>Daphnia magna</i>)	8,840	1,004 to 7.78E04	1	0.96	0.07	0.66
Threeridge	<i>Amblema</i>	<i>plicata</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	7,850	2,025 to 3.05E04	1	0.95	0.24	0.89
Western pearlshell	<i>Margaritifera</i>	<i>falcata</i>	Daphnid (<i>Daphnia magna</i>)	1.72E04	8,760 to 3.36E04	1	0.95	0.15	0.87
Amphipod	<i>Gammarus</i>	<i>minus</i>	Fathead minnow (<i>Pimephales promelas</i>)	7.60E04	2.16E04 to 2.67E05	1	0.95	0.04	0.72
Fatmucket	<i>Lampsilis</i>	<i>siliquoidea</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	1.40E04	7,276 to 2.70E04	1	0.94	0.22	0.94
Paper pondshell	<i>Utterbackia</i>	<i>imbecillis</i>	Daphnid (<i>Ceriodaphnia dubia</i>)	1.71E04	9,118 to 3.22E04	1	0.94	0.17	0.88
Amphipod	<i>Allorchestes</i>	<i>compressa</i>	Bluegill (<i>Lepomis macrochirus</i>)	3,650	1,211 to 1.10E04	1	0.92	0.05	0.62
Isopod	<i>Asellus</i>	<i>aquaticus</i>	Bluegill (<i>Lepomis macrochirus</i>)	7.83E04	1.26E04 to 4.87E05	1	0.9	0.36	1.09
Midge	<i>Paratanytarsus</i>	<i>dissimilis</i>	Bluegill (<i>Lepomis macrochirus</i>)	9.51E04	1.53E04 to 5.90E05	1	0.88	0.49	0.85
Oligochaete	<i>Tubifex</i>	<i>tubifex</i>	Fathead minnow (<i>Pimephales promelas</i>)	5.17E04	1.18E04 to 2.27E05	1	0.86	0.52	1.03
Tadpole physa	<i>Physella</i>	<i>gyrina</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.19E04	2,354 to 6.05E04	1	0.84	0.58	1.22
Swamp lymnaea	<i>Lymnaea</i>	<i>stagnalis</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.22E04	1,797 to 8.32E04	1	0.84	0.59	1.2
Midge	<i>Paratanytarsus</i>	<i>dissimilis</i>	Fathead minnow (<i>Pimephales promelas</i>)	9.23E04	2.38E04 to 3.59E05	1	0.84	0.52	0.86

Common Name	Genus	Species	Surrogate Species	LC50 or EC50 (µg/L)	95% CI	CI Diff	R ²	MSE	Slope
Oligochaete	<i>Lumbriculus</i>	<i>variegatus</i>	Fathead minnow (<i>Pimephales promelas</i>)	4.44E04	1.32E04 to 1.50E05	1	0.81	0.43	0.94
Swamp lymnaea	<i>Lymnaea</i>	<i>stagnalis</i>	Bluegill (<i>Lepomis macrochirus</i>)	8,710	1,004 to 7.56E04	1	0.8	0.82	1.25
Amphipod	<i>Hyalella</i>	<i>azteca</i>	Bluegill (<i>Lepomis macrochirus</i>)	4,860	1,644 to 1.44E04	1	0.8	0.95	1.05
Copepod	<i>Acartia</i>	<i>clausi</i>	Fathead minnow (<i>Pimephales promelas</i>)	5,150	1,113 to 2.39E04	1	0.8	0.23	0.88
Copepod	<i>Acartia</i>	<i>clausi</i>	Bluegill (<i>Lepomis macrochirus</i>)	2,230	510 to 9,712	1	0.8	0.27	0.81
Oligochaete	<i>Limnodrilus</i>	<i>hoffmeisteri</i>	Daphnid (<i>Daphnia magna</i>)	9.13E04	2.58E04 to 3.22E05	1	0.8	0.35	0.7
Tadpole physa	<i>Physella</i>	<i>gyrina</i>	Bluegill (<i>Lepomis macrochirus</i>)	8,940	1,319 to 6.06E04	1	0.77	0.85	1.27
Copepod	<i>Tigriopus</i>	<i>japonicus</i>	Fathead minnow (<i>Pimephales promelas</i>)	7.49E04	1.25E04 to 4.47E05	1	0.72	0.13	0.77
Eastern oyster	<i>Crassostrea</i>	<i>virginica</i>	Fathead minnow (<i>Pimephales promelas</i>)	1.20E04	4,641 to 3.10E04	1	0.66	0.48	0.84
Paper pondshell	<i>Utterbackia</i>	<i>imbecillis</i>	Fathead minnow (<i>Pimephales promelas</i>)	7,060	1,287 to 3.87E04	1	0.65	0.85	0.86
Fatmucket	<i>Lampsilis</i>	<i>siliquoidea</i>	Fathead minnow (<i>Pimephales promelas</i>)	9,110	2,151 to 3.86E04	1	0.64	0.93	0.93
Eastern oyster	<i>Crassostrea</i>	<i>virginica</i>	Bluegill (<i>Lepomis macrochirus</i>)	8,140	4,571 to 1.45E04	1	0.63	0.51	0.75
Rainbow trout	<i>Oncorhynchus</i>	<i>mykiss</i>	Mysid (<i>Americamysis bahia</i>)	1.25E04	8,157 to 1.92E04	1	0.62	0.71	0.66

LC50 = lethal concentration 50%; EC50 = half maximal effective concentration; CI = confidence interval

F.1.1.2 Species Sensitivity Distribution (SSD) - Algae

The SSD Toolbox is a resource created by EPA that can fit SSDs to environmental hazard data (Etterson, 2020a). The SSD Toolbox runs on MATLAB 2018b (9.5) for Windows 64-bit. For the *trans*-1,2-dichloroethylene risk evaluation, EPA calculated an algal SSD with the SSD Toolbox v1.1 using empirical EC50 hazard data for the analog trichloroethylene that included nine algal species. The SSD is used to calculate a hazardous concentration for 5% of species (HC05) along with a lower and upper

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confidence interval of this value. In other words, HC05 estimates the hazard concentration that is expected to be protective for 95% of species. In the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#)) this HCO5 was used as the COC, however this method has been updated since the publication of that document. Now the EPA will use the lower 95th confidence interval of the HC05 in order to be more protective without the additional step of using an assessment factor. There are a few other minor differences between the algal SSD found in the *Risk Evaluation for Trichloroethylene* ([U.S. EPA, 2020d](#)) and the one found below in Figure_Apx F-3. One study used in the trichloroethylene risk evaluation was reassessed and found to be uninformative and therefore was excluded from the SSD this time around. The other difference is not using the Burr and Gumbel distributions which poorly fit the maximum likelihood fitting method as seen in Figure_Apx F-1.

For the algae SSD, algae hazard data were curated to prioritize study quality and to ensure comparability between toxicity values (e.g., comparing EC50s to EC50s). The dataset included both saltwater and freshwater species, because the only saltwater species value was within the range of values reported for freshwater species. Table_Apx F-3 shows the data that was used in the algae SSD, as well as data that was not included in the SSD and why. With this dataset, the Toolbox was used to apply a variety of algorithms to fit and visualize SSDs with different distributions. Figure_Apx F-1 shows the Toolbox interface after each distribution and fitting method was fit to the data. A HC05 and is calculated for each.

Table_Apx F-3. Algal Toxicity Data for Trichloroethylene Used in SSD

Genus	Species	EC50 for Growth (mg/L)	Source (Quality Rating)	Used in SSD
Saltwater				
<i>Skeletonema</i>	<i>costatum</i>	95	(Ward et al., 1986) (medium)	Yes
Freshwater				
<i>Chlamydomonas</i>	<i>reinhardtii</i>	36.5	(Brack and Rottler, 1994)(high)	Yes
<i>Chlamydomonas</i>	<i>reinhardtii</i>	520	(Lukavsky et al., 2011) (medium)	Yes
<i>Chlorella</i>	<i>Kessleri</i>	321, geometric mean of 2 population growth rate values	(Lukavsky et al., 2011) (medium)	Yes
<i>Desmodesmus</i>	<i>quadricauda</i>	447, geometric mean of 2 population rate values	(Lukavsky et al., 2011) (medium)	Yes
<i>Desmodesmus</i>	<i>Subspicatus</i>	536, geometric mean of 2 population growth values	(Lukavsky et al., 2011) (medium)	Yes
<i>Mycrocystis</i>	<i>aeruginosa</i>	130	(Lukavsky et al., 2011) (medium)	Yes

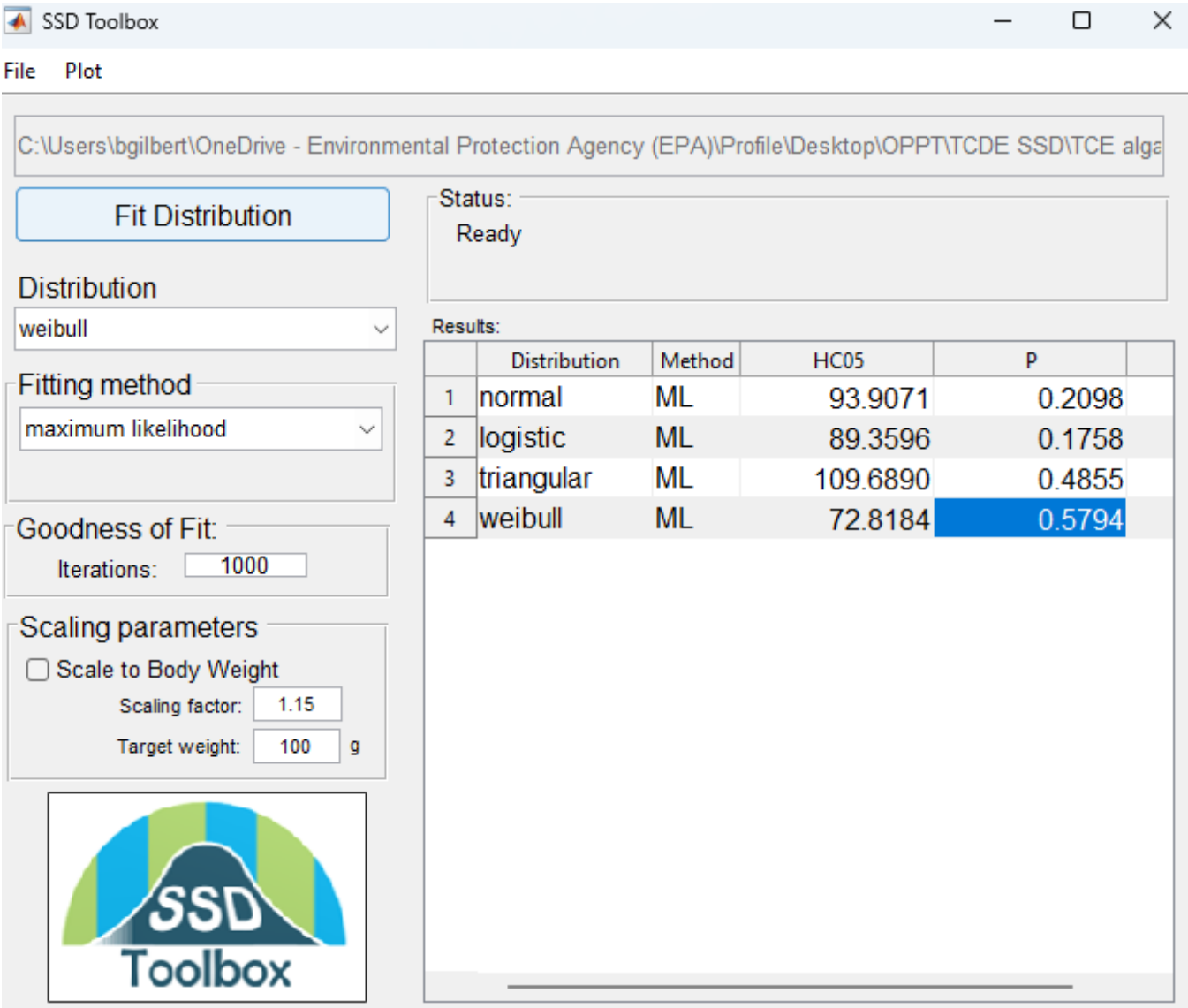
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Genus	Species	EC50 for Growth (mg/L)	Source (Quality Rating)	Used in SSD
<i>Raphidocelis</i>	<i>subcapitata</i>	315	(Lukavsky et al., 2011) (medium)	Yes
<i>Synechococcus</i>	<i>elongatus</i>	800	(Lukavsky et al., 2011) (medium)	Yes
<i>Synechococcus</i>	<i>leopoliensis</i>	424 geometric mean of 2 population growth rate values	(Lukavsky et al., 2011) (medium)	Yes
<i>Chlamydomonas</i>	<i>reinhardtii</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Chlamydomonas</i>	<i>reinhardtii</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Chlorella</i>	<i>kessleri</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Chlorella</i>	<i>kessleri</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Raphidocelis</i>	<i>subcapitata</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Raphidocelis</i>	<i>subcapitata</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Desmodesmus</i>	<i>quadricauda</i>	500	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a

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Genus	Species	EC50 for Growth (mg/L)	Source (Quality Rating)	Used in SSD
				more biologically relevant effect than photosynthesis.
<i>Desmodesmus</i>	<i>quadricauda</i>	600	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Desmodesmus</i>	<i>subspicatus</i>	400	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Desmodesmus</i>	<i>subspicatus</i>	400	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Synechococcus</i>	<i>elongatus</i>	600	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Synechococcus</i>	<i>elongatus</i>	700	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Synechococcus</i>	<i>leopoliensis</i>	480	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Synechococcus</i>	<i>leopoliensis</i>	450	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
<i>Microcystis</i>	<i>Aeruginosa</i>	100	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.

Genus	Species	EC50 for Growth (mg/L)	Source (Quality Rating)	Used in SSD
<i>Microcystis</i>	<i>aeruginosa</i>	250	(Lukavsky et al., 2011) (medium)	No, because an EC50 measuring population growth rate was available in the same study for this species and that was considered a more biologically relevant effect than photosynthesis.
Reproduced from Table 3-1 of the <i>Risk Evaluation for Trichloroethylene</i> (U.S. EPA, 2020d)				

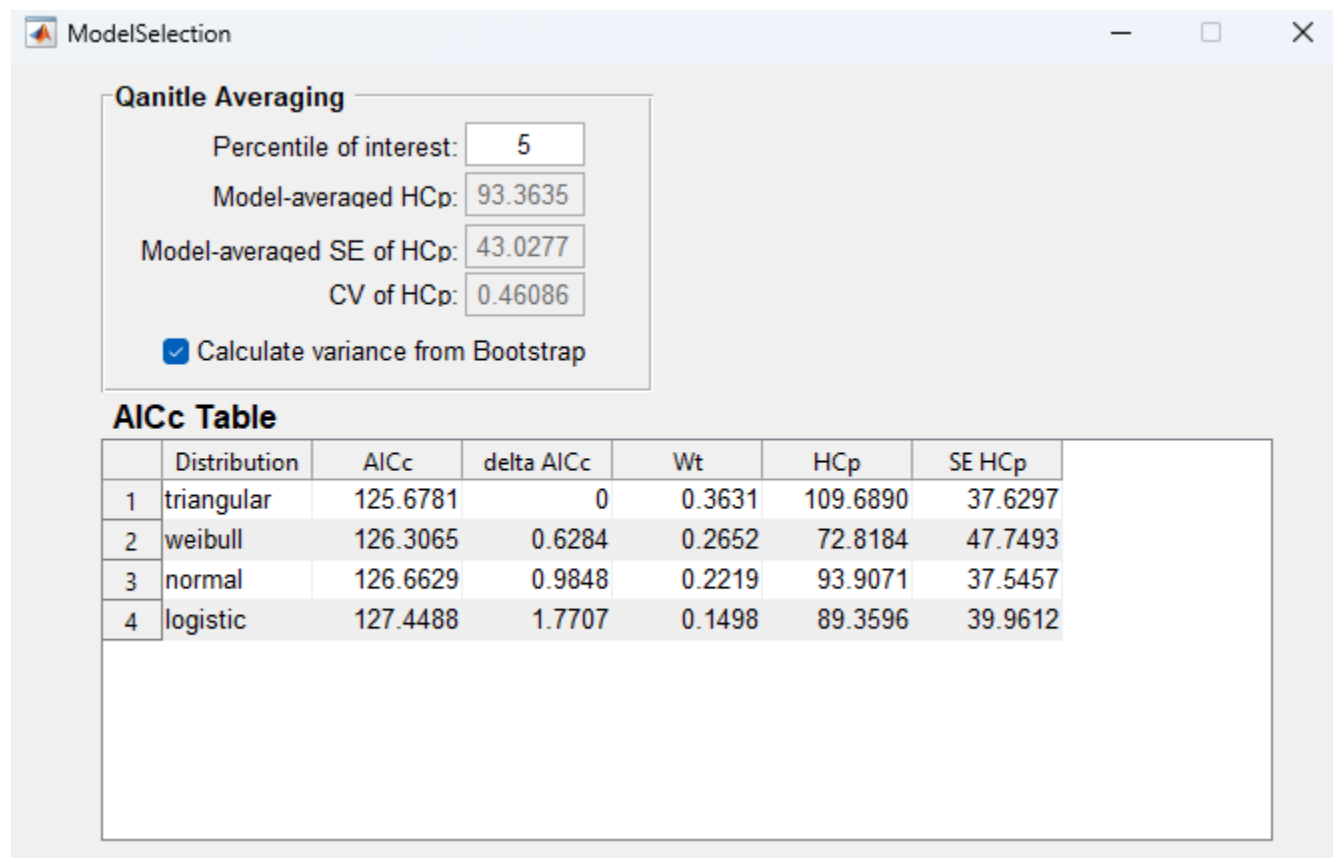


Figure_Apx F-1. SSD Toolbox Interface and List of HC05s for Each Distribution and Fitting Method Using Trichloroethylene Algae Hazard Data ([Etterson, 2020a](#))

The SSD Toolbox’s output contained several methods for choosing an appropriate distribution and fitting method, including goodness-of-fit, standard error, and sample-size corrected Akaike Information Criterion (AICc) ([Burnham and Anderson, 2002](#)). However, choosing the distribution with the best fit was challenging with a small dataset (e.g., hazard data for 9 algae species). All P values for goodness of-

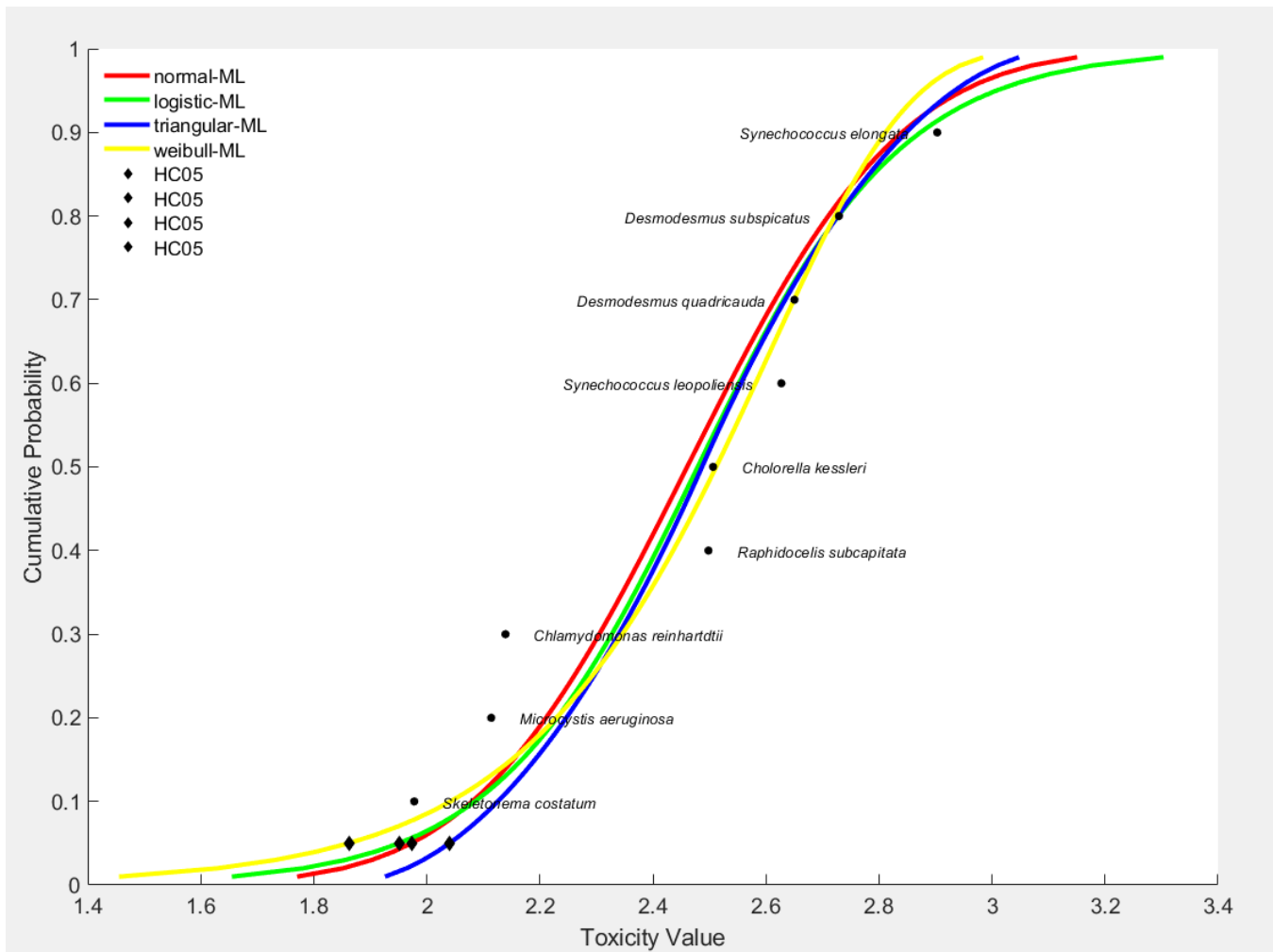
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fit were above 0.05 showing no evidence for lack of fit, providing no help in discriminating among distributions (Figure_Apx F-1). The AICc Table (Figure_Apx F-2) showed that none of the distributions were outliers wither for best of fit or standard error. Because the ability for these measures to distinguish between distributions was limited, visual inspection of the distributions was used; however, no distributions could be eliminated through this method either after plotting the SSD (Figure_Apx F-3).



Figure_Apx F-2. AICc Table for Algae Hazard Data (Etterson, 2020a)

Because there was no obvious distribution that was the best fit using goodness-of-fit, standard error, and sample-size corrected AICc, EPA used all four distributions to calculate an HC05. Using the normal, logistic, triangular, and Weibull distributions, EPA calculated a modeled average HC05 of 93.36 mg/L. A modeled average lower confidence interval of the HC05 was calculated to be 51.47 mg/L.



Figure_Apx F-3. Trichloroethylene Algae Data Fit with All Distributions Using the Maximum Likelihood Fitting Method ([Etterson, 2020a](#))

F.1.1.3 Species Sensitivity Distribution (SSD) – Aquatic Acute Hazard

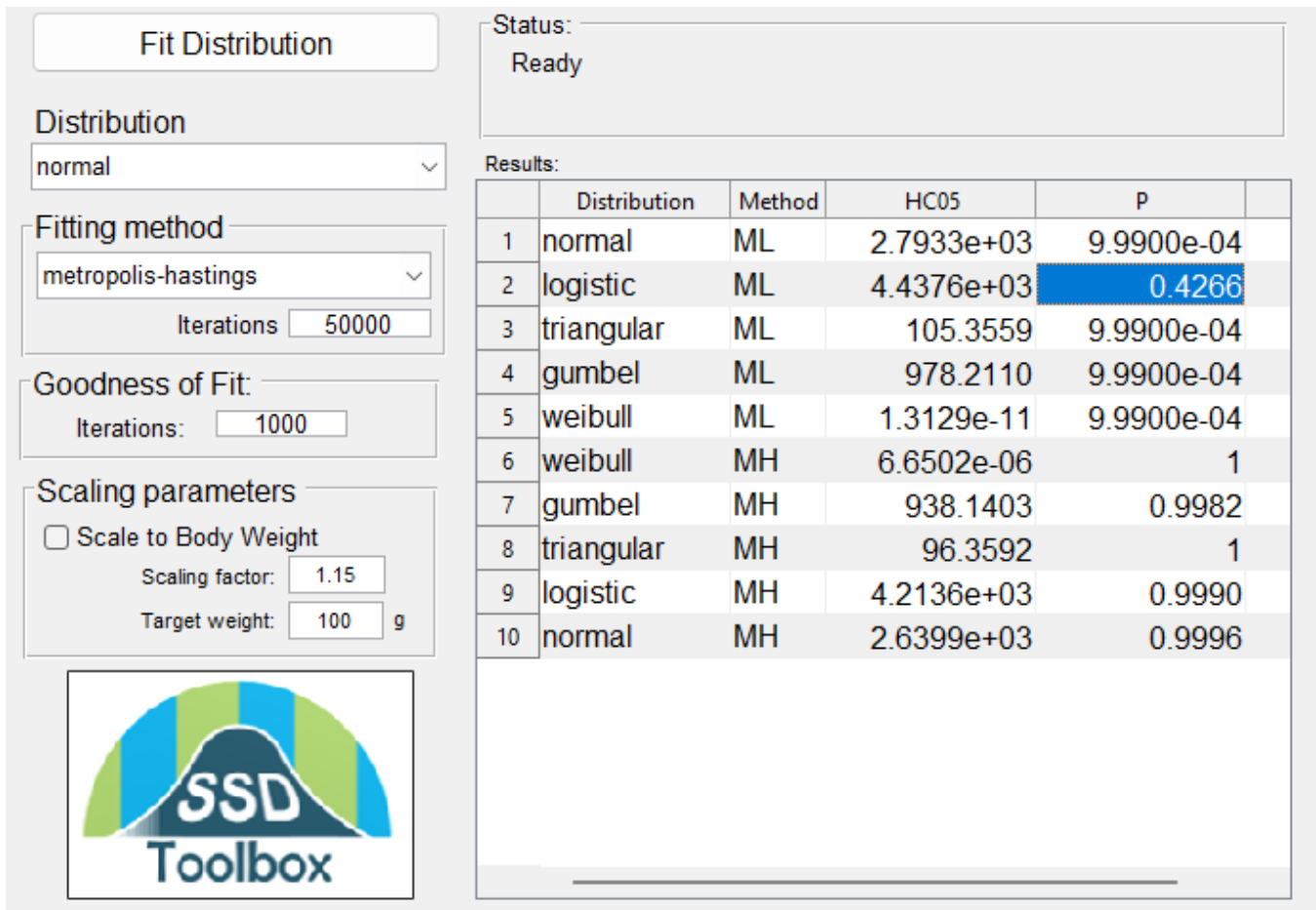
The SSD Toolbox is an EPA resource that can fit SSDs to environmental hazard data ([Etterson, 2020a](#)). The SSD Toolbox runs on MATLAB 2018b (9.5) for Windows 64-bit. For the *trans*-1,2-dichloroethylene risk evaluation, EPA calculated an SSD representing aquatic and benthic species with the SSD Toolbox v1.1 using acute EC50 and LC50 hazard data for *trans*-1,2-dichloroethylene and the analog trichloroethylene from systematic review. EPA estimated data from the Web-ICE application that included 69 species. The SSD was used to calculate an HC05. In other words, HC05 estimates the concentration that is expected to be protective for 95% of species. The lower confidence interval of the HC05 was also calculated.

The SSD Toolbox contains functions for fitting up to six distributions (normal, logistic, triangular, Gumbel, Weibull, and Burr) across four model estimation methods (maximum likelihood, moment estimators, graphical methods, and Bayesian methods, in this case the Metropolis-Hastings algorithm). Maximum likelihood was used to model the data for *trans*-1,2-dichloroethylene due to its general acceptance for fitting SSDs ([Etterson, 2020b](#)), its low sampling variance, and the fact that models can also be compared a posteriori using information theoretic methods, in this case Akaike's Information Criterion corrected for sample size (AICc). The AICc table for this SSD can be found in Figure_Apx F-6. AICc was used along with a comparison of p-values and a visual assessment of Q-Q plots, which

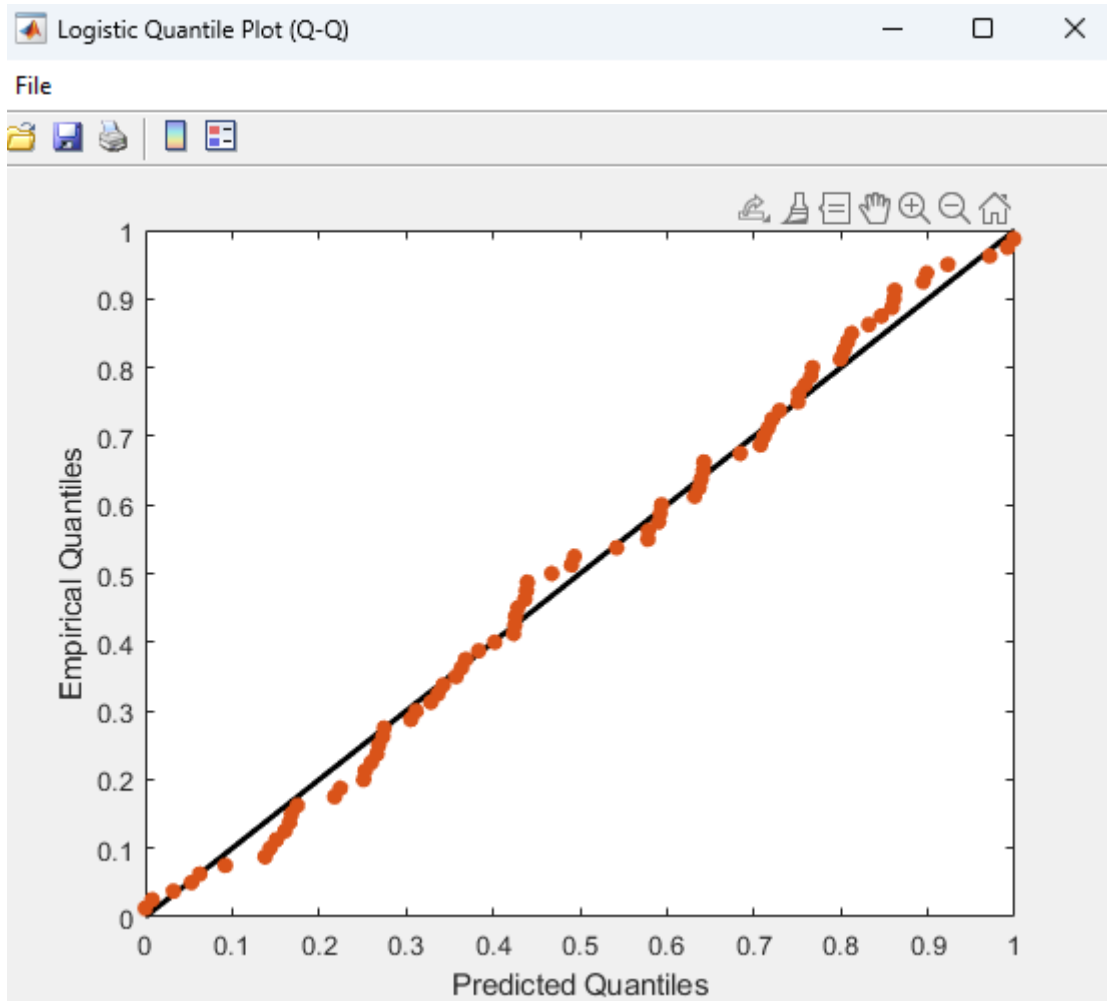
are methods available to all model estimation methods, to select the distribution used to calculate the HC05 for this analysis. The Q-Q plot for the selected distribution can be found in Figure_Apx F-5. Based on the guidance documents for use of the SSD Toolbox ([Etterson, 2020b](#)), the Burr distribution is provided only for comparison and is not used for modeling; thus, it was not included.

The SSD Toolbox uses a parametric bootstrap method to calculate a p-value to compare goodness-of-fit across distributions. In this type of test, p-values exceeding 0.05 are required ([Etterson, 2020b](#)). A quick look at the p-values made the selection of a distribution easy as only one distribution for maximum likelihood had a value over the required 0.05, logistic with a p-value of 0.4266. The p-values can be found in Figure_Apx F-4.

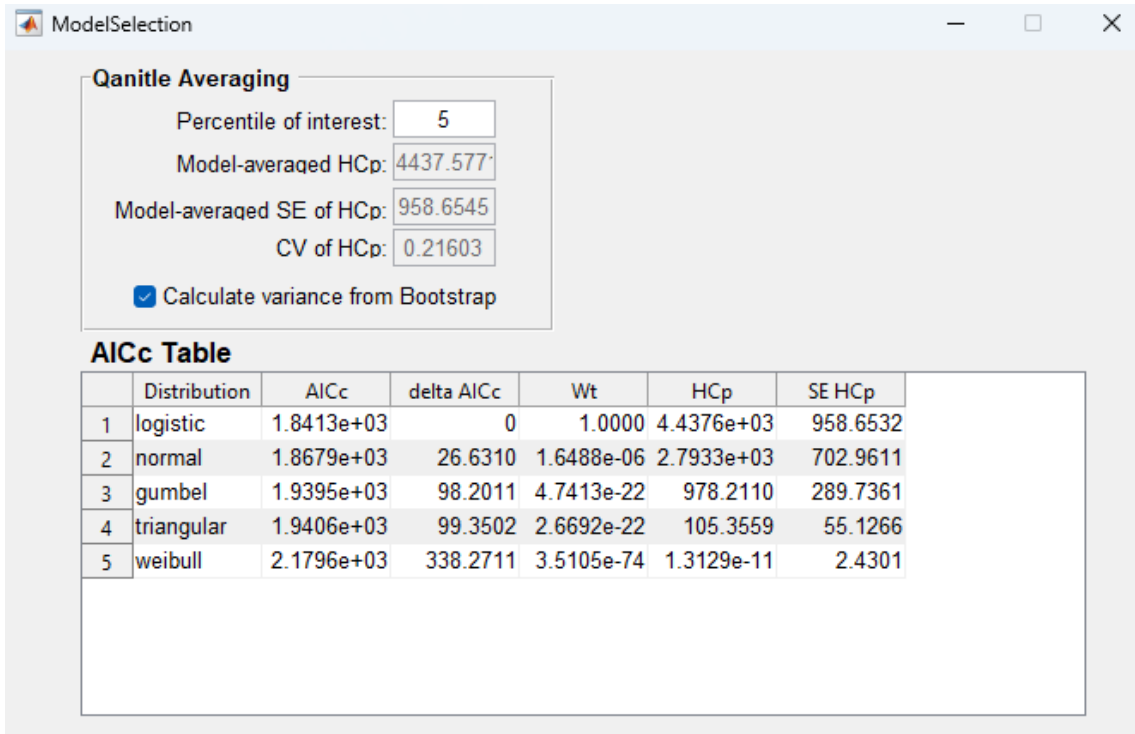
This distribution was then plotted along with data points for both measured and modeled species. This plot can be found in Figure_Apx F-8. The calculated HC05 was 4,437 µg/L (95% CI = 3,005 µg/L–6,508 µg/L). The lower 95% CI of the HC05 (3,005 µg/L) was then selected as the acute aquatic COC. The confidence intervals of the HC05 can be found in Figure_Apx F-7.



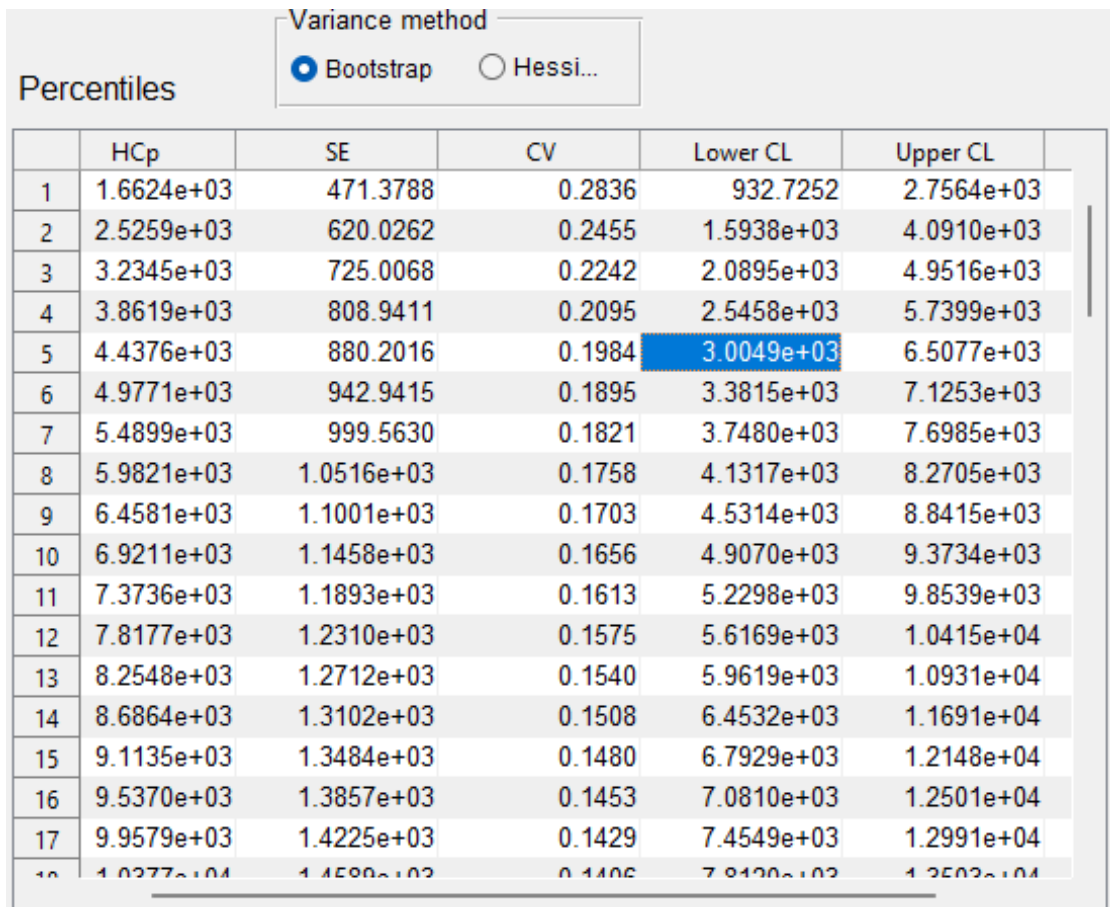
Figure_Apx F-4. SSD Toolbox Interface and List of HC05s for Each Distribution and Fitting Method Using Acute Aquatic Hazard Data ([Etterson, 2020a](#))



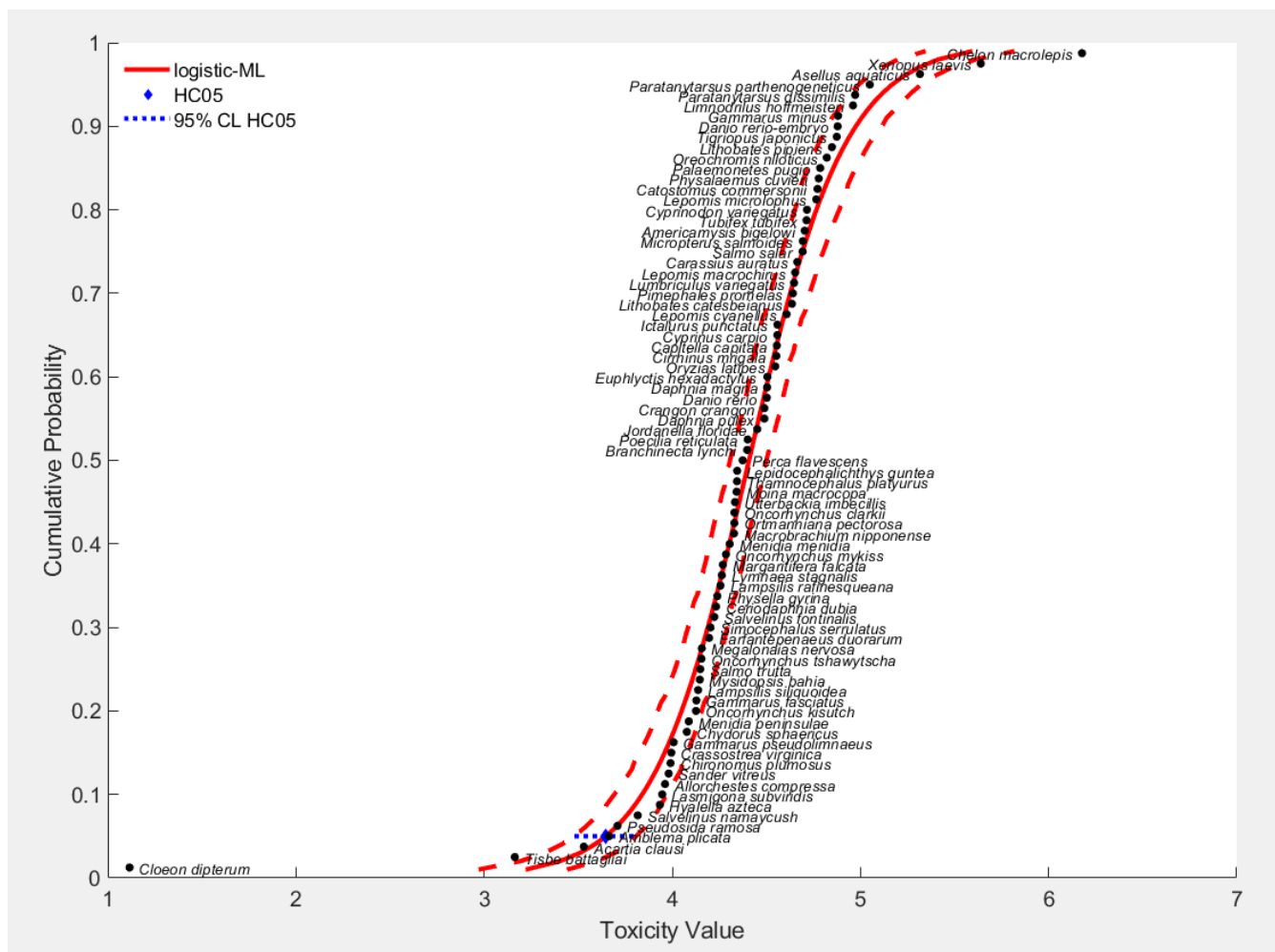
Figure_Apx F-5. Q-Q Plot for Acute Aquatic Hazard Data Using Logistic Distribution and Maximum Likelihood Fitting Method ([Etterson, 2020a](#))



Figure_Apx F-6. AICc Table for Acute Aquatic Hazard Data ([Etterson, 2020a](#))



Figure_Apx F-7. Acute Aquatic Percentiles Table Using Logistic Distribution and Maximum Likelihood Fitting Method ([Etterson, 2020a](#))



Figure_Apx F-8. Acute Aquatic Data SSD Fit with All Logistic Distribution Using the Maximum Likelihood Fitting Method (Etterson, 2020a)

F.1.2 Evidence Integration

Data integration includes analysis, synthesis, and integration of information for the risk evaluation. During data integration, EPA considers quality, consistency, relevancy, coherence, and biological plausibility to make final conclusions regarding the weight of scientific evidence. As stated in the Draft Systematic Review Protocol (U.S. EPA, 2021), data integration involves transparently discussing the significant issues, strengths, and limitations, as well as the uncertainties of the reasonably available information and the major points of interpretation.

The general analytical approaches for integrating evidence for environmental hazard is discussed in Section 7.4 of the Draft Systematic Review Protocol (U.S. EPA, 2021).

The organization and approach to integrating hazard evidence is determined by the reasonably available evidence regarding routes of exposure, exposure media, duration of exposure, taxa, metabolism and distribution, effects evaluated, the number of studies pertaining to each effect, as well as the results of the data quality evaluation.

The environmental hazard integration is organized around effects to aquatic and terrestrial organisms as well as the respective environmental compartments (e.g., water column, benthic, soil). Environmental hazard assessment may be complex based on the considerations of the quantity, relevance, and quality of

the available evidence.

For *trans*-1,2-dichloroethylene, environmental hazard data from toxicology studies identified during systematic review have used evidence that characterizes apical endpoints; that is, hazard endpoints that could have population level effects such as reproduction, growth, or mortality. EPA also considered predictions from Web-ICE to supplement the empirical data found during systematic review.

F.1.2.1 Rubric for Weight of Scientific Evidence

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 and illustrated in Table_Apx F-5.

The evidence considerations and criteria detailed within ([U.S. EPA, 2021](#)) will guide 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 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)).

EPA used the strength-of-evidence and uncertainties from ([U.S. EPA, 2021](#)) for the hazard assessment to qualitatively rank the overall confidence using evidence for environmental hazard. Confidence levels of robust (+ + +), moderate (+ +), slight (+), or indeterminate are assigned for each evidence property that corresponds to the evidence considerations ([U.S. EPA, 2021](#)). The rank of the Quality of the Database consideration is based on the systematic review data quality rank (high, medium, or low) for studies used to calculate the hazard threshold, and whether there are data gaps in the toxicity dataset. Another consideration in the Quality of the Database 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 ranks correspond to the evidence table ranks of robust (+ + +), moderate (+ +), or slight (+), respectively. The evidence considerations are weighted based on professional judgement 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 below.

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.

- Indeterminant (NA) corresponds to entries in evidence tables where information is not available within a specific evidence consideration.

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_Apx F-5).

- 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 F-4 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 F-4. *trans*-1,2-Dichloroethylene Evidence Table Summarizing the Overall Confidence Derived from Hazard Thresholds

Types of Evidence	Quality of the Database	Consistency	Strength and Precision	Biological Gradient/ Dose-Response	Relevance ^a	Hazard Confidence
Aquatic						
Acute aquatic assessment	+++	+++	+++	+++	+++	Robust
Acute benthic assessment	NA	NA	NA	NA	NA	NA
Chronic aquatic assessment	++	+++	+++	++	+++	Moderate
Chronic benthic assessment	NA	NA	NA	NA	NA	NA
Algal assessment	++	+++	+++	+++	++	Moderate-to- Robust
Terrestrial						
Chronic mammalian oral assessment	++	++	++	+++	++	Robust
Chronic mammalian inhalation assessment	+	+++	++	+++	++	Moderate
Chronic avian assessment						Indeterminate
Soil invertebrate assessment	+++	+++	+++	++	+++	Moderate-to- Robust
Terrestrial plant assessment	+++	++	+++	+++	+++	Moderate-to- Robust
^a Relevance includes biological, physical/chemical (including use of analogs), and environmental relevance. +++ 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 hazard estimate. ++ Moderate confidence suggests some understanding of the scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize hazard estimates. + Slight confidence is assigned when the weight of 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. ^b N/A indicates that a slight, moderate, or robust confidence cannot be assigned due to the lack of reasonably available data. ^c Indeterminate is noted when a hazard confidence cannot be assigned to an assessment.						

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Table Apx F-5. Considerations That Inform Evaluations of the Strength of the Evidence Within an Evidence Stream

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 provided below 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 (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. ^a
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; see (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	• 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.

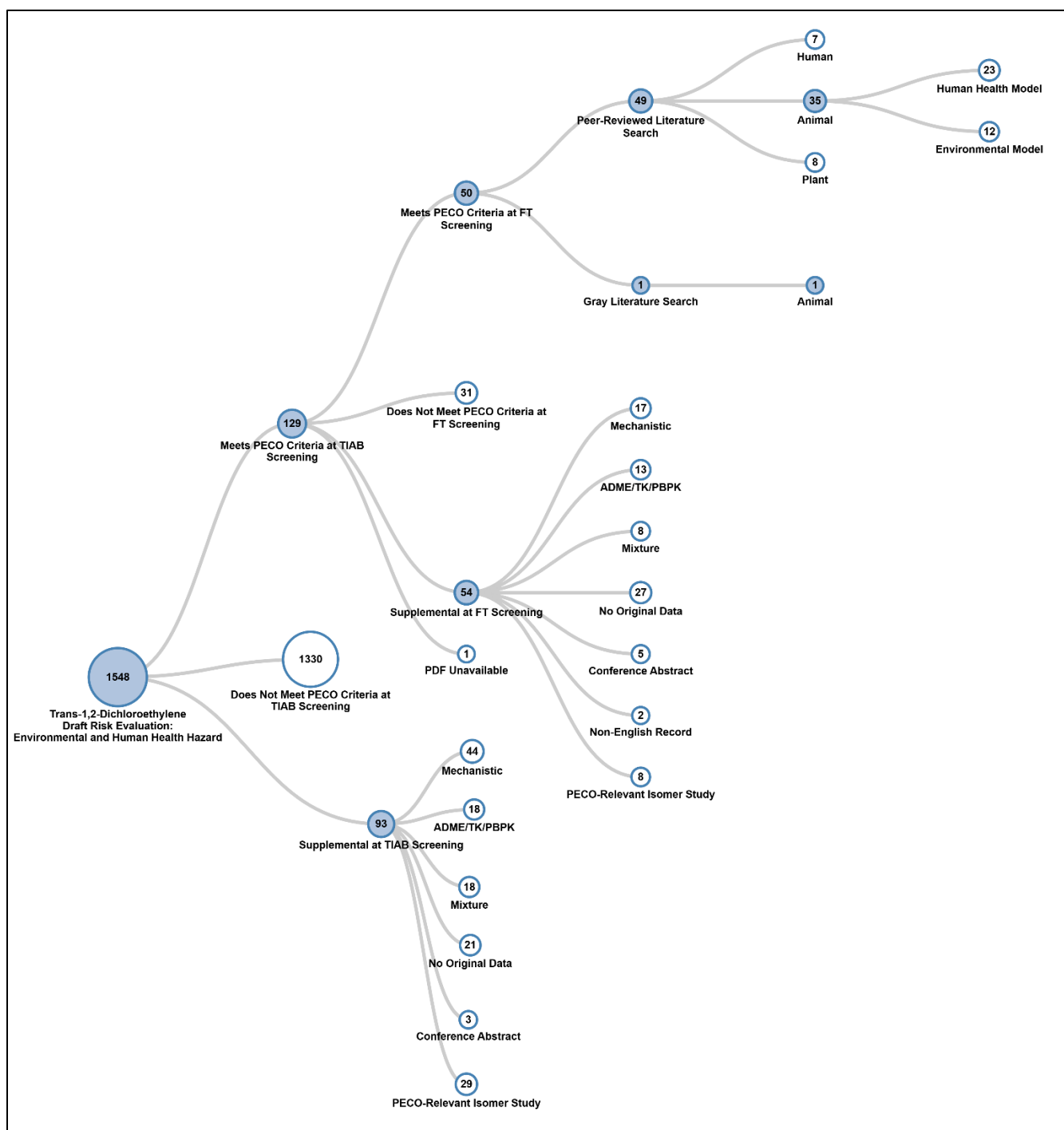
Consideration	Increased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)	Decreased Evidence Strength (of the Apical Endpoints, Mechanistic, or Field Studies Evidence)
	duration-dependent. • Dose-response may not be a monotonic dose-response (monotonicity should not necessarily be expected; for example, different outcomes may be expected at low vs. high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses). • Decreases in a response after cessation of exposure (e.g., return to baseline fecundity) also may increase strength by increasing certainty in a relationship between exposure and outcome (this particularly applicable to field studies).	• In experimental studies, strength may be decreased when effects resolve under certain experimental conditions (e.g., 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 chemical and the conditions of exposure, see (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 (e.g., 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 (e.g., 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 is 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 (e.g., 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.		

Appendix G LITERATURE INVENTORY TREES

During data screening, EPA followed the process described in Appendix H, Section H.5.11 of the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)), to conduct title-abstract (TIAB) and full-text screening for *trans*-1,2-dichloroethylene literature search results, as guided by the PECO statement. PECO stands for Population, Exposure, Comparator or Scenario, and Outcomes for Exposure Concentration or Dose. Full details and screening results for all the identified studies will be described in the *Draft Systematic Review Protocol for trans-1,2-Dichloroethylene*, to be released with the risk evaluation package.

G.1 Hazard

The same PECO statement was used during TIAB and full-text screening for references obtained during the initial 2019 search for the evaluation of environmental and human health hazard (including both epidemiology and animal toxicology) resulting from exposure to *trans*-1,2-dichloroethylene. An updated human health hazard PECO was used for the April 2025 literature update that focused on *in vivo* information specific to cancer and immunotoxicity. Environmental hazard also performed an updated literature search in April 2025. Relevant studies were not identified from the updated search for any discipline. Figure_Apx G-1 presents the number of references that report environmental and human health hazard data that met PECO screening criteria at TIAB and full-text screening for *trans*-1,2-dichloroethylene.



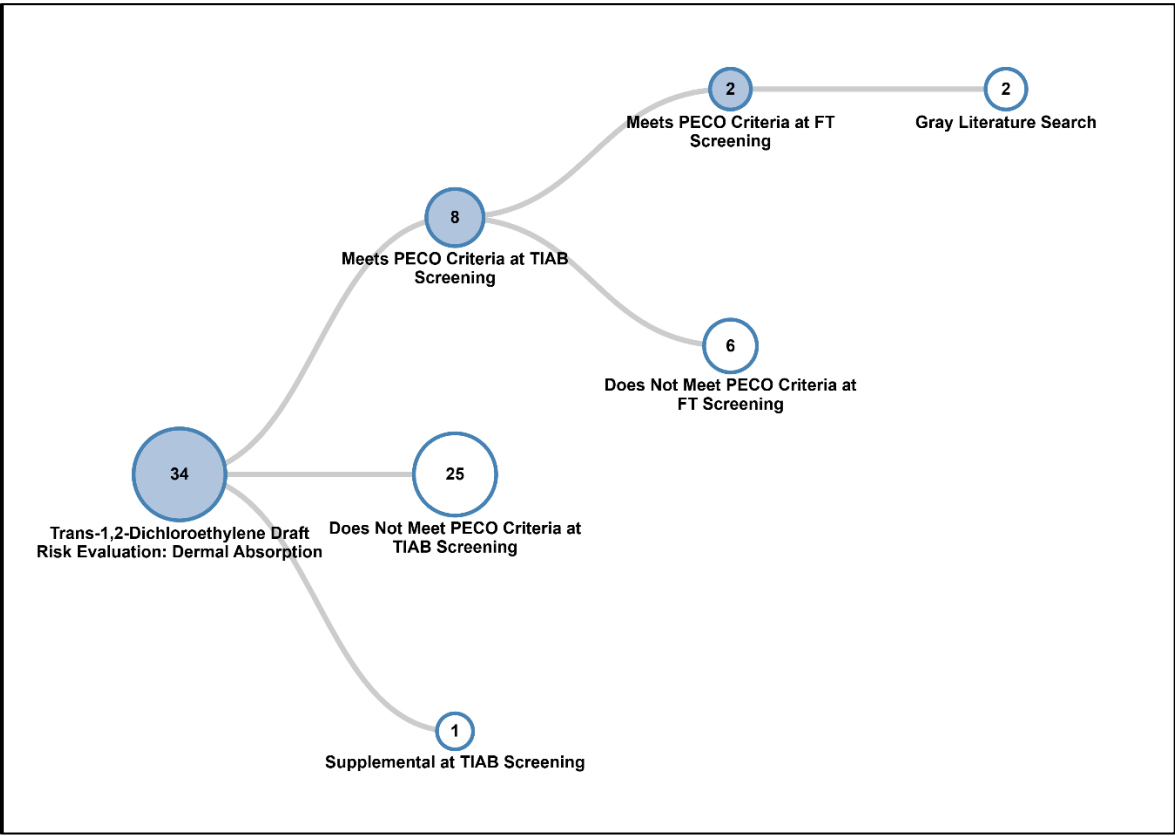
Figure_Apx G-1. Literature Inventory Tree for Environmental and Human Health Hazard

View the interactive literature inventory tree in [HAWC](#). Data in this figure represents all references obtained from the publicly available databases and gray literature references that were included in systematic review as of May 14, 2026.

G.2 Dermal Absorption

The same PECO statement was used during TIAB and full-text screening for references obtained during the initial 2019 search for the evaluation of environmental and human health hazard (including both epidemiology and animal toxicology) resulting from exposure to *trans*-1,2-dichloroethylene. An updated PECO was used for the April 2025 literature update that focused on *in vivo* information specific to

4512 cancer. Figure_Apx G-2 presents the number of references that report environmental and human health
4513 hazard data that met PECO screening criteria at TIAB and full-text screening for *trans*-1,2-
4514 dichloroethylene.
4515



4516
4517 **Figure_Apx G-2. Literature Inventory Tree for Environmental and Human Health Hazard**
4518 View the interactive literature inventory tree in [HAWC](#). Data in this figure represents all references obtained from
4519 the publicly available databases and gray literature references that were included in systematic review as of May
4520 14, 2026.
4521

Appendix H ETHICS REVIEW FOR [Lehmann and Schmidt-Kehl \(1936\)](#)

H.1 Memorandum

June 3, 2026

MEMORANDUM

Subject: Ethics Review for the Lehmann and Schmidt-Kehl (1936) Study included in the assessment of *trans*-1,2-Dichloroethylene (CAS 156-60-5)

From: James S. Brown, Human Research Ethics Review Officer
Existing Chemicals Risk Assessment Division (ECRAD),
Risk Assessment Branch 6, Office of Pollution Prevention and Toxics (OPPT)

To: Seema Schappelle, Branch Chief
Existing Chemicals Risk Assessment Division, Risk Assessment Branch 4
Office of Pollution Prevention and Toxics

Cc: Collin Beachman, Acting Deputy Division Director, ECRAD, OPPT;
Daniel Chang, Branch Chief, Risk Assessment Branch 3; Acting Branch Chief, Risk
Assessment Branch 6, ECRAD, OPPT

H.2 Introduction

An ethics review was requested for the [Lehmann and Schmidt-Kehl \(1936\)](#) study used in the Human Health and Environmental Hazard Assessment for *trans*-1,2-dichloroethylene (CAS No. 156-60-5). The study under consideration (Lehmann and Schmidt-Kehl, 1936) predates a modern process for ethical review of studies.

I have completed a temporally appropriate ethics review of the human experimental research conducted by Lehmann and Schmidt-Kehl (1936) by comparison to the ten basic principles of the Nuremberg Code (1947). I found the experimental methods and self-experimentation were relatively well aligned with the Nuremberg Code which suggests ethical standards were being followed by the investigators.

Appropriate ethical conduct of the investigators is also supported by the Lehmann and Schmidt-Kehl (1936) human study results being the basis, in whole and in part, for the EPA's 2008 Acute Exposure Guidelines EGLs for *trans*-1,2-Dichloroethylene. Although human data may be important in deriving AEGL values that protect the general public, utmost care must be exercised to ensure first of all that such data has been developed in accordance with ethical standards. No data on humans known to be obtained through force, coercion, misrepresentation, or any other such means will be used in the development of AEGLs.

The overall conclusion of my ethics review was that there was no clear and convincing evidence that the study was fundamentally unethical or significantly deficient with respect to the ethical standards prevailing when the research was conducted. The details related to my review are contained in the attached checklist for ethics reviews.

H.3 Ethical Assessment for Lehmann and Schmidt-Kehl (1936)

H.3.1 Checklist for review

1. Citation: Lehmann, K.B, L. Schmidt-Kehl. Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie. 116:131-268, 1936. (only 131-266 in pdf, some pages illegible)

Partial translation: The 13 most important chlorinated hydrocarbons of the aliphatic series from the standpoint of occupational hygiene. Arch Hyg Bakteriol 116:132-200. (some tables illegible)

The pdf of the above was available for review.

2. Name and address of research institution:

The Wurzburg Hygiene Institute, Wurzburg, Germany

3. Is there evidence that this study was subject to independent ethical review, by an Institutional Review Board (IRB) or equivalent?

This study predates a modern process for ethical review of studies.

4. Is there evidence to indicate the research institution subscribed to an appropriate standard of ethical research conduct?

The authors did not mention particular ethical standards for their research. Therefore, a temporally appropriate and critical evaluation of their experimental methods and self-experimentation was based on the Nuremberg Code under Item 5 below. The Nuremberg Code has ten basic principles ([Ghooi, 2011](#)): (1) voluntary consent of human subjects to participate, (2) experiment must be designed to benefit society, (3) experiment must be designed and based on results of animal research, (4) experiment must be designed to avoid all unnecessary physical and mental suffering and injury, (5) no experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects, (6) degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem, (7) proper preparations and adequate facilities must be provided to protect the experimental subject against even remote possibilities of injury, disability, or death, (8) experiment should be conducted by scientifically qualified persons, (9) subjects should be at liberty to withdraw from the experiment if they reach a physical or mental state where continuation of the experiment seems to be impossible, and (10) scientist in charge must be prepared to terminate the experiment at any stage, if they have probable cause to believe that continuation of the experiment is likely to result in injury, disability, or death to an experimental subject.

5. Provide information about the study methodology and treatment of human subjects.

Description of experimental studies design and conduct

Human investigations were conducted by commission of the German Society for Occupational Hygiene from 1928 to 1933. Prior to the experiments, the use of chlorinated hydrocarbons of the aliphatic series had undergone a very strong increase in the world. A common feature of the aliphatic series of chlorinated hydrocarbons was their usefulness as solvents for fats, resins, essential oils, and many other substances. All of them are colorless, nearly water-insoluble liquids of highly differing boiling points. All of them have a narcotic effect on humans as vapors and besides this, some of them unmistakably have a strong local irritating effect. The narcosis usually disappears after a brief period in the open air, and secondary diseases and death are observed after cases of acute, severe intoxication, at times after apparent recovery.

In 1903-1910, K.B. Lehmann and his students performed studies on cats of the quantitative effect of precisely measured air-gas mixtures containing chlorinated hydrocarbons. All solvents used for their investigations were supplied by the I.G. Farbenindustrie A.G., Ludwigshafen on Rhine, in the purest commercial grade. Before each experiment, Dr. Lehman and/or his students subjected solvents to additional purification by fractional distillation. Solvents were evaporated and mixed with a side stream of air to create “a stream of poisonous air” whose stable concentration was administered to an animal chamber. After four air exchange times, two animals were introduced into the chamber. The solvent concentration in the chamber was both calculated and measured. Because animals absorbed the solvents through their skin and respiration, calculated concentrations were lower than those measured.

The animal symptoms were uniform for all the chlorinated hydrocarbons, narcosis predominated, accompanied by symptoms of irritation, and changes in the respiration frequency. In order of severity, nervous symptoms were: (a) unsteadiness, (b) totally unable to stand, (c) mild narcosis (either cornea or extremity reflex remained present), (d) deep narcosis (both cornea and extremity reflex were absent). Immediately following removal from the chamber, rectal body temperature was measured in cats with deep narcosis. The animals were then observed in the experimental room until: (a) the corneal and toe reflexes had been restored, (b) they were standing on their own, and (c) they were able to walk about again. Subsequently, they were placed in heated cages. The follow-up observations lasted at least 8 days. Any of the animals that died underwent macroscopic sections. Table 30 (p. 20) reports results of microscopic exams for animals that died after exposures to carbon tetrachloride. For some solvents, eight-hour workday exposures over a full a month were conducted to determine concentrations causing no unequivocal changes in the behavior of the animals.

“The [brief human] experiments were performed in small chambers of known volume, in which a weighed amount of poison had been finely sprayed at the start of the experiment. With good mixing of the air, the poison content of the air was always determined simultaneously by chemical means and the behavior of the subjects (usually two) was recorded.” The solvent concentration for half-hour human exposures to *trans*-1,2-dichloroethylene was selected to cause discomforting effects on human subjects but already found to have caused no distinct narcotic effect in animals following 8-hour exposures. From Table 32, the odor threshold and level causing an unpleasant effect for *trans*-1,2-dichloroethylene in humans were 1.1 and 8.8 mg/liter, respectively. Table 34 (p. 30, only partially legible) reports self-experimentation results of two doctoral candidates³ (Esche and

³ Description as “two doctoral candidates” from p. 10 of AEGL for 1,2-Dichloroethylene ([U.S. EPA, 2022](https://www.epa.gov/assessing-and-managing-chemical-hazard-initiatives/assessing-chemical-hazard-initiative-12-dichloroethylene)).

Schwarzweiler) to *trans*-1,2-dichloroethylene including mild burning of eyes and nausea, each of which persisted for a half hour after exposure. More extreme effects were noted for acute (<5 minutes) human exposures to carbon tetrachloride which ranged from slight drowsiness to formication in hands followed by loss of consciousness. For dichloroethylene, Drs. Lehmann and Schmidt-Kehl noted that, "It would be of particular interest to perform chronic tests on humans for which the means are presently unavailable to us. Observations of factory practice where no doses, often no analyses of the substances used, and no exact exposure times are known are no substitute for this; we have found no volunteers for this purpose among the students."

Evaluation of experiments alignment with the Nuremberg Code

Details related to the experimental animal and human studies material to compare to the Nuremberg Code were discussed above. In the below, the ten elements of the Nuremberg Code are specifically named, followed by a description of the study's consistency or lack of consistency with that element. Overall, as described below the experiments appeared to have adequate safeguards for brief 30-minute human exposures, the exposures levels were concentrations not having a distinct narcotic effect in animals after 8-hour exposures, the self-experimentation appeared to be voluntary (i.e., not coerced), and the societal benefit likely exceeded the risk to volunteers. These aspects suggest that the human experiments were conducted in an appropriately ethical manner.

- (1) Voluntary consent – Drs. Lehmann and Schmidt-Kehl noted that it would be of particular interest to perform chronic tests on humans, but "...we have found no volunteers for this purpose among the students." This suggests that the self-experimentation of investigators and some students was voluntary. Otherwise, it might be expected that students may have been coerced into participating in chronic experiments.
- (2) Benefit to society – With the growing usage of chlorinated hydrocarbons around the world, an evaluation of differences in acute risks from exposure could be key to decisions related to which solvents might be preferable to use.
- (3) Foundation in animal research – The investigators had conducted years of animal research with evaluated outcomes ranging from unsteadiness (off balance) to death. The solvent concentration for half-hour human exposures to *trans*-1,2-dichloroethylene was selected to cause discomforting effects on human subjects but already found to have caused no distinct narcotic effect in animals following 8-hour exposures.
- (4) Avoidance of injury – Exposures of humans followed years of animal research. The human participants knowingly accepted risks of acute physical suffering and injury. Two participants were usually exposed at the same time in the chamber. This helped to ensure consistent responses and by comparison between the subjects which avoided unanticipated severe responses. Precautions were in place to remove participants quickly from the exposure chamber.
- (5) No expectation of fatal human outcomes – The solvent concentration for half-hour human exposures to *trans*-1,2-dichloroethylene was selected to cause discomforting effects on human subjects but already found to have caused no distinct narcotic effect in animals following 8-hour exposures. Although there was not an explicit probation of self-experimentation in the Nuremberg Code, paternalism might have been advised to prevent allowing exposures to the point of unconsciousness which was a questionable ethical decision and unnecessary risk on the part of the investigators and participants. However, the investigators well recognized the risk and did not downplay the seriousness of the exposure, frequently referring to it as "poisonous air."
- (6) Degree of risk versus benefit – The study posed a known risk of acute discomfort which may persist for hours following exposure. The benefit of participants was the publication of their results. The societal benefit was discussed under Item 2 above.

- (7) Adequate preparation and adequate facilities – There was adequate preparation for studies in facilities which were adequate for their intended purpose.
- (8) Qualified personnel – The investigators and their students had years of experience working with animals exposed to various chlorinated hydrocarbons and recording the effects of the exposures.
- (9) Right to withdraw from study – There is no criteria to evaluate this right other than involvement appeared voluntary.
- (10) Duty to terminate study due to imminent threat – Perhaps due to the investigators experience and preparation, there was no discussion of the investigators willingness or need to terminate studies.

H.3.2 Other Considerations

Data used for developing Acute Exposure Guideline Levels (AEGLs) must be developed in accordance with ethical standards. From the below, it is implied that the ethical conduct of Drs. Lehmann and Schmidt-Kehl was considered adequate for the use of their data in the development of AEGLs.

From the “Standing operating procedures for developing acute exposure guideline levels (AEGLs) for hazardous chemicals,” [NRC \(2001\)](#), p. 53: “Although human data may be important in deriving AEGL values that protect the general public, utmost care must be exercised to ensure first of all that such data have been developed in accordance with ethical standards. No data on humans known to be obtained through force, coercion, misrepresentation, or any other such means will be used in the development of AEGLs.”

The [Lehmann and Schmidt-Kehl \(1936\)](#) human study results are basis, in whole and in part, for the 2008 AEGLs for *trans*-1,2-Dichloroethylene ([U.S. EPA, 2022](#)). Specifically, the AEGL-1 (nondisabling) was based wholly on ocular irritation in humans, the AEGL-2 (disabling) was based in part on anesthetic effects in humans, and the AEGL-3 (lethality) was based in part on nausea, intracranial pressure, and dizziness in humans from [Lehmann and Schmidt-Kehl \(1936\)](#).

H.4 Overall Conclusion

There was no clear and convincing evidence that the study was fundamentally unethical or significantly deficient with respect to the ethical standards prevailing when the research was conducted.

H.5 References

- [Ghooi, RB.](#) (2011). The Nuremberg Code - A critique. PICR 2: 72-76.
<https://hero.epa.gov/reference/13283289/>
- [Lehmann, KB; Schmidt-Kehl, L.](#) (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116: 131-268.
<https://hero.epa.gov/reference/29046/>
- [NRC.](#) (2001). Standing operating procedures for developing acute exposure guideline levels (AEGLs) for hazardous chemicals. Washington, DC: National Academies Press.
<https://hero.epa.gov/reference/192042/>
- [U.S. EPA.](#) (2022). *trans*-1,2-Dichloroethylene results - AEGL Program. Available online at <https://hero.epa.gov/reference/10366916/>

Appendix I LIST OF SUPPLEMENTAL FILES FOR TSD

Below is a list of supplemental files associated with this technical support document (TSD). All of these files are available as part of the package for SACC review on the peer review docket ([EPA-HQ-OPPT-2026-2246](#)). Charge questions for *trans*-1,2-dichloroethylene will be included among questions for other chemicals undergoing peer review at the same meeting and will be made available on the docket ahead of the meeting.

Systematic Review Files

Data Quality Evaluation Information for Human Health Hazard Epidemiology for trans-1,2-Dichloroethylene ([U.S. EPA, 2026n](#))

Data Quality Evaluation Information for Dermal Absorption for trans-1,2-Dichloroethylene ([U.S. EPA, 2026l](#))

Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for trans-1,2-Dichloroethylene ([U.S. EPA, 2026m](#))

Data Quality Evaluation Information for Environmental Hazard for trans-1,2-Dichloroethylene ([U.S. EPA, 2026e](#))

Data Extraction Information for Environmental and Human Health Hazard Animal Toxicology and Epidemiology for trans-1,2-Dichloroethylene ([U.S. EPA, 2026c](#))

Supplemental Assessment Files

Draft Benchmark Dose Modeling Results for trans-1,2-Dichloroethylene ([U.S. EPA, 2026a](#))

Draft Mammalian Reference Value (TRV) Calculator for trans-1,2-Dichloroethylene ([U.S. EPA, 2026g](#))

Draft Tool Settings and Analog List for Environmental Hazard Assessment for trans-1,2-Dichloroethylene ([U.S. EPA, 2026j](#))

Draft Dermal Absorption Calculations for trans-1,2-Dichloroethylene ([U.S. EPA, 2026f](#))