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Draft Hazard Assessment for Ethylene Dibromide
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KEY ABBREVIATIONS AND ACRONYMS

ACR	Acute-to-chronic ratio
ADAF	Age-dependent adjustment factor
ADME	Absorption, distribution, metabolism, and elimination
AIC	Akaike Information Criterion
AOP	Adverse outcome pathway
ATSDR	Agency for Toxic Substances and Disease Registry
BICc	Bayesian Information Criterion
BMC	Benchmark concentration
BMCL	Benchmark concentration lower 95% confidence limit
BMD	Benchmark dose
BMDL	Benchmark dose lower 95% confidence limit
BMR	Benchmark response
CA	Chromosomal aberrations
CARB	California Air Resources Board
CASRN	Chemical Abstracts Service Registry Number
CDNB	1-Chloro-2,4 dinitrobenzene
CDR	Chemical Data Reporting
ChV	Chronic value
CI	Confidence interval
CMG	S-carboxymethyl glutathione
COC	Concentration(s) of concern

450	COU	Condition of use
451	CT	Central tendency
452	CYP	Cytochrome P450
453	DDEF	Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors
454		for Interspecies and Intraspecies Extrapolation
455	EC50	Effective concentration (concentration that induces a biological response to 50% of test
456		organisms)
457	EPA	Environmental Protection Agency (U.S.)
458	FAA	Federal Aviation Administration (U.S.)
459	GD	Gestational day
460	GSH	Glutathione
461	GST	Glutathione <i>S</i> -transferase
462	HAWC	Health Assessment Workplace Collaborative
463	HC05	Hazard Concentration (protective of 95% of the species in the sensitivity distribution)
464	HE	High-end
465	HEC	Human equivalent concentration
466	HED	Human equivalent dose
467	IARC	International Agency for Research on Cancer
468	IUR	Inhalation unit risk
469	IVIVE	<i>In vitro</i> to <i>in vivo</i> Extrapolation
470	LC50	Lethal concentration (concentration that is lethal to 50% of test organisms)
471	LD50	Lethal dose (dose that is lethal to 50% of test organisms)
472	LT50	Lethal time (time when 50% of test organisms died)
473	LOAEC/L	Lowest-observed-adverse-effect concentration/level
474	LOEC/L	Lowest-observed-effect concentration/level
475	MFO	Mixed function oxidases
476	MIE	Molecular initiation event
477	MOA	Mode of action
478	MOE	Margin of exposure
479	MRL	Minimal risk level
480	MTD	Maximum tolerated dose
481	NAD+	Nicotinamide adenine dinucleotide
482	NADPH	Nicotinamide adenine dinucleotide phosphate
483	NCI	National Cancer Institute
484	NIOSH	National Institute for Occupational Safety and Health
485	NOAEC/L	No-observed-adverse-effect concentration/level
486	NOEC/L	No-observed-effect concentration/level
487	NTP	National Toxicology Program
488	OCSPP	Office of Chemical Safety and Pollution Prevention (EPA)
489	OECD	Organisation for Economic Co-operation and Development
490	OES	Occupational exposure scenario
491	OEHHA	Office of Environmental Health Hazard Assessment (California)
492	OPPT	Office of Pollution Prevention and Toxics (EPA)
493	OR	Odds ratio
494	OSF	Oral slope factor
495	OQD	Overall quality determination
496	PBPK	Physiologically-based pharmacokinetic
497	PECO	Population, exposure, comparator, and outcome
498	PESS	Potentially exposed and susceptible subpopulations

499	POD	Point of departure
500	PPE	Personal protective equipment
501	Q-Q	Quantile-quantile
502	QSAR	Quantitative structure-activity relationship
503	RfC	Reference concentration
504	RfD	Reference dose
505	RGDR	Regional gas dose ratio
506	ROS	Reactive oxygen species
507	SCE	Sister chromatid exchange
508	SSD	Species sensitivity distribution
509	STIR	Screening Tool for Inhalation Risk
510	TSCA	Toxic Substances Control Act
511	TWA	Time-weighted average
512	UF	Uncertainty factor
513	U.S.	United States
514	VOC	Volatile organic compound
515	Web-ICE	Web-based Interspecies Correlation Estimation

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Docket

Supporting information can be found in the public docket, Docket ID: [EPA-HQ-OPPT-2026-2246](#) and [EPA-HQ-OPPT-2018-0488](#).

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SUMMARY

This technical support document (TSD) is part of the Toxic Substances Control Act (TSCA) *Draft Risk Evaluation for Ethylene Dibromide* (also called the “draft risk evaluation”) ([U.S. EPA, 2026h](#)). EPA considered all reasonably available information identified through its systematic review process under TSCA to characterize environmental and human health hazard endpoints for ethylene dibromide.

Human Health Hazard

Upon evaluating the reasonably available information to characterize non-cancer and cancer hazards associated with exposure to ethylene dibromide, points of departure (PODs) were derived from oral and inhalation exposure data from animal studies. The PODs were used to estimate risks from ethylene dibromide exposure for acute, intermediate, and chronic exposure scenarios in the draft risk evaluation. Evidence integration identified cancer effects—primarily from animal studies—via all major routes of exposure, as well as the following four categories of non-cancer health effects that are critical and were used for dose response analysis in ethylene dibromide exposure as described in Sections 2.3.1.1 through 2.3.1.4.4: reproductive/developmental, hepatic, gastrointestinal, and respiratory. The reproductive/developmental health outcomes included male reproductive, female reproductive, and fetal-developmental adverse effects. EPA determined that ethylene dibromide “is likely to be carcinogenic to humans,” with robust evidence across all evidence streams for multi-site cancers, and the weight of scientific evidence conclusions support a mutagenic mode of action (MOA). This classification is consistent with the carcinogenicity evaluations conducted by other authoritative bodies ([National Toxicology Program \(NTP\), 2016](#); [NICNAS, 2013](#); [U.S. EPA, 2004b](#); [IARC, 1999](#)). No suitable human dose-response data were available for any duration or route of exposure. Therefore, EPA derived preliminary human equivalent concentrations (HECs) and human equivalent dose (HEDs) as appropriate from sensitive animal studies to approximate human hazard values.

Ethylene dibromide is rapidly absorbed via the oral route of exposure, followed by absorption from the gastrointestinal tract and distribution to the liver, where metabolism predominantly occurs ([Hissink et al., 2000](#)). Oral absorption has been found to be approximately 100% across several species, lending support that animal studies may serve as a reasonable model for human exposure ([U.S. EPA, 2004b](#)). Inhalation studies also found systemic absorption and widespread distribution of ethylene dibromide following exposure, where studies in rats report 50% absorption via the respiratory tract ([Stott and Mckenna, 1984](#)). Although dermal absorption has not been quantified, topical application in guinea pigs results in rapid increase of ethylene dibromide concentration in blood ([Jakobson et al., 1982](#)). Animal studies have identified that ethylene dibromide metabolism involves two competing pathways: an oxidative route catalyzed by cytochrome P450 (CYP) and a conjugative route mediated by glutathione S-transferases (GSTs). These metabolic pathways are consistent across exposure routes, indicating similar metabolism following oral and inhalation exposure once systemic absorption occurs. Elimination occurs primarily via the formation of mercapturic acids in the kidneys.

EPA performed dose-response analysis for multiple non-cancer endpoints for inhalation studies under each hazard domain. Fetal malformation and late resorptions were selected as the most robust and sensitive inhalation endpoint for use in risk characterization of acute and intermediate exposures, with a HEC of 20 ppm (150 mg/m³); these represent the best available science. The only endpoint available for dose-response analysis for characterizing intermediate oral exposure that was of sufficient quality was cell proliferation and hyperkeratosis in the forestomach ([Ghanayem et al., 1986](#)). Cell proliferation and hyperkeratosis may be analogous to hyperplasia—a possible precursor to cancer in humans. The HED derived from benchmark dose (BMD) modeling was 2.7 mg/kg/day. Due to a lack of suitable dose-response studies with acute durations, this value was also used as the POD for acute oral exposures because intermediate toxicity values generally are protective of acute exposures ([U.S. EPA, 2002a](#)).

The forestomach is a rodent-specific structure lined with squamous epithelium and is not present in humans. Rodents also possess a glandular stomach, which is more closely comparable to the human stomach due to its specialized mucosal epithelium involved in secretion of gastric enzymes and acid. Even though effects observed in the rodent forestomach are not assumed to be directly relevant to humans, they may be reconsidered when supported by MOA evidence. While effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case it was being examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. Proctor et al. (2007) provides three criteria that determine human health relevance of forestomach tumors observed in rodent studies: (1) well-established genotoxicity, (2) its ability to induce tumors at multiple sites across a range of doses, and (3) the observation that these effects occur in the absence of forestomach irritation. Ethylene dibromide meets these criteria, which suggests forestomach effects are relevant to the cancer assessment because it is likely to cause cancer via oral exposure in humans, despite the anatomical differences in rodents.

Both chronic oral and inhalation studies showed hepatic endpoints, including peliosis and necrosis, as the most robust and sensitive non-cancer endpoints, where calculated human equivalent values are 3.3 mg/kg/day and 1.5 ppm (11 mg/m³), respectively.

EPA derived an inhalation, multi-tumor unit risk (IUR) of 0.68 per ppm (8.9×10^{-5} per $\mu\text{g}/\text{m}^3$) for humans based on animal data. An oral (multi-tumor) slope factor (OSF) of 0.24 per mg/kg/day was also derived based on animal data. The adult inhalation unit risk to be used for occupational and consumer scenarios is 0.43 per ppm (5.6×10^{-5} per $\mu\text{g}/\text{m}^3$). The adult oral slope factor to be used for occupational and consumer scenarios is 0.15 per mg/kg/day.

Due to a lack of empirical data, to characterize human health hazard resulting from dermal exposure to ethylene dibromide, EPA conducted route-to-route extrapolation using two methodologies in a tiered manner to derive dermal human equivalent doses for non-cancer and cancer endpoints. As described in Section 2.4.7.4, the default route-to-route approach (based on allometric scaling) was used first to derive an acute/intermediate dermal HED of 28 mg/kg/day from inhalation data. Chronic dermal HEDs of 2.2 mg/kg/day and 3.3 mg/kg/day were also derived through route-to-route extrapolation using the default approach, from inhalation and oral data, respectively. A dermal multi-tumor cancer slope factor was calculated to be 0.48 per mg/kg/day through route-to-route extrapolation. The adult dermal cancer slope factor to be used for occupational and consumer scenarios is 0.30 per mg/kg/day.

Additionally, a more refined dermal exposure was estimated by using a physiologically-based pharmacokinetic (PBPK) modeling-based route-to-route extrapolation. An existing PBPK model (Hissink et al., 2000) was modified to include a flux-based dermal exposure route to derive dermal equivalent doses from rat oral and inhalation PODs. PBPK modeling provides an enhanced, scenario-specific basis for dermal risk evaluation. This mechanism-based, route-to-route extrapolation defined human equivalent dermal exposures as a function of ethylene dibromide surface concentration (potency) as well as contact volume and time. The approach accounts for real-world factors such as finite residues, evaporation of ethylene dibromide, and variable exposure patterns. The PBPK analysis indicates that a mass-only metric may be insufficient for dermal risk evaluation, and achieving exposures equivalent to animal toxicity PODs would require concentrations high enough to sustain systemic exposure via skin absorption. Moreover, at lower concentrations typical of some condition of use (COUs) under TSCA and exposure scenarios, deriving meaningful HEDs was not feasible. The same chronic oral and inhalation toxicity studies were used for the default and PBPK modeling-based route-to-route extrapolations. The PBPK-based human equivalent dermal exposure estimates are specific to

COU/occupational exposure scenario (COU/OES) and were generally higher than those estimated by the lower-tier, default approach using route-to-route extrapolation.

To be consistent with the exposure metrics, all dermal HEDs are reported as retained doses. A retained dose is defined as the amount of dose that has permeated into the skin (*i.e.*, the part of the dose that has not evaporated or washed off). An applied dose is defined as the total amount of the chemical that comes in contact with the skin (*i.e.*, the total potential exposure). Retained and applied doses are both considered external doses in this case and not to be confused with the term “internal dose” seen throughout this draft TSD, which is defined as the concentration or amount of a substance that is associated with a hazardous effect in the target tissue (and is the metric, or internal dose metric, by which hazard is assessed). Thus, dermal HEDs report the dose of chemical that must get into the skin (retained dose) in order to reach the internal dose of hazard. For the purposes of this preliminary assessment, the internal dose metric associated with hazard is the amount of ethylene dibromide metabolized in the liver through the GST pathway per liter liver (as described in Section 2.2.5.2).

For endpoints used to estimate human health risk, EPA has (1) slight-to-moderate overall confidence in the assessments for non-cancer acute and intermediate PODs selected based on reproductive/developmental and gastrointestinal toxicological endpoints, and (2) robust overall confidence for the non-cancer chronic POD selected based on hepatic endpoints. Additionally, EPA has robust overall confidence in the assessment for all cancer endpoints selected. These confidence ratings are based on the weight of scientific evidence and include consideration of potentially exposed and susceptible subpopulations (PESS).

Non-Cancer Hazard

EPA identified hepatic effects as the most sensitive and robust non-cancer hazard associated with both chronic oral and inhalation exposure to ethylene dibromide in experimental animal models based on the best available science (Section 2.3.1.2). Previous assessments of ethylene dibromide have also identified hepatic effects as the most sensitive and robust non-cancer effect following chronic exposure to ethylene dibromide, citing the same references EPA selected for POD determination ([ATSDR, 2018](#); [U.S. EPA, 2004b](#)). The Agency also considered epidemiologic evidence qualitatively as part of hazard identification and characterization. However, epidemiologic evidence for ethylene dibromide was not considered quantitatively due to limitations and uncertainties in exposure characterization. Qualitative use of epidemiologic evidence is consistent with existing assessments and TSCA requirements regarding the weight of scientific evidence.

For each exposure route, a single POD was determined to be relevant for both acute and intermediate durations. Based on the strengths, limitations, and uncertainties discussed in Sections 2.5.1.1 and 2.5.1.2, EPA reviewed the weight of scientific evidence and has slight (acute duration) and moderate (intermediate duration) overall confidence in the values derived for risk estimation.

For intermediate inhalation, EPA identified data from Short ([1978](#)) as the basis for POD determination. Fetal malformation and late resorptions were selected as the most robust inhalation endpoint for use in risk characterization of intermediate exposures, with an HEC of 20 ppm (150 mg/m³), and represent the best available science. Because the effect was on fetal development and the window of susceptibility is not known, this POD was also applied to acute inhalation exposures. Default route-to-route extrapolation was used to derive acute and intermediate dermal HEDs of 28 mg/kg/day from inhalation data.

For the intermediate oral POD, EPA selected Ghanayem (1986) as a basis for POD determination. Forestomach epithelial cell proliferation and hyperkeratosis was selected as the basis for the POD used for characterizing risk from exposure to ethylene dibromide due to the severity of outcomes and the progression to tumors seen after longer dosing regimens. Due to a lack of suitable dose-response studies with acute durations, this value was also used as the POD for acute oral exposures as well, because intermediate toxicity values should be protective of acute exposures (U.S. EPA, 2002a). Although effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case these effects were examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. The only endpoint available for dose-response analysis for oral exposure that was of sufficient quality was cell proliferation and hyperkeratosis in the forestomach (Ghanayem et al., 1986). Cell proliferation and hyperkeratosis may be analogous to hyperplasia—a possible precursor to cancer in humans. The HED from benchmark dose modeling was calculated to be 2.7 mg/kg/day.

For chronic oral exposure, EPA identified data from the National Cancer Institute (NCI, 1978) as the basis for POD determination. At 38 mg/kg/day, co-critical effects of liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy were identified in rats. The chronic inhalation study utilized for POD determination of non-cancer endpoints describes similar hazards (NTP, 1982): at 10 ppm ethylene dibromide inhalation exposure in rats, the critical effect of liver necrosis was identified. At 38 mg/kg/day, co-critical effects of liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy were identified in rats. The calculated human equivalent values for chronic inhalation and oral, are 1.5 ppm (11 mg/m³) and 3.3 mg/kg/day, respectively. Chronic dermal HEDs of 2.2 mg/kg/day and 3.3 mg/kg/day were also derived through route-to-route extrapolation using the default approach, from inhalation and oral data, respectively.

In conducting the default route-to-route extrapolation, the Agency has converted all PODs to HEDs (using ³/₄-body weight scaling) or HECs (by adjusting to continuous exposure and applying a regional gas dose ratio [RGDR]). This justifies the use of an animal-to-human uncertainty factor (*i.e.*, interspecies variability; UF_A) of 3. The within-human variability uncertainty factor (*i.e.*, intraspecies variability; UF_H) was set at 10. Thus, a total uncertainty factor (UF) of 30 is applied for use as the benchmark margin of exposure (MOE)—except when the HEC was based on a lowest-observed-adverse-effect concentration (LOAEC) instead of a benchmark concentration lower 95% confidence limit (BMCL), where an additional LOAEC-to-NOAEC (no-observed-adverse-effect concentration) uncertainty factor (UF_L) of 3 was included. In these cases, the total uncertainty factor (UF) of 100 is applied for use as the benchmark MOE. For the PBPK-based route-to-route extrapolation, a UF of 3 was used to address interspecies differences in toxicodynamics, while interspecies differences in toxicokinetics were addressed by PBPK modeling.

To address within-human variability, a UF of 10 was used to cover differences in toxicokinetics and toxicodynamics. For PBPK-based route-to-route extrapolation, EPA used an intermediate rat inhalation study where a NOAEC was not identifiable (Short et al., 1979). Thus, an additional UF_L of 3 was included, resulting in a total uncertainty factor of 100 to set the benchmark MOE. The chronic dermal PODs were derived using the same references as those used for the default route-to-route extrapolation.

The seventh column in Table S-1 below includes the benchmark MOE, which represents the total uncertainty factor for the corresponding non-cancer POD. In general, the benchmark MOE was 30 for all endpoints except for acute and intermediate inhalation, where the benchmark MOE was 100. This corresponds to UF_A of 3, UF_H of 10, and a UF_L of 3 for acute and intermediate inhalation since an

LOAEC was used for the POD. Because the acute and intermediate dermal PODs were derived from inhalation-to-dermal route-to-route extrapolation, the benchmark MOE of 100 was used.

Cancer Hazard

EPA identified multi-site carcinogenic effects associated with chronic oral, inhalation, and dermal exposure to ethylene dibromide based on evidence from experimental animal studies (Section 2.4.3). Existing assessments of ethylene dibromide also identified carcinogenic effect following oral, inhalation, and dermal chronic exposure to ethylene dibromide—including the development of tumors such as squamous cell carcinoma in the stomach and hemangiosarcoma. The International Agency for Research on Cancer classified ethylene dibromide as Group 2A (probable human carcinogen) in 1999 ([IARC, 1999](#)); EPA's Integrated Risk Information System (IRIS) Program classified ethylene dibromide as group B2 "probable human carcinogen" in 1988 and revised this to "likely to be carcinogenic to humans" in 2004 ([U.S. EPA, 2004b](#)); and the Australian Department of Health classified ethylene dibromide as Category 2, "may cause cancer", in 2013 ([NICNAS, 2013](#)).

Additional tumor types observed across multiple studies include adenomas and carcinomas in the nasal cavity; adenomas in the pituitary gland; hemangiosarcoma in the spleen; fibroadenomas in the mammary gland; and skin papillomas and papillary, alveolar or bronchiolar adenomas of the lung. EPA has robust confidence in cancer endpoints that are used for the draft risk estimation of ethylene dibromide.

For inhalation carcinogenicity, EPA selected NTP ([1982](#)) as the basis for POD determination. Carcinogenic effects were observed in male and female F344 rats and B6C3F1 mice, including increased incidences of carcinomas, adenocarcinomas, and adenomas of the nasal cavity in both sexes. Nasal cavity adenomatous polyps in male rats were selected as the basis for POD derivation due to their occurrence at exposure concentrations as low as 10 ppm (LOAEC). This inhalation POD of 10 ppm (LOAEC) was used for PBPK modeling. Respiratory tract tumors were seen in the oral ([NCI, 1978](#)) and dermal ([Van Duuren et al., 1979](#)) cancer studies. In the critical study in rats, there was a significant increase in non-respiratory tract tumors as well; for example, the incidence in male rats of mesotheliomas of the tunica vaginalis was 1/50 in the control (0 ppm), 8/40 in the low dose group (10 ppm), and 25/50 in the high dose group (40 ppm) ([NTP, 1982](#)).

For oral exposure, EPA selected NCI ([1978](#)) as a basis for POD determination for the cancer endpoint. At a dose of 38 mg/kg/day, significant increased incidences of forestomach squamous-cell carcinomas were observed in both male and female Osborne-Mendel rats, along with an increased incidence of hemangiosarcoma in male rats. EPA extrapolated oral POD to derive a dermal POD, using the oral study as the POD for dermal exposure assessment ([NCI, 1978](#)). This oral POD of 38 mg/kg/day was used for PBPK modeling.

Inhalation POD exposures were as converted to HECs by adjusting to continuous exposure and applying the RGDR. EPA converted oral POD doses to HEDs using body weight ³/₄-scaling. Inhalation POD exposures were as converted to HECs by adjusting to continuous exposure and applying the RGDR.

For inhalation carcinogenicity, the POD derived from HEC/BMDL (benchmark dose lower 95% confidence limit) modeling was used to estimate the IUR of 8.9×10^{-5} per $\mu\text{g}/\text{m}^3$ (0.68 per ppm). For oral cancer risk assessment, an OSF of 0.24 per mg/kg/day was applied. A dermal cancer slope factor (CSF) of 0.48 per mg/kg/day was derived from route-to-route extrapolation from inhalation to dermal. These cancer potency estimates include an age-dependent adjustment factor (ADAF) of 1.59 to account for increased susceptibility to those under the age of 16 (see Section 2.4.7.2 for derivation of the ADAF and incorporation into the slope factor and IUR values). ADAFs are applied based on the determination of a

787 mutagenic MOA (Section 2.4.6) and in accordance with ([U.S. EPA, 2005b](#)) for estimating risk to
788 children under the age of 16 in the general population. For occupational and consumer scenarios, where
789 all individuals being exposed are over the age of 16, adult slope factors were calculated without using an
790 ADAM as consistent with EPA guidance ([U.S. EPA, 2005b](#)). For inhalation, this is an adult inhalation
791 unit risk of 5.6×10^{-5} per $\mu\text{g}/\text{m}^3$ (0.43 per ppm). For oral, this is an adult OSF of 0.15 per mg/kg/day. For
792 dermal exposure, this is an adult dermal CSF of 0.30 per mg/kg/day.

793
794 EPA has robust confidence in cancer endpoints that are used for risk estimation (Table S-1). This
795 confidence rating is based on the weight of scientific evidence including consideration of PESS.

796 **Table S-1. Non-Cancer PODs, HECs, and HEDs Used to Estimate Human Health Risks for Ethylene Dibromide**

Target Organ System(s)	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Study	OQD ^c	POD Selection Confidence ^d
Acute and intermediate inhalation POD									
Reproductive/developmental	Mouse	24 hours/day, 10 days (starting GD 6)	LOAEC = 20 ppm/day	Fetal developmental abnormalities and increased late resorptions	HEC = 150 mg/m ³ (20 ppm)	100 (UF _A = 3, UF _H = 10, UF _L = 3)	Short et al. (1978)	High	Slight (acute duration) Moderate (intermediate duration)
Acute and intermediate oral POD									
Gastrointestinal	Rat	5 days/week, 2 weeks	LOAEL = 80 mg/kg/day	Forestomach epithelial cell proliferation and hyperkeratosis	HED = 2.7 mg/kg-bw/day	30 (UF _A = 3, UF _H = 10)	Ghanayem et al. (1986)	High	Slight (acute duration) Moderate (intermediate duration)
Acute and intermediate dermal POD									
Reproductive/developmental	Mouse	24 hours/day, 10 days (starting GD 6)	LOAEC = 20 ppm/day	Fetal developmental abnormalities and increased late resorptions	HED = 28 mg/kg/day (this is the default route-to-route extrapolation from the acute and intermediate inhalation PODs)	100 (UF _A = 3, UF _H = 10, UF _L = 3)	Short et al. (1978)	High	Slight (acute duration) Moderate (intermediate duration)
Reproductive/developmental	Rat	7 hours/day, 5 days/week, 10 weeks	LOAEC = 89 ppm/day	Testicular atrophy, lowered fertility	HE = 38–40 mg/kg/d (9–33 mL) CT = 43–45 mg/kg/d (24–100 mL) (This is a PBPK route-to-route extrapolation from the acute and intermediate inhalation PODs)	100 (UF _A = 3, UF _H = 10, UF _L = 3)	Short et al. (1979)	High	Slight (acute duration) Moderate (intermediate duration)
Chronic inhalation POD									
Liver	Rat	6 hours/day, 5 days/week, 2 years	LOAEC = 10 ppm	liver necrosis	HEC = 11 mg/m ³ (1.5 ppm)	30 (UF _A = 3, UF _H = 10)	NTP (1982)	High	Robust
Chronic oral POD									
Liver, adrenal, reproductive	Rat	5 days/week, 49 weeks	LOAEL = 38 mg/kg/day	liver peliosis, adrenal cortex degenerative	HED = 3.3 mg/kg-bw/day	30 (UF _A = 3, UF _H = 10)	NCI (1978)	Medium	Robust

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Target Organ System(s)	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Study	OQD ^c	POD Selection Confidence ^d
				lesions, and testicular atrophy					
Chronic dermal POD									
Liver	Rat	6 hours/day, 5 days/week, 2 years	LOAEC = 10 ppm	liver necrosis	BMDL = 2.2 mg/kg/day (This is the default route-to-route extrapolation from the chronic inhalation POD)	30 (UF _A = 3, UF _H = 10)	NTP (1982)	Medium	Robust
Liver	Rat	6 hours/day, 5 days/week, 2 years	BMDL = 9 ppm from LOEC = 10 ppm	liver necrosis	HE = 3.3–3.8 (1–3 mL) CT = 3.4–3.6 mg/kg/d (3–8 mL) (This is a PBPK route-to-route extrapolation from the chronic inhalation POD)	30 (UF _A = 3, UF _H = 10)	NTP (1982)	Medium	Robust
Liver, adrenal, reproductive	Rat	5 days/week, 49 weeks	LOAEL = 38 mg/kg/day	liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy	BMDL = 3.3 mg/kg/day (This is the default route-to-route extrapolation from the chronic oral POD)	30 (UF _A = 3, UF _H = 10)	NCI (1978)	Medium	Robust
Liver, adrenal, reproductive	Rat	5 days/week, 49 weeks	BMDL = 11 mg/kg/day From LOAEL = 11 mg/kg/d	liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy	HE = 5.5–5.7 mg/kg/d (1–5 mL) CT = 5.6–6 mg/kg/d (1–7 mL) (This is the PBPK route-to-route extrapolation from the chronic oral POD)	30 (UF _A = 3, UF _H = 10)	NCI (1978)	Medium	Robust
Cancer inhalation IUR ^e									
Cancer (inhalation IUR)	Rat	Low-dose animals: 5 days/week, 103 weeks High-dose males: 5 days/week, 88 weeks	10 ppm	Carcinomas, adenocarcinomas, adenomas of the nasal cavity	IUR = 8.9×10^{-5} (μg/m ³) ⁻¹ (0.68(ppm) ⁻¹) IUR (adult) = 5.6×10^{-5} (μg/m ³) ⁻¹ (0.43 [ppm] ⁻¹)	N/A	NTP (1982)	High	Robust

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Target Organ System(s)	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Study	OQD ^c	POD Selection Confidence ^d
		High-dose females: 5 days/week, 91 weeks							
Cancer oral OSF ^f									
Cancer	Rat	5 days/week, 49 weeks	38 mg/kg/day	Incidence of all primary tumors	OSF = 0.24 (mg/kg/day) ⁻¹ OSF (adult) = 0.15 (mg/kg/day) ⁻¹	N/A	NCI (1978)	Medium	Robust
Dermal CSF route-to-route extrapolation ^g									
Cancer	Rat	Low-dose animals: 5 days/week, 103 weeks High-dose males: 5 days/week, 88 weeks High-dose females: 5 days/week, 91 weeks	10 ppm	Carcinomas, adenocarcinomas, adenomas of the nasal cavity	IUR = 8.9E-05 (μg/m ³) ⁻¹ (0.68(ppm) ⁻¹) IUR (adult) = 5.6E-05 (μg/m ³) ⁻¹ (0.43(ppm) ⁻¹)	N/A	NTP (1982)	Medium	Robust

CSF = cancer slope factor; CT = central tendency; HE = high-end; HEC = human equivalent concentration; HED = human equivalent dose; IUR = inhalation unit risk; MOE = margin of exposure; NOAEL = no-observed-adverse-effect level; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level; CT = central tendency; HE = high-end estimate; BMDL = benchmark dose lower 95% confidence limit; OSF = oral slope factor; PBPK = physiologically-based pharmacokinetic; POD = point of departure; UF = uncertainty factor

^a HED/HEC values were derived in accordance with the appropriate guidance (HED ([U.S. EPA, 2011b](#)); HEC ([U.S. EPA, 1994](#))). Exposure values used in the critical study were converted to HED/HEC values and benchmark dose modeling (BMD) was performed for all endpoints except for acute and intermediate inhalation, where benchmark dose (BMD) modeling was not possible. More details on non-cancer HEC/HED derivation and BMD modeling in Section 2.3.2.5; more details on cancer HEC/HED derivation and BMD modeling in Section 2.4.7.2.

^b 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

^c Overall quality determination (OQD) is a rating that is reported for each health outcome per study that undergoes data quality evaluation. Section 2.1.1 provides a brief overview and lists the data quality evaluation and extraction supplemental files relevant for studies identified for the characterization of environmental and human health hazard. Full details regarding the systematic review process for all the identified studies are described in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)).

Target Organ System(s)	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Study	OQD ^c	POD Selection Confidence ^d
^d POD selection confidence is based on an evaluation of the identified POD and the confidence in the alignment of this POD with the assigned route/duration and any uncertainties associated with the POD being used for risk estimates (<i>e.g.</i> , route-to-route extrapolation, duration adjustment). These considerations are summarized in Section 2.5.1. ^e Cancer inhalation unit risk for ethylene dibromide based on nasal tumors in male and female rats from (NTP, 1982). ^f Cancer oral slope factor (OSF) for ethylene dibromide was based on incidence of primary tumors in male rats from (NCL, 1978). ^g Dermal cancer slope factor (CSF) was derived from the calculated IUR from (NTP (1982)) and extrapolated to the dermal route to derive the corresponding dermal slope factor.									

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Environmental Hazard

Upon evaluating the reasonably available information, environmental hazard thresholds were derived for aquatic vertebrates, aquatic invertebrates, terrestrial vertebrates, and terrestrial invertebrates used to estimate risks from ethylene dibromide environmental exposures in the draft risk evaluation of ethylene dibromide. Table S-2 summarizes the hazard thresholds determined for aquatic and terrestrial receptor groups, as well as the associated confidence for the respective hazard thresholds.

Aquatic Species: An acute aquatic concentration of concern (COC) for vertebrates and invertebrates was derived for ethylene dibromide from species sensitivity distributions (SSDs) that contained empirical and modeled 48- to 96-hour LC50s. The acute vertebrate SSD was based on 4 vertebrate species identified in systematic review as well as an additional 33 species with predicted lethal concentration to 50% of the test organisms (LC50) and effective concentration to 50% of the organisms (EC50) values from the Web-Based Interspecies Correlation Estimation (Web-ICE) (v4.0) toxicity value estimation tool ([Raimondo et al., 2010](#)). The acute invertebrate SSD was based on 4 invertebrate species identified in systematic review as well as an additional 48 species from Web-ICE. The acute COC for aquatic vertebrates was identified as 550 µg/L, while the acute COC for aquatic invertebrates was 190 µg/L. Because there was only one chronic vertebrate study and no chronic invertebrate studies with aquatic exposure to ethylene dibromide that received high- or medium-quality ratings, EPA used an acute-to-chronic ratio (ACR = 10) based on the chemical classification of ethylene dibromide and an assessment factor (assessment factor = 10) to derive the chronic COCs. The chronic aquatic vertebrate and invertebrate COCs are 43 and 36.1 µg/L, respectively.

Terrestrial Species: Wildlife mammalian hazard data were not reasonably available, so ecologically-relevant reproductive endpoints from laboratory rodent studies were used to derive an inhalation hazard value for terrestrial mammals. Empirical ethylene dibromide toxicity data for mice and rats were used to estimate acute and chronic inhalation hazard thresholds for terrestrial mammals of 150 and 77 mg/m³, respectively.

The avian hazard threshold for acute exposure to ethylene dibromide was derived by applying allometric scaling to reasonably available mammalian and avian toxicity data using the Screening Tool for Inhalation Risk (STIR) due to the lack of available empirical data for inhalation routes of exposure in avian taxa. Available empirical acute mortality data from rats (via inhalation and oral exposure) and Japanese quail (via oral exposure) were used as input parameters in the STIR model to estimate an acute inhalation LD50 (*i.e.*, lethal dose that is lethal to 50% of test organisms)) for Japanese quail. Specifically, empirical toxicological mortality data for Japanese quail exposed to ethylene dibromide via oral exposure, mortality data for rats resulting from acute oral exposure to ethylene dibromide, and acute inhalation mortality data for rats estimated from empirical data were used to estimate an acute mortality hazard threshold for Japanese quail of 2.0 µg/m³ for inhalation exposure to ethylene dibromide.

The terrestrial invertebrate hazard threshold for exposure to ethylene dibromide via inhalation was derived from SSD analysis. Specifically, a hazard threshold of 30 mg/m³ was derived for terrestrial invertebrates. EPA's rationale and weight of scientific evidence approach for selecting these hazard thresholds is described in Section 3.3.2.

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Table S-2. Environmental Hazard Thresholds Used to Derive Environmental Risk for Ethylene Dibromide

Receptor Group	Exposure Duration	Hazard Value	Effect	Assessment Factor	Hazard Threshold	Reference (Overall Quality Determination)	Hazard Threshold Confidence
Aquatic vertebrates	Acute	See Table_Apx E-1 and Table_Apx E-2	Mortality	N/A	550 µg/L ^b	SSD ^c (see Section 3.2.1.1)	Robust
	Chronic	4.3 mg/L ^a	Mortality	10	43 µg/L ^b	Kszos et al. (2003) (High) (see Section 3.2.3.2)	Slight
Aquatic invertebrates	Acute	Table_Apx E-1 and Table_Apx E-2	Mortality/ Immobility	N/A	190 µg/L ^b	SSD ^c (see Section 3.2.2.1)	Robust
	Chronic	3.61 mg/L ^a	Mortality	10	36.1 µg/L ^b	Kszos et al. (2003) (High) (see Section 3.2.4.1)	Slight
Terrestrial mammal (inhalation)	Acute	150 mg/m ³	Inhalation	N/A	150 mg/m ³	Short et al. (1978) (High)	Robust
	Chronic	77 mg/m ³	Inhalation	N/A	77 mg/m ³	NTP (1982) (High)	Robust
Terrestrial avian (inhalation)	Acute	See Table_Apx H-1 and Table_Apx H-2	Inhalation	N/A	2.0 µg/m ³	STIR ^d (see Section 3.3.1)	Slight
Terrestrial invertebrates	Acute	See Table_Apx E-6	Mortality	N/A	30 mg/m ³	SSD ^c (see Section 3.3.2)	Robust
^a Hazard value was obtained from an acute study. An acute-to-chronic ratio (ACR) of 10 was also used to derive the hazard threshold, and the units were converted to µg/L. ^b Hazard threshold for aquatic organisms is called a concentration of concern (COC). ^c Species sensitivity distributions (SSDs) were used to estimate aquatic vertebrate, aquatic invertebrate, and terrestrial invertebrate hazard thresholds. ^d Screening Tool for Inhalation Risk (STIR) was used to estimate avian inhalation hazard thresholds.							

1 INTRODUCTION

This draft TSD presents the preliminary human health hazard and environmental hazard assessments in support of the *Draft Risk Evaluation for Ethylene Dibromide* ([U.S. EPA, 2026h](#)) conducted under the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which amended TSCA on June 22, 2016. This law includes 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 ID: [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. Ethylene dibromide is one of the chemicals designated as a High-Priority Substance for risk evaluation.

Ethylene dibromide is a common name for the chemical substance 1,2-dibromoethane (CASRN 106-93-4), which is a colorless and sweet-smelling volatile organic chemical (VOC). It has an annual total production volume in the United States of less than 1 million pounds (lb) as reported in the most recent Chemical Data Reporting (CDR) for the 2024 reporting year ([U.S. EPA, 2026a](#)). Ethylene dibromide may be released during industrial activities, manufacturing (including import activities), and disposal, with most releases occurring into air. The main use of ethylene dibromide is in fuels and related products (*i.e.*, lead scavenger) in commercial and consumer leaded aviation fuel to prevent engine fouling ([U.S. EPA, 2026b](#)). Lead is added to aviation gasoline (“avgas”) to increase the octane level and prevent engine knock ([Wells and Wells, 2014](#)). The form of lead added to avgas is tetraethyllead ([Wells and Wells, 2014](#)). When burned in an internal combustion engine, the tetraethyllead reacts with oxygen to form lead oxide ([Shell Global, 2025](#)). Ethylene dibromide added to the fuel rapidly reacts at engine temperatures and pressures in the gas phase to form lead bromide, which is sufficiently volatile to exist as a gas at the temperature that the engine operates at, facilitating the elimination of lead from the engine via the exhaust ([Shell Global, 2025](#)). In the absence of ethylene dibromide or a similar compound, internal combustion engines fueled with leaded gasoline would foul with the buildup of lead oxide deposits that may cause subsequent engine damage ([Shell Global, 2025](#)).

In 1974, EPA mandated that lead content of fuels be reduced, and by 1996, lead and lead scavengers, including ethylene dibromide, were largely removed from conventional automobile fuels—only remaining in avgas and certain racing fuels ([U.S. EPA, 2008](#)) for which suitable alternatives are not widely available. Airplanes used in general aviation have a significantly longer time-in-service compared to automobiles (>50 years vs. 12 years on average), meaning that a substantial fraction of older airplane engines are still in service and require compatible fuel to continue operation ([Moran, 2024](#)). The Eliminate Aviation Gasoline Lead Emissions (EAGLE) initiative, a partnership between the Federal Aviation Administration (FAA) and industry, is currently seeking to eliminate leaded aviation fuels in piston-engine aircraft by the end of 2030 (2032 for the Alaskan market). Furthermore, outreach confirmed that the industry is looking to transition away from use of ethylene dibromide in aviation fuel by 2035 (FR 2026-00296). In addition to the use as a leaded fuel additive, ethylene dibromide has also historically used as a pesticide. Many pesticidal uses of ethylene dibromide as an active ingredient were banned in 1983 (*e.g.*, spot fumigation of grain mills), with minor low volume pesticidal uses allowed to continue until 1984 (*e.g.*, garment fumigant) where human exposure would be limited by the use of protective clothing, use of applicators, reinforcement of label directions and other low-cost measures designed to reduce applicator exposure to ethylene dibromide ([U.S. EPA, 1983](#)). However, there are currently no active registrations of pesticides with ethylene dibromide used as an active ingredient. (Note that “any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act [7 U.S.C. 136 et seq.]) when manufactured, processed, or distributed in commerce for use as a pesticide” is

excluded from the definition of “chemical substance” subject to regulation under TSCA, see 15 U.S.C. § 2602(2)(B)(ii).)

EPA’s process for considering and incorporating of reasonably available information for the characterization of environmental and human health hazard is described in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)). This draft human health hazard assessment/TSD includes EPA’s assessment of both non-cancer and cancer toxicity resulting from exposure to ethylene dibromide. The Agency’s approach and methodology for identifying and using human epidemiologic data and experimental laboratory animal data for the characterization of non-cancer and cancer effects are described in Sections 2.3 and 2.4, respectively. For the characterization of environmental hazard resulting from exposure to ethylene dibromide, EPA assessed the toxicity of ethylene dibromide to aquatic and terrestrial organisms as described in Sections 0 and 0, respectively.

2 HUMAN HEALTH HAZARD ASSESSMENT

2.1 Approach and Methodology

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

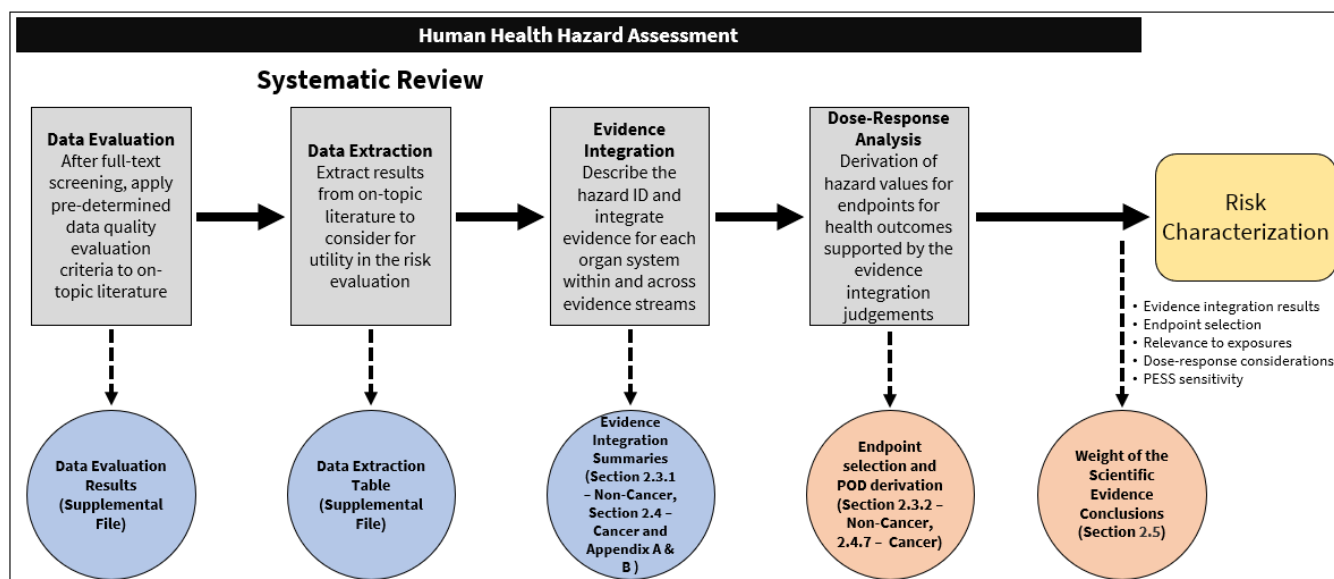


Figure 2-1. Approach for Human Health Hazard Identification, Evidence Integration, and Dose-Response Analysis for Ethylene Dibromide

2.1.1 Human Health Systematic Review

The searching and screening steps of the systematic review process for ethylene dibromide 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 April 2025. Full details and screening results for all the identified studies are described in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)).

For the consideration of all reasonably available information to characterize human health hazard, EPA first screened titles and abstracts and then full texts of potentially relevant data sources, if available, using population, exposure, comparator, and outcome (PECO) screening criteria. All studies that met human health hazard screening criteria were then evaluated for data quality using pre-established quality criteria and metrics, and relevant data were extracted. The data quality rating for each individual study is reported as an overall quality determination (OQD).

The results of data quality evaluation and extraction of data for the characterization of human health hazard are presented in the following supplemental files:

- *Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026f](#))
- *Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Ethylene Dibromide* ([U.S. EPA, 2026e](#))
- *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026e](#))

As described in Section 7 of the Draft Systematic Review Protocol ([U.S. EPA, 2021](#)) and Section 6 of the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)), evidence integration is the last step of systematic review, encompassing the consideration of the quality and relevance of the data while taking into account the strengths and limitations of the data to appropriately evaluate evidence presented in this technical support document.

EPA used the approach described below and in the identified documents to evaluate, extract, and integrate evidence for ethylene dibromide human health hazard and conduct dose-response modeling (Figure 2-1). This section provides an overview of the approach, which is based on the Draft Systematic Review Protocol ([U.S. EPA, 2021](#)), with any updates in the implementation of the systematic review processes presented in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)) and the *Framework for Human Health Risk Assessment to Inform Decision Making* ([U.S. EPA, 2014a](#)). Since the publication of the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)), and because ethylene dibromide studies were originally evaluated and extracted, EPA has continued to improve and refined the systematic review process—including how studies for human health assessment are prioritized for data evaluation and extraction (e.g., whether or not a study includes 3+ levels of exposure). Data evaluation and extraction are independent steps from data integration and applicability for the use of specific endpoints for quantitative (e.g., dose-response) analysis used for a specific chemical risk evaluation. The goal of data quality evaluation is to objectively review considerations regarding experimental design and the resulting measured and observed effects and is not the only consideration when determining which endpoints are candidates for quantitative analysis. This is because other chemical-specific considerations for a given (draft) risk evaluation should also weigh into the relevancy of the available endpoints for a specific exposure route and/or duration.

For the preliminary human health hazard assessment, EPA systematically reviewed data sources identified in the initial literature search conducted in September 2019 and the updated peer-review literature search conducted in April 2025. Following the initial and updated literature searches, EPA first screened titles and abstracts and then full texts for relevancy using PECO screening criteria. All epidemiology studies that met the PECO screening criteria—as well as inhalation, oral, and dermal animal toxicology studies that met the PECO screening criteria—were evaluated for data quality using pre-established quality criteria and metrics. The data quality rating for each study is reported as an OQD.

EPA relied primarily on studies with apical (phenotypic) endpoints to identify possible candidates for dose-response. Sub-organ level effects (referred to as “mechanistic effects”) generally did not formally undergo data quality evaluation or extraction. For this reason, the Agency has not developed such criteria for toxicokinetics data other than dermal absorption studies; however, mechanistic studies were considered and characterized as relevant below for each organ system in Sections 2.3 and 2.4. Additionally, EPA considered relevant genotoxicity studies.

The Agency gave greater weight to studies that received medium or high overall quality determination ratings for hazard identification, evidence integration, and dose-response analysis. Information from studies of low or uninformative quality was considered for hazard identification and evidence

integration to support the weight of scientific evidence as appropriate but were not used quantitatively for dose-response analysis.

After evaluating individual studies for data quality, EPA summarized hazard information by hazard outcome and considered the strengths and limitations of individual evidence streams (*i.e.*, human studies of apical [phenotypic] endpoints if available, animal toxicity studies with apical endpoints, and supplemental mechanistic information). The Agency integrated data from these evidence streams to arrive at an overall evidence integration conclusion for each health outcome category (*e.g.*, reproductive toxicity). When weighing and integrating evidence to estimate the potential that ethylene dibromide might cause a given human health hazard outcome, EPA uses several factors adapted from Nomura and Lieber (1981). These elements include consistency, dose-response relationship, strength of the association, temporal relationship, biological plausibility, and coherence, among other considerations. Section 2.3.1 presents hazard identification and evidence integration conclusions for key non-cancer outcomes. For the cancer assessment, Section 2.4.1 presents hazard identification.

Finally, EPA assigned confidence ratings for each human health hazard outcome chosen for acute, intermediate, and chronic exposure scenarios. These ratings considered evidence integration conclusions as well as additional factors such as relevance of the health outcome (and associated health effect[s]) to the exposure scenario (acute, intermediate, or chronic) and biological factors that increase susceptibility to ethylene dibromide human health hazards (*e.g.*, identification of susceptible subpopulations). This overall weight of scientific evidence analysis is presented in Section 2.5.

2.1.2 Human Health Problem Formulation and Focus of Analysis

Throughout each human health hazard analysis step, EPA considered results from previous assessments (ATSDR, 2018; NICNAS, 2014, 2013; U.S. EPA, 2004b) (summarized in both Table_Apx C-1 and Figure_Apx C-1) to better understand the scope and data gathering used to support various cancer and non-cancer endpoints, including hazard identification and dose-response relationships. No acute, intermediate, or chronic oral or inhalation minimal risk levels (MRLs) were derived in the previous assessments from the Agency for Toxic Substances and Disease Registry (ATSDR) evaluations due to limitations in the available data, including insufficient dataset and/or the observation of serious adverse effects that were not considered appropriate for MRL derivation. EPA considered previous assessment PODs for chronic exposure in both non-cancer (Section 2.3) and cancer (Section 2.4) studies. For example, the Agency utilized NTP (1982) for the determination of chronic inhalation non-cancer and cancer PODs in agreement with a previous EPA IRIS Program assessment (U.S. EPA, 2004b). However, for shorter dermal and ocular exposure durations (*i.e.*, acute or intermediate), other agencies did not identify hazard values, citing insufficient data; or like EPA's IRIS Program, acute values are not typically derived. The Agency also determined that dermal and ocular evidence is insufficient to directly calculate dermal and/or ocular PODs for acute, intermediate, and chronic timepoints; however, EPA has characterized dermal and ocular endpoints further in Appendix A.1, where they are considered together in the assessment of irritation evidence. The majority of identified references described oral and inhalation data, which were utilized for POD selection.

This hazard assessment builds on the hazard database and conclusions from prior assessments, updated based on current EPA guidance, systematic review results, and in accordance with the best available science. The Agency 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 Sections 2.3.1, 2.4.1, and 0. Other non-critical hazard outcomes that are less supported/documented are summarized in Appendix B.

2.2 Toxicokinetics

This section provides a comprehensive overview of the absorption, distribution, metabolism, and elimination (ADME) of ethylene dibromide across various exposure routes. This summary aims to elucidate the factors influencing the ADME processes of ethylene dibromide, highlighting the breadth of data available for each route of exposure. For ethylene dibromide, the Agency used PBPK models to understand and evaluate the relationship between administered/applied external doses and absorbed/retained internal doses—including the extent of metabolism and formation of toxic metabolites.

2.2.1 Absorption

Ethylene dibromide is a highly volatile compound that can be readily absorbed at tissue sites. Its physical-chemical properties promote rapid systemic uptake, but absorption efficiency at tissue sites varies by route of exposure. The following sections describe absorption via oral, inhalation, and dermal pathways, which inform the overall exposure.

Human Studies

Although no controlled human studies on inhalation, oral, or dermal absorption have been conducted, reports of systemic toxicity following ingestion of contaminated food and drinking water provide qualitative evidence that ethylene dibromide is absorbed from the gastrointestinal tract in humans. No quantitative absorption fractions have been determined ([ATSDR, 2018](#)).

Laboratory Animal Studies

Oral: Ethylene dibromide is readily absorbed following oral exposure, with absorption occurring throughout the gastrointestinal tract. Available data indicate that gastrointestinal uptake can be described by first-order metabolism processes likely involving transfer from the stomach to the intestines and subsequently from the intestines to the liver ([Hissink et al., 2000](#)). Oral absorption of ethylene dibromide is characterized as rapid, with systemic concentrations approaching peak levels within approximately 30 minutes post-ingestion. Specifically, pharmacokinetic data from minipigs (a relevant reference animal model) indicate that a single oral dose of 1 g produced a serum concentration of approximately 1 ppm within 15 minutes, demonstrating efficient gastrointestinal uptake and rapid entry into systemic circulation ([U.S. EPA, 2004b](#)). The relatively low circulating concentration of the parent compound, despite the high administered dose, is attributed to extensive first-pass metabolism and rapid biotransformation, which substantially reduces the detectable levels of ethylene dibromide in blood ([U.S. EPA, 2004b](#)). *In vivo* studies involving oral and intravenous exposure in animals indicate that the extent of absorption in humans is expected to be comparable to that observed in rats, suggesting that systemic uptake of ethylene dibromide is substantial across species. EPA identified one oral toxicokinetic study by Hissink et al., ([2000](#)) that provided data on oral absorption of ethylene dibromide in rats. In this study, groups of rats received ethylene dibromide via oral gavage (50 and 150 mg/kg) and intravenous administration (10 and 50 mg/kg). Pharmacokinetic analyses demonstrated rapid systemic uptake following oral and intravenous dosing ([Hissink et al., 2000](#)).

Inhalation: Animal data demonstrate that systemic uptake occurs in multiple species, including rats, mice, rabbits, guinea pigs, and monkeys following acute (typically ≤ 24 hours), intermediate (≥ 30 –90 days), and chronic (> 90 days) exposures. Inhalation studies in animals further provide direct evidence that ethylene dibromide rapidly enters the systemic circulation following respiratory exposure ([Short et al., 1978](#)). For example, Scott et al., ([1984](#)) reported that approximately 50% of the administered dose was absorbed in Fisher 344 rats when delivered to either the upper or lower respiratory tract, at a flow

rate equivalent to the animals' respiratory minute volume (53 mL/min), allowing accurate estimation of the ethylene dibromide absorbed into systemic circulation ([Stott and Mckenna, 1984](#)).

Dermal: Experimental studies in animals confirm dermal absorption of ethylene dibromide, though the extent of absorption has not been quantified. In a dermal absorption study in guinea pigs, occluded topical application (to approximately 3.1 cm² of skin) of 1 mL ethylene dibromide for 6 hours resulted in a rapid increase in blood concentration to 2.1 µg/mL at 1 hour, followed by a slight decline to 1.8 µg/mL at 6 hours, indicating substantial dermal absorption ([Jakobson et al., 1982](#)). The purity or grade of ethylene dibromide was not specified, even though the grade of some of the other test materials was provided by the study authors.

2.2.2 Distribution

Human Studies

Despite a general lack of analytically measured human data (*e.g.*, serum or organ concentrations) regarding the distribution of ethylene dibromide following oral exposure, case reports have shown that the intentional ingestion of ethylene dibromide resulted in distribution to the kidneys and liver, as indicated by the presence of kidney lesions and centrilobular hepatic necrosis—likely due to either ethylene dibromide or the production of ethylene dibromide metabolites (as discussed below) ([Saraswat et al., 1986](#); [Olmstead, 1960](#)). Although there are documented cases in which humans have been exposed to ethylene dibromide in occupational settings via inhalation, the distribution of ethylene dibromide following inhalation exposure has not been well studied in humans or animals. Furthermore, while no studies have been identified regarding distribution after dermal exposure in humans or animals, the toxic effects observed in experimental animals following dermal contact suggest systemic distribution of ethylene dibromide ([ATSDR, 2018](#)).

Laboratory Animal Studies

Oral, Inhalation, and Intraperitoneal: The distribution of ethylene dibromide following oral exposure has been extensively studied in experimental animals. In male rats, following gastrointestinal absorption, ethylene dibromide is rapidly distributed throughout the body, with the highest retention observed in the kidneys, liver, and spleen ([Plotnick et al., 1979](#)). After oral administration of 15 mg/kg of ¹⁴C-ethylene dibromide, approximately 3% of the administered radiolabeled ethylene dibromide remained in tissues 24 hours post-exposure—primarily localized to the kidneys, liver, and spleen. At 48 hours, about 1% of the radiolabeled ethylene dibromide was retained in the liver ([Plotnick et al., 1979](#)). However, when male Sprague-Dawley rats were fed a diet containing 0.05% disulfiram, a compound known to inhibit oxidative metabolism by CYP (specifically the CYP2E1 isoform) and enhance the toxicity of ethylene dibromide, significant increases in tissue concentrations (liver, kidneys, spleen, testes, and brain) were found—with reduced urinary elimination and significant retention noted in the testes, brain, lungs, and erythrocytes ([U.S. EPA, 2004b](#); [Plotnick et al., 1979](#)). This indicates that inhibition of CYPs, specifically of CYP2E1, increases the concentration of parent compound systemically. The metabolism of ethylene dibromide is further described below in Section 2.2.3.

Studies have also examined tissue distribution following intraperitoneal administration. In both male RF/Hiraki mice ([Edwards et al., 1970](#)) and guinea pigs ([Plotnick and Conner, 1976](#)), the kidneys and liver retained the greatest proportion of the administered dose. Autoradiographic studies in mice injected intraperitoneally with 40 mg/kg of ¹⁴C-ethylene dibromide demonstrated radioactivity primarily in the intestines, kidneys, liver, blood, fat, and spleen. Approximately 1% of the administered dose per gram of wet tissue was detected in the kidneys and stomach tissue, while 6.2% was measured in whole blood and 2.6% in plasma at 24 hours post-treatment ([Edwards et al., 1970](#)).

In a study by Plotnick et al. (1976), guinea pigs received a single intraperitoneal injection of 30 mg/kg of radiolabeled ¹⁴C-ethylene dibromide in corn oil. Most of the dose was recovered in the urine (65.9%), indicating significant renal excretion with smaller amounts found in the liver (2.16%) and feces (3%). By 72 hours post-injection, approximately 10 to 12% of the dose had been eliminated through the lungs via exhalation (Plotnick and Conner, 1976). The authors selected guinea pigs for this study due to their metabolic and biotransformation pathways being similar to those of humans. They found that the target organs for ethylene dibromide in guinea pigs were the same as those in rats, though tissue concentrations were generally higher in guinea pigs (Plotnick and Conner, 1976).

Overall, ATSDR (2018) concluded that the intraperitoneal injection findings are consistent with observations from oral administration studies, suggesting that ethylene dibromide is rapidly absorbed and widely distributed across the body. Additionally, ATSDR (2018) concluded that ethylene dibromide is primarily retained in the kidneys and liver, regardless of the exposure route or species examined.

2.2.3 Metabolism

Human Studies

Direct studies on the metabolism of ethylene dibromide in humans are not available; however, animal studies provide valuable insights into its metabolic pathways, specifically the role of key metabolic enzymes such as CYPs and glutathione *S*-transferase (GST). Conservation of such key enzymes in the metabolic pathway strongly suggests that similar processes may occur in humans, which was also noted by ATSDR (2018).

Laboratory Animal Studies

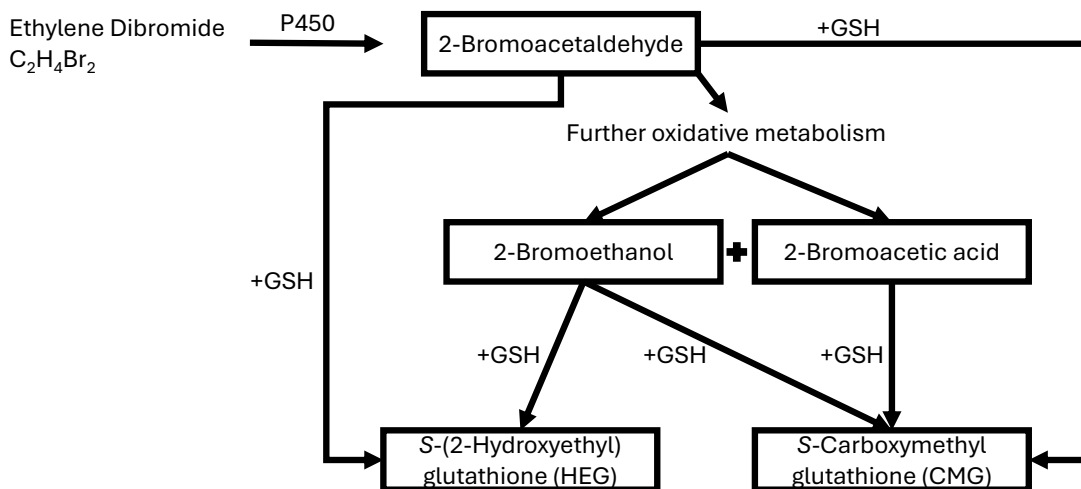
Animal studies reveal that ethylene dibromide is metabolized via two competing pathways shown in Figure 2-2: an oxidative pathway catalyzed by CYP and a conjugative pathway mediated by GSTs. These pathways produce reactive electrophilic intermediates with diverse toxicological effects as summarized by IRIS (U.S. EPA, 2004b), which highlights the roles of oxidative and conjugative pathways in generating reactive intermediates that are crucial for understanding the compound's toxicological effects and potential health risks.

In Vitro Studies: Metabolism studies using human tissue and *in vitro* to *in vivo* extrapolation calculations provided human-specific metabolic parameters for the two pathways responsible for the metabolism of ethylene dibromide (Hissink et al., 2000; Johnson and Tenuta, 1979). Wiersman et al., (1986) conducted *in vitro* experiments (enzyme assays) and used human liver tissue obtained from three patients undergoing liver resection to examine: (1) whether the GST and mixed function oxidases (MFO) systems of human liver metabolized ethylene dibromide, (2) whether these human liver activities resulted in adducts formation/modification of DNA, and (3) to compare the extent of DNA and protein binding resulting from GST and MFO metabolism (Wiersma et al., 1986). After 20 minutes of incubation and in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and GSH, compared to controls, ethylene dibromide was metabolized by human liver cytosolic, microsomal GST, and microsomal MFO. In addition to these findings, only microsomal MFO bound irreversibly to ethylene dibromide metabolites. Furthermore, compared with controls, microsomes and cytosol resulted in a greater amount of DNA adducts when incubated in the presence of NADPH or GSH (Wiersma et al., 1986).

In another study, Ansari et al., (1987) assessed the association between ethylene dibromide exposure and GST activity level in human erythrocytes. Erythrocytes were obtained from the blood of healthy human donors and purified for subsequent inhibition studies. The inhibition studies were performed at pH of 6.5 with 1-chloro-2,4 dinitrobenzene (CDNB) as the electrophilic substrate and incubated with several doses

of ethylene dibromide for 1 hour each. Compared to controls, ethylene dibromide inhibited GST activity in a dose-dependent manner, with a maximum inhibition of 60% observed at 10×10^{-3} M concentration. The study authors indicated that these findings suggest that ethylene dibromide exposure may reduce the ability of erythrocyte GST to detoxify xenobiotics and that additional studies could further evaluate the potential of usefulness of erythrocyte GST activity as a biomarker of exposure (Ansari et al., 1987).

A: Oxidative Pathway



B: Conjugative Pathway

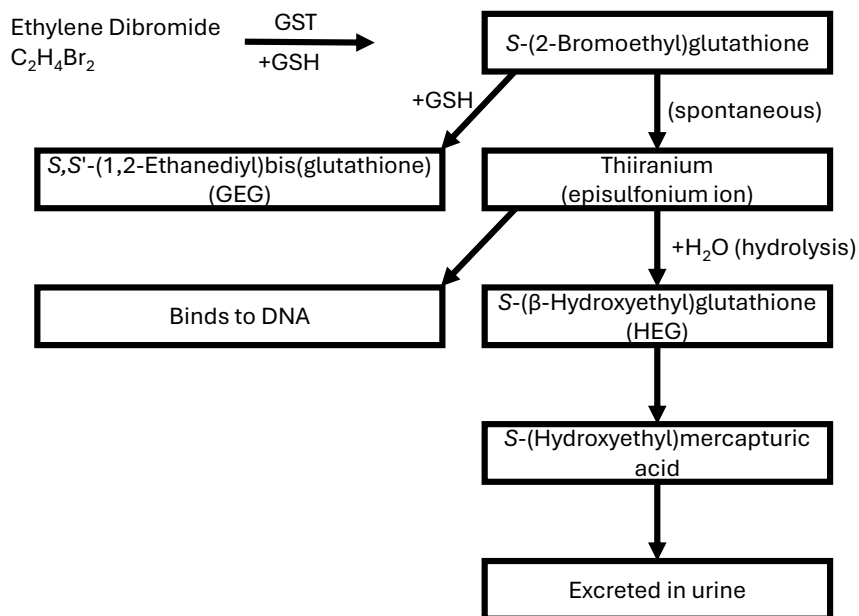


Figure 2-2. Schematic Illustration of Ethylene Dibromide Metabolic Activation via (A) the Oxidative Pathway by Cytochrome P450 and (B) the Conjugative Pathway by GST

Adapted from U.S. EPA (2004b); P450 = cytochrome P450; GSH = glutathione; GST = glutathione S-transferase

Oxidative Pathway: The oxidative metabolism of ethylene dibromide is primarily facilitated by CYP2E1. This enzyme converts ethylene dibromide into 2-bromoacetaldehyde (2-BA), a highly reactive electrophilic intermediate. 2-BA can covalently bind to microsomal proteins, leading to hepatotoxicity, or undergo further oxidative metabolism. It may conjugate directly with GSH to form S-(2-

hydroxyethyl)glutathione (HEG) or *S*-carboxymethyl glutathione (CMG), a process believed to be catalyzed by GST. Alternatively, 2-BA can be further oxidized to 2-bromoethanol and 2-bromoacetic acid, both of which subsequently undergo glutathione conjugation to produce *S*-(2-hydroxyethyl)glutathione (HEG) and carboxymethylglutathione (CMG). Additionally, 2-BA can be metabolized by aldehyde dehydrogenase in the presence of nicotinamide adenine dinucleotide (NAD⁺) to yield bromoacetic acid, which is excreted in the urine. Under hypoxic conditions, microsomal and hepatocyte assays have demonstrated the formation of free radical intermediates, suggesting the potential for oxidative stress to contribute to the observed toxicity associated with metabolic activation and glutathione depletion ([U.S. EPA, 2004b](#); [Tomasi et al., 1983](#)). Metabolism through the CYP pathway may contribute to lipid peroxidation, linking ethylene dibromide exposure to oxidative stress responses ([U.S. EPA, 2004b](#)). This pathway may also explain some interindividual variability in susceptibility, given differences in CYP2E1 expression among humans. Ethylene dibromide exposure can also lead to substantial GSH depletion ([Cmarik et al., 1990](#)), which reflects the continuous consumption of GSH in detoxifying reactive metabolites and the exhaustion of cellular reserves at higher exposure levels ([U.S. EPA, 2004b](#)).

Conjugative Pathway: Ethylene dibromide can also undergo direct conjugation with GSH via a GST-mediated reaction, yielding *S*-(2-bromoethyl)-glutathione. This intermediate metabolite can spontaneously cyclize to a highly reactive episulfonium ion (also referred to as thiiranium ion), which can directly bind to DNA or undergo hydrolysis to generate *S*-(β-hydroxyethyl)-glutathione (HEG). In addition, a second glutathione conjugation may occur, yielding *S,S'*-1,2-ethanedithiol-bis-glutathione (GEG). The formation of these glutathione-derived metabolites correlates with marked intracellular GSH depletion, estimated at approximately 70% ([Jean and Reed, 1992](#)). *In vitro* studies indicate that around 60% of the episulfonium ion is trapped as *S,S'*-ethanedithiol-bis-glutathione, while the remaining fraction reacts with water to form *S*-(2-hydroxyethyl)glutathione ([U.S. EPA, 2004b](#)). Once formed, *S*-(2-hydroxyethyl)glutathione enters the mercapturic acid pathway, where it is excreted in urine, serving as a key biomarker of the GSH-dependent activation pathway for chemicals such as ethylene dibromide ([ATSDR, 2018](#); [U.S. EPA, 2004b](#)).

An alkylating agent is defined as “a substance that causes replacement of hydrogen by an alkyl group especially in a biologically important molecule, specifically one with mutagenic activity that inhibits cell division and growth...” ([Merriam-Webster, 2026](#)). Ethylene dibromide is a bifunctional alkylating agent following metabolic activation, meaning it can react twice, either at the same site or as a cross-linking agent. In particular, the glutathione conjugation pathway generates a highly reactive episulfonium ion intermediate. Owing to its electrophilic nature, this intermediate readily reacts with nucleophilic sites in DNA. It forms several covalent DNA adducts, including major DNA adducts such as *S*-[2-(*N*⁷-guanyl)ethyl]mercaptopuric acid (2-GEMA) and *N*²- and *O*⁶-guanyl, which are strongly associated with the induction of mutagenic and carcinogenic effects ([Guengerich et al., 1995](#); [Cmarik et al., 1990](#)). The significance of these adducts and their role in mutagenesis and carcinogenesis are discussed further in Section 2.4.6.

Oxidative metabolism accounts for approximately 80% of ethylene dibromide biotransformation in rats, with the oxidative to conjugative ratio reported to be about 4:1. This indicates that ethylene dibromide is preferentially metabolized to 2-bromoacetaldehyde, which is then conjugated with glutathione ([Van Bladeren et al., 1980](#)). Although both pathways can generate DNA-reactive metabolites, the direct DNA reactivity of 2-bromoacetaldehyde is relatively slow. Consequently, the oxidative pathway is generally considered less relevant to the carcinogenic potential of ethylene dibromide, while the GST-mediated pathway, through episulfonium ion formation, is believed to play the central role in its mutagenic and

carcinogenic effects (Van Duuren et al., 1985). See Figure 2-3 for a schematic of all metabolism and elimination pathways for ethylene dibromide.

2.2.4 Elimination

Human Studies

No studies specifically evaluating the excretion of ethylene dibromide in humans following inhalation or oral exposure were identified.

Laboratory Animal Studies

In rats, oral administration results in the formation of mercapturic acid derivatives, with approximately 74 and 3% of the mercapturic acid derivatives excreted in urine and feces, respectively (Plotnick et al., 1979; Plotnick and Conner, 1976). In guinea pigs, approximately 10 to 12% of intraperitoneal injection was eliminated via respiration, with the remainder primarily excreted in urine (Plotnick and Conner, 1976).

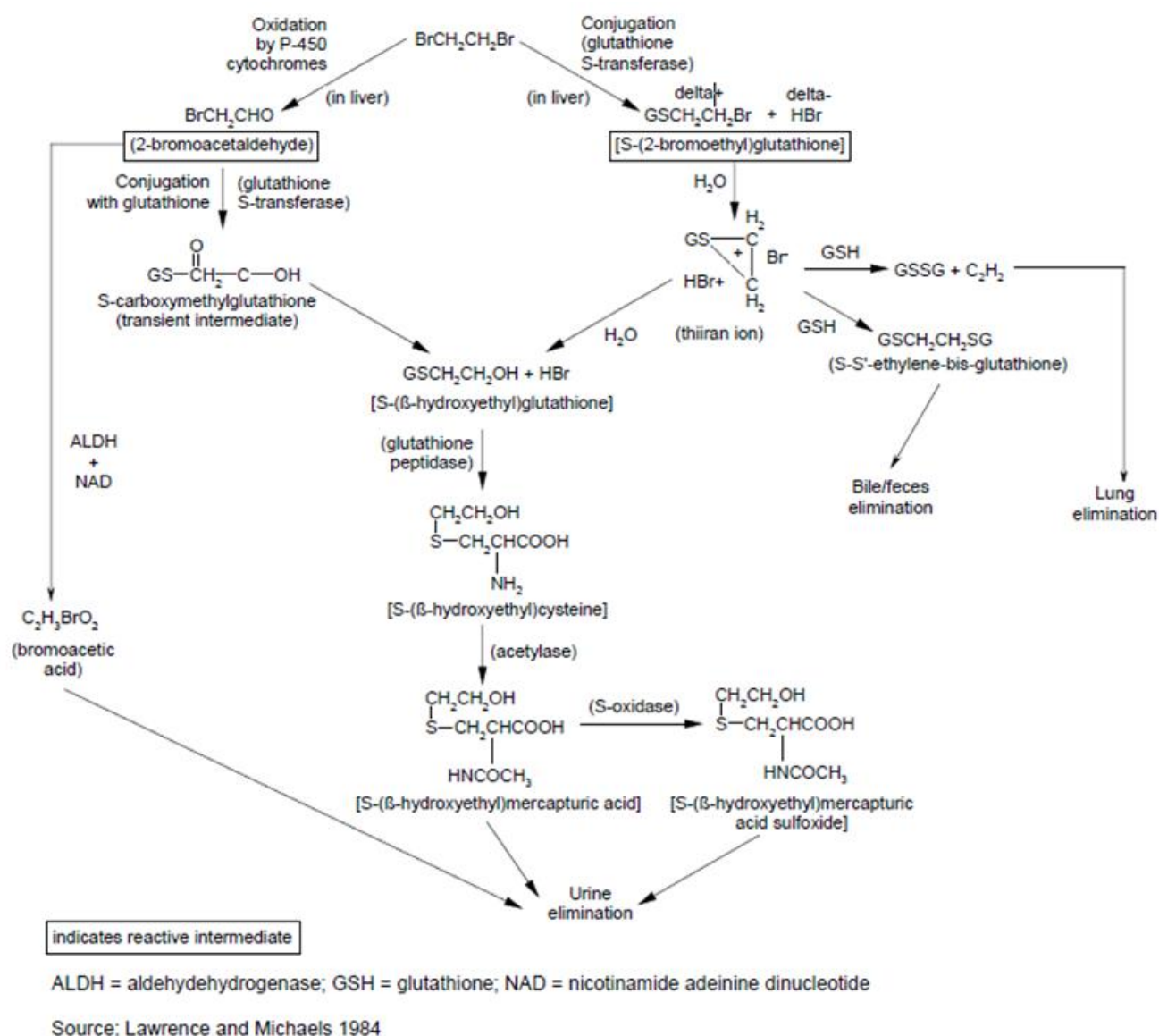


Figure 2-3. Schematic of Ethylene Dibromide Metabolism and Elimination

Urinary Excretion: Urinary excretion is the primary route of elimination. Several studies have identified the production of *S*-(hydroxyethyl)mercapturic acid, an ethylene dibromide-specific metabolite in rats. *In vivo* metabolic studies have confirmed the presence of multiple urinary metabolites following oral exposure. In albino rats exposed to 100 mg/kg of ethylene dibromide, the major urinary metabolite identified was *S*-(hydroxyethyl) mercapturic acid, with *S*-(β -hydroxyethyl)cysteine detected to a lesser extent ([Nachtomí et al., 1966](#)). In Wistar rats given 50 and 150 mg/kg of ^{14}C -ethylene dibromide orally, the major urinary metabolites included *S*-(hydroxyethyl)mercapturic acid, thiodiacetic acid, and thiodiacetic acid sulfoxide. The formation of thiodiacetic acid was shown to depend on CYP-mediated oxidation rather than glutathione conjugation ([Wormhoudt et al., 1998](#)). Additional metabolites have been reported following intraperitoneal administration, including *S*-[2-(N^7 -guanyl)ethyl]-*N*-acetylcysteine, a urinary mercapturic acid derived from the nucleic acid adduct *S*-[2-(N^7 -guanyl)ethyl]glutathione ([ATSDR, 2018](#); [Kim and Guengerich, 1989](#)).

The evidence indicates that (1) urinary excretion is the predominant elimination route for ethylene dibromide regardless of route of exposure, and (2) the metabolite profiles observed across studies reflect the underlying metabolic pathways engaged. Following oral exposure, most metabolites excreted in urine arise from GSH conjugation (*S*-(hydroxyethyl)mercapturic acid) ([Nachtomí et al., 1966](#)). Some urinary metabolites (e.g., thiodiacetic acid) are generated through CYP-mediated oxidation, indicating multiple enzymatic pathways contribute to urinary elimination ([Wormhoudt et al., 1998](#)). Following intraperitoneal exposure, the metabolite appears to be reflecting the metabolic processing of DNA adducts formed by reactive intermediates, and these metabolic products are also eliminated primarily in urine ([Kim and Guengerich, 1989](#)).

In summary, ATSDR ([2018](#)) concluded that while the route of exposure may influence the specific metabolites formed, mainly from glutathione-mediated conjugation, CYP-mediated oxidation, and to a lesser extent, the turnover of DNA adducts, the urinary pathway remains the major route of elimination.

Exhalation: Elimination through expired air is a significant secondary pathway. In studies involving intravenous administration, a notable proportion of the dose was recovered in expired air, indicating that exhalation is an important route of excretion, especially following intravenous exposure ([Wormhoudt et al., 1998](#)). Plotnick et al., ([1976](#)) reported that 10 to 12% of the ethylene dibromide dose was excreted via the lung within 72 hours following intraperitoneal injection of 30 mg/kg ^{14}C -ethylene dibromide in guinea pigs. Most of the dose was recovered in the urine (65.9%), with smaller amounts in the liver (2.16%) and feces (3%) ([Plotnick and Conner, 1976](#)).

Fecal Excretion: Excretion via feces represents a minor pathway. In rats administered 50 and 150 mg/kg or 10 and 50 mg/kg of ^{14}C -ethylene dibromide intravenously, about 75 to 82% of the measured radioactivity was recovered in the urine within 48 hours, 3.2 to 4% in the feces within 48 hours, and 0.53 to 7.2% in the expired air within 2 hours. In one rat study, oral administration of 15 mg/kg ^{14}C -ethylene dibromide resulted in about 1.65% of the dose being excreted in feces ([ATSDR, 2018](#); [Plotnick et al., 1979](#)).

Clearance of the Parent Compound: Ethylene dibromide as the parent compound is rapidly eliminated from the blood, primarily through metabolism, with exhaled air serving as a secondary route of elimination ([Plotnick et al., 1979](#)). Following an oral dose of 50 mg/kg in rats, the estimated half-lives are 25 minutes for the distribution phase and 121 minutes for the terminal phase. This indicates that more than 99% of absorbed ethylene dibromide in rats would be eliminated within 24 hours. Systemic clearance is observed to be dose-dependent in rats; after a 150 mg/kg oral dose, clearance is measured at 55 mL/minute/kg, compared to 125 mL/minute/kg at a 50 mg/kg dose, suggesting capacity-limited

metabolism. Pharmacokinetics of the parent compound following intravenous administration are reported to be similar to those observed after oral dosing ([Hissink et al., 2000](#)).

For rats exposed to intravenous injections of ethylene dibromide, the half-lives vary depending on the dose, ranging from 15 to 85 minutes at 10 mg/kg and 38 to 77 minutes following a 50 mg/kg dose of ethylene dibromide ([Hissink et al., 2000](#)). Systemic clearance is slower (28 mL/minute/kg) following a 50 mg/kg intravenous dose compared to a 10 mg/kg dose (75 mL/minute/kg) ([Hissink et al., 2000](#)).

The data indicates rapid and extensive metabolism and systemic clearance following ethylene dibromide exposure in rats, with little evidence of tissue retention. Accordingly, low-level exposures are not expected to result in the accumulation of ethylene dibromide or its metabolites in tissues. However, at higher exposure levels, saturation of metabolic pathways could occur, potentially allowing ethylene dibromide to persist longer in the body ([Hissink et al., 2000](#)).

2.2.5 PBPK Modeling Approach

EPA identified a previously published PBPK model for ethylene dibromide in rats and humans ([Hissink et al., 2000](#)). That model, which had been developed with *in vitro* to *in vivo* extrapolation methods using species-specific *in vitro* metabolism data, had been verified with oral and intravenous experimental data ([Hissink et al., 2000](#); [Ploemen et al., 1997](#)). Because dermal exposure was not originally included in the model by Hissink et al. (2000), EPA added a dermal route of exposure to the existing Ethylene Dibromide PBPK Model. The modified model was then used to derive acute, intermediate, and chronic dermal HEDs from oral or inhalation systemic toxicity studies in rats. For this draft assessment, dermal HEDs are expressed as retained doses, rather than total applied doses. A retained dose is defined as the amount of dose that has permeated into the skin (*i.e.*, the part of the dose that has not evaporated or washed off) and is available for systemic exposure. An applied dose is defined as the total amount of the chemical that comes in contact with the skin (*i.e.*, the total potential exposure).

Because ethylene dibromide is volatile, a portion of its dermal application can evaporate before it penetrates the skin barrier. As a result, the total amount placed on the skin surface does not represent the biologically relevant systemic dose. To address the uncertainty in dermal exposure associated with the unknown fraction of the applied dose that evaporates, this draft hazard assessment and *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)), both quantify the dose that is retained (*i.e.*, absorbed) into the skin after accounting for evaporation loss. This ensures consistency between both hazard and exposure assessments. Throughout this draft hazard assessment TSD for ethylene dibromide, note that retained and applied doses are both considered external doses and not to be confused with the term “internal dose,” which is defined as the concentration or amount of a substance that is associated with a hazardous effect in the target tissue (and is the metric, or internal dose metric, by which hazard is assessed). A full review of the Ethylene Dibromide PBPK Model can be found in the *Draft PBPK Reporting Document for Ethylene Dibromide* ([U.S. EPA, 2026g](#)).

The pharmacokinetics of ethylene dibromide are dependent on various factors, including route of exposure and species. PBPK models account for species- and route-specific differences in the estimation of internal doses (*e.g.*, concentrations in specific tissues such as blood, liver, or fat) associated with toxicity, facilitating various extrapolations (*e.g.*, across species, across routes) based on the equivalence in biologically effective dose rather than the administered doses. The Hissink et al. (2000) PBPK model for ethylene dibromide was developed to describe ADME of ethylene dibromide in rats via inhalation, oral, and intravenous (IV) dosing. That model was developed using an *in vitro* to *in vivo* extrapolation approach (IVIVE), which biologically scales up *in vitro* metabolism parameters to the corresponding *in vivo* parameters and predicts *in vivo* ADME of ethylene dibromide in rats. The rat IVIVE-PBPK model

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was extended to humans by using *in vitro* human metabolism parameters and human physiological parameters (Hissink et al., 2000; Ploemen et al., 1997). This was done by following a parallelogram framework that has previously applied in regulatory settings (Mallick et al., 2020; U.S. EPA, 2019; Yoon et al., 2015). The Ethylene Dibromide PBPK Model structure used herein, which includes both CYP-oxidation and GST-conjugation metabolism pathways, has been well accepted and applied to other relevant VOCs (Sweeney and Gargas, 2016; Andersen et al., 1987; Ramsey and Andersen, 1984). In addition, *in vitro* metabolism data have been used for PBPK modeling of volatile chemicals (JC and GL, 2002; Kedderis et al., 1993).

Due to a lack of dermal-relevant *in vitro* or *in vivo* data for model development, an *in silico* dermal sub-model was added to the existing PBPK model for humans. This model is flux-based and describes ethylene dibromide absorption through the skin barrier using the Potts-Guy equation (Potts and Guy, 1992), whereas evaporation flux from the exposed skin surface is described in Deacon et al. (2024). These *in silico* models include model parameters based on physicochemical properties of ethylene dibromide, including molecular weight, lipophilicity, and volatility. Through the use of *in vitro* and *in silico* approaches, this model combines New Approach Methods (NAMs) with the established PBPK Model Framework (Hissink et al., 2000) and is also referred to as “NAM-PBPK” model.

Figure 2-4 provides the EPA’s workflow of applying NAM-PBPK modeling to route-to-route extrapolation, estimating human dermal PODs under the human relevant dermal exposure conditions as described in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* (U.S. EPA, 2026b).

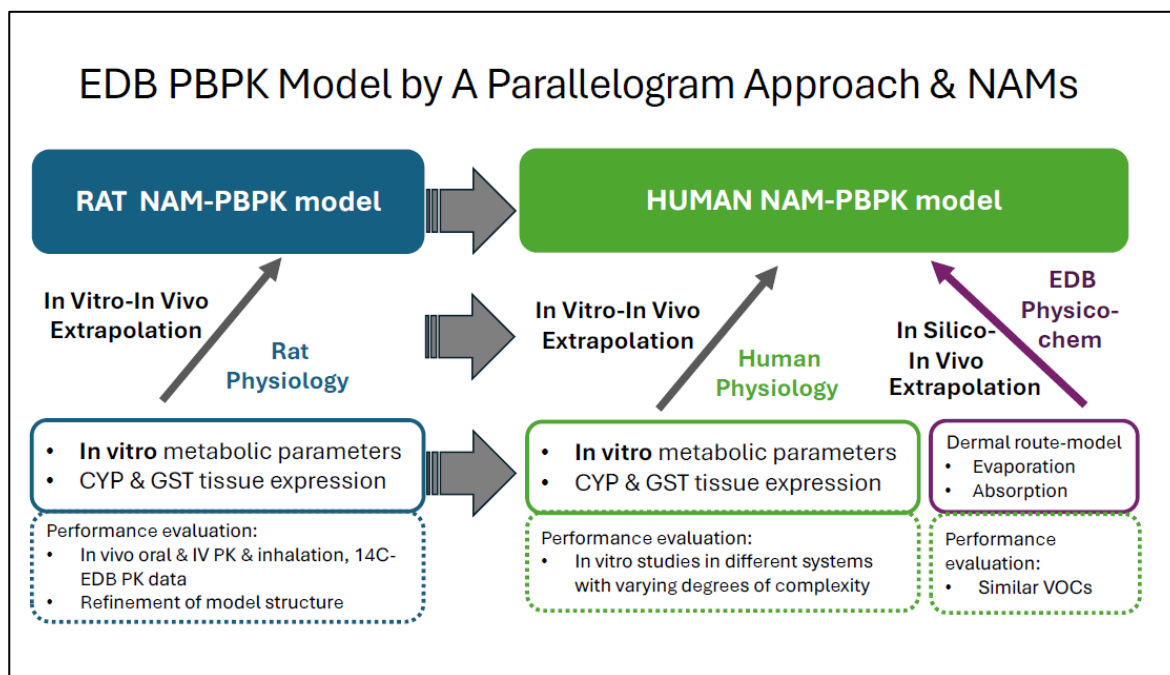


Figure 2-4. PBPK Modeling Workflow Using Parallelogram Approach and New Approach Methods (NAMs)

2.2.5.1 NAM-PBPK Model Description

The Hissink et al. (2000) PBPK model for ethylene dibromide in rats and humans is intended to support human health risk assessment by enabling biologically-based extrapolation (*i.e.*, predicting external dose levels that lead to equivalent internal dose levels across species, exposure routes, and dose levels). The

rat model performance was evaluated based on the agreement between the model predictions and the *in vivo* PK data following IV and oral exposure. The parallelogram approach was used to evaluate the validity of the model development approach (*i.e.*, IVIVE-PBPK) in one species (*i.e.*, the rat), and the same approach was then applied to another species (*i.e.*, human). This shift in model evaluation approaches reflects the shift of parameter sources, from model fitting against *in vivo* data to biological scaling of *in vitro*-derived parameters.

The ethylene dibromide model consists of a set of mass-balance differential equations representing individual anatomical compartments connected by blood flow. Each compartment is assumed to be well-stirred and perfusion-limited (Campbell et al., 2012). Chemical transfer between blood and tissues is governed by tissue-to-blood partition coefficients. Pulmonary exchange is described using a blood-to-air partition coefficient and ventilation rate. In the model, ethylene dibromide metabolism is described using a combination of saturable and first-order kinetics, depending on the metabolic pathway, as oxidative metabolism (via CYP2E1) or GSTs-mediated conjugation (Figure 2-2). CYP2E1 was assumed to be the dominant oxidative enzyme. The model also assumes that tissue partitioning is the same for both rats and humans. Oxidative metabolism via CYP2E1 is modeled as a saturable process and represented using Michaelis-Menten kinetics with maximum metabolic rate ($V_{\max}$) and enzyme affinity (K_m). CYP2E1 metabolism is primarily hepatic in both humans and rats but also occurs in other tissues depending on species. In rats, CYP2E1 activity was included in liver, kidney, and lung compartments. In humans, CYP2E1 activity was included in liver and lung compartments. GSTs-mediated conjugation is represented as a first-order process. For both humans and rats, GST activity was included (based on enzyme expression data) in liver, lungs, kidneys, stomach, small intestine, muscle, and testes. The model only predicts metabolism in those tissues with quantified enzyme expression data. The rate of GST-mediated metabolism in each tissue is linear with respect to concentration of ethylene dibromide in that tissue, but there is a lack of data to describe GST kinetics for an exposure range higher than what was reported.

The model follows the general structure of PBPK models for volatile compounds as described by Campbell et al. (2012) and Ramsey and Andersen (1984), with explicit compartments for the lung (gas exchange), liver, kidneys, adipose tissue, skeletal muscle, stomach, small intestine, testes, rapidly-perfused tissues, and slowly-perfused tissues. Species-specific organ volumes and blood flows are from published reference values (Brown et al., 1997). The original Hissink et al. (2000) model supports IV, oral, and inhalation routes of exposure for ethylene dibromide. *In vivo* blood time course data were available for model evaluation for IV and oral routes of exposure. Oral absorption is described as first-order processes, which transfer ethylene dibromide from stomach to intestines and intestines to liver, followed by partial uptake into gastrointestinal tissues. It is assumed that 100% of the dose is absorbed in the gastrointestinal tract. Absorption parameters were then empirically adjusted after fitting the model to *in vivo* rat data. The blood concentration time-course data from Hissink et al. (2000), and further *in vivo* disposition data from Wormhoudt et al. (1998), provided justification for the PBPK model through mass-balance closure and pulmonary and metabolic elimination, as well as identifying metabolic pathways and their dose-dependent shifts in metabolic routing. These findings provide support for model structural assumptions, parameterization of competing pathways, and application for route-specific risk analysis for systemic effects.

Dermal Route of Exposure

The dermal route of exposure sub-model added to the systemic PBPK model simulates two competing processes that remove ethylene dibromide from the skin surface: permeation of the chemical into the skin, and evaporation of the chemical from the vehicle on the skin surface. Together, these processes determine the time-dependent skin uptake of ethylene dibromide. For VOCs, evaporation competes

directly with skin absorption, influencing the effective dermal dose, the time-dependent concentration in the vehicle, and the lag-time of systemic exposure. Note that retained HEDs are less sensitive to evaporation parameters because they represent the dose that has entered the skin and is available for systemic uptake. However, the reported volume that accompany each HED corresponds to the volume of the applied dose.

The Potts and Guy method ([1992](#)) is an empirical correlation that is used to predict the permeability coefficient K_p (cm/h) of chemicals through human skin, based on their octanol:water partition coefficient ($\log K_{OW}$ = a measure of lipophilicity) and molecular weight (MW, g/mol). The method assumes passive diffusion through the skin. Originally calibrated for small organic molecules and developed with experimental skin permeation data, the relationship is predicted by Potts and Guy ([1992](#)) as follows:

$$\log K_p = -2.72 + 0.71 \log K_{ow}$$

$$\rightarrow K_p \approx 0.0034 \text{ cm/h}$$

Evaporation flux was accounted for using Equation 4 from Deacon et al. ([2024](#)), which presents evaporation flux as a diffusion-controlled and vapor pressure-driven process. This makes the *in silico* approach chemical-specific and not driven by wind-speed, as previously used by Grégoire et al. ([2021](#)).

Evaporation flux (J_{evap} , $\frac{\text{mol}}{\text{cm}^2 \text{ h}}$) is defined using Fick's First Law of diffusion in the gas phase, such that:

$$J_{evap} = -D_{evap} \times \frac{M_s - M_a}{h} \left(\frac{\text{umol}}{\text{cm}^2 \text{ h}} \right)$$

Where:

D_{evap}	=	Diffusion coefficient (cm^2/h)
M_s	=	Gas-phase molar concentration of solvent at the vehicle surface ($\mu\text{mol/L}$, calculated using Equation 3 of Deacon et al. (2024))
M_a	=	Ambient gas-phase concentration (assumed to be 0)
h	=	Diffusion path length

For dermal exposures in which chemicals are present in a vehicle on the skin, the time-varying changes in volume and thus concentration must also be estimated—not just the dose expressed in mass (amount applied) per unit area. Thus, both evaporation and absorption of ethylene dibromide depend on its molecular availability at the skin surface, with mole fraction directly determining the effective surface concentration that drives both processes. The molar fraction governs thermodynamic availability, and dermal uptake is driven by concentration gradients. A lower molar fraction indicates a lower effective surface concentration and affects bioavailability. The time- and concentration-dependent bioavailability of ethylene dibromide, the fraction absorbed to the systemic circulation, is calculated by the model and is the absorbed percentage of the total applied mass (mg) of ethylene dibromide for a specific COU formulation as well as volume, surface area, and exposure conditions. The percentage of absorbed dose changes as the volume of the solution decreases over time, which subsequently alters the molar concentration at the surface of the skin. This informs the reported retained dose, or part of the applied dose that permeates into the skin and is not evaporated or washed, which represents the biologically relevant dose driving systemic exposure. See *Draft PBPK Reporting Document for Ethylene Dibromide*

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(U.S. EPA, 2026g) for a discussion of concentration-dependent bioavailability as it pertains to dermal applications of ethylene dibromide.

Figure 2-5 shows the model schematic for the PBPK model adapted and modified from Hissink et al. (2000) with the addition of a skin compartment for dermal exposure. Note that Hissink et al. (2000) only provided a simple written description of the model but not the actual model equations, code, or model schematic. As such, EPA replicated the model described below from the textual description in the Hissink et al. (2000). See the *Draft PBPK Reporting Document for Ethylene Dibromide* (U.S. EPA, 2026g) for the EPA-adapted PBPK model validation against experimental time-course data reported in Hissink et al. (2000).

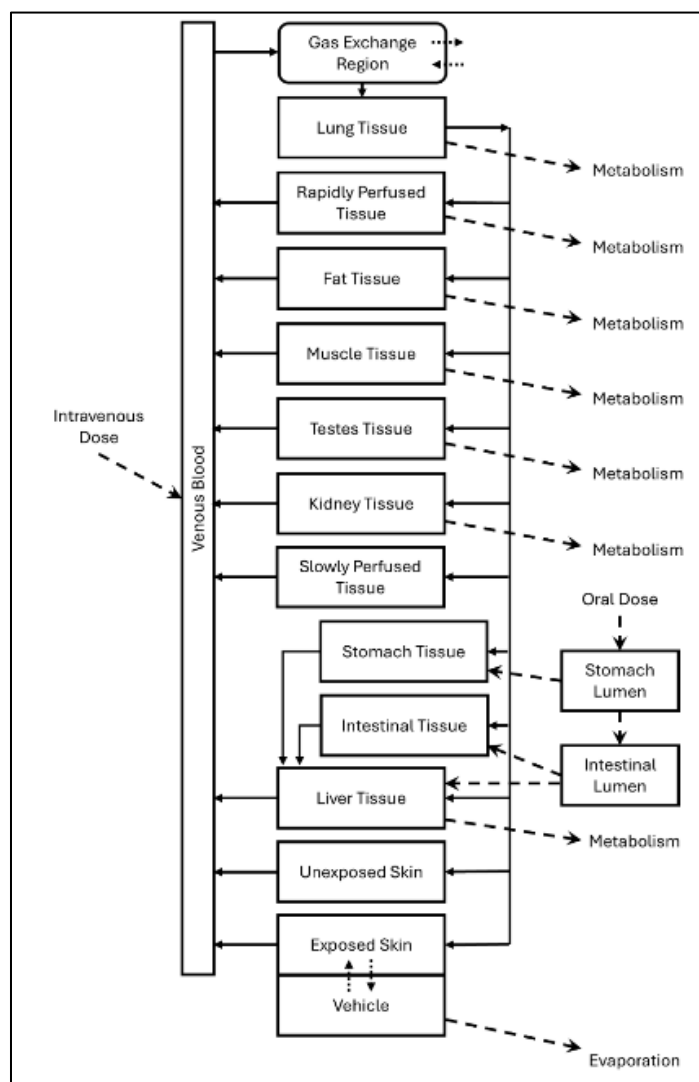


Figure 2-5. Model Schematic for Ethylene Dibromide

Adapted from model schematic as described in [Hissink et al. \(2000\)](#).

Note that Hissink et al., (2000) provided descriptions of tissues and oral and IV exposure routes, but no equations. The dermal route of exposure was not originally included in the Hissink Model; it was added by EPA as described in this draft TSD.

2.2.5.2 Application of PBPK Model for Dermal Dose Extrapolation

The PBPK method to derive HEDs is described below. The application of the PBPK model is independent of endpoint (cancer or non-cancer) and is applied consistently across Sections 2.3.2.2 and 2.4.7.

Step 1: Identify Animal PODs Associated with Toxicity Studies

Convert non-cancer PODs to BMDLs or BMCLs. For cancer, use a dose-response model that was fit to the tumor data to estimate the doses associated with a benchmark response.

Step 2: Estimate Internal Doses from Animal PODs

For each non-cancer and cancer POD that is relevant for route-to-route extrapolation (*i.e.*, PODs for systemic effects), simulate the exposure conditions reported in each study and use forward dosimetry to calculate the internal doses with the PBPK model parameterized for rats. It is assumed that the hazardous internal dose for humans is the same as that for rats.

Step 3: Calculate Dermal HEDs to Reach Target Internal Dose Metrics

With the PBPK model (parameterized for an average human adult), use reverse dosimetry to estimate the dermal dose and formulation volume necessary to reach the target internal dose (from Step 2) at the level observed in rats at the selected POD. In context of this flux-based dermal PBPK model, the dermal dose is defined by the combination of the following factors: ethylene dibromide concentration at the skin surface; volume of applied media containing ethylene dibromide (octanol as a surrogate for carrying vehicle); surface area of exposed skin; and the duration/frequency of contact with exposed skin. This PBPK-estimated dermal dose differs from the “default method,” which defines dermal dose as a fixed fraction of total mass of ethylene dibromide applied to the skin. For a given concentration, volume, exposed surface area, and contact time, PBPK-estimated retained doses can be converted to a mass-based dose (mg/kg/day). However, the converted mass is interpretable only in the context of the defined exposure factors. Accordingly, PBPK route-to-route extrapolation expresses the HED as a set of exposure conditions rather than a single mass-based dose value.

Exposure Scenarios and COUs: Dermal exposure assumptions and dermal exposure simulation scenarios (acute and chronic) for occupational and consumers used for PBPK modeling are described in Sections 5.6.1.4.4, 5.6.2.4.4, 5.6.3.4.4, and 5.6.5.4.4 of the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)). PBPK-modeled retained hazard values in conjunction to the central tendency (CT) and high end (HE) exposure scenarios for each of the COUs where workers or consumers are expected to have dermal exposure to ethylene dibromide liquid. Occupational non-users (ONUs) are unlikely to directly handle liquid formulations containing ethylene dibromide, and were therefore not assessed for dermal exposure, as described further in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)). The surface area of the exposed skin was assumed to be 1,070 cm² (for HE, front and back of 2 hands), 535 cm² (for HE, front and back of 1 hand or CT palm of 2 hands), or 267.5 cm² (for CT, palm of 1 hand). For PBPK simulations of OESs, CT and HE concentrations for each of the following COUs under TSCA were tested:

- Manufacture – Import (CT – 45 wt %, HE – 60 wt %);
- Processing – Repackaging (CT – 50 wt %, HE – 100 wt %);
- Processing – Incorporation into a formulation, mixture, or reaction product – Fuels and fuel additives in all other petroleum and coal products manufacturing (CT – 30 wt %, HE – 60 wt %);
- Processing – Incorporation into a formulation, mixture, or reaction product – Fuels and fuel additives in petroleum refineries (CT – 30 wt %, HE – 60 wt %);

- Processing – As a reactant (CT – 55 wt %, HE – 100 wt %);
- Industrial use – Fuel agent in petroleum refineries (CT – 0.085 wt %, HE – 0.1 wt %);
- Industrial use – Other use – Processing aid not otherwise specified; Pigment and dye manufacturing (CT – 55 wt %, HE – 100 wt %);
- Commercial use – Fuels and related products (CT – 0.085 wt %, HE – 0.1 wt %);
- Commercial use – Other uses – Laboratory chemical (CT – 50 wt %, HE – 100 wt %); and
- Disposal (CT – 50 wt %, HE – 100 wt %).

The PBPK model also simulated HE and CT consumer use for one or two hands, which falls under the COU of Consumer use – Fuels and related products (CT – 0.085 wt %, HE – 0.1 wt %, for 1 and 2 hands). Consumers are assumed to be pilots or use fuels and related products commercially. *Exposure Duration Assumptions:* Occupational exposure duration assumptions are described in Section 5.6 of the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)). Acute occupational exposures were modeled as single, 1-day events with an initial 5-minute dermal exposure that is washed off after 8 hours. Chronic occupational exposures were modeled as 5 events per week for 4 weeks. As noted earlier, the PBPK model shows that steady state is reached in less than 4 weeks. Consumer exposure duration assumptions are described in Section 9.3 of the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)) for pilots. High-end consumer exposures assumed 1 exposure event per week, where each exposure was a single 5-minute ([U.S. EPA, 2025](#)) event without wash-off for 5 hours. The 5-hour wait is representative of a typical consumer delay and was determined from stakeholder input and professional judgement, as discussed in ([U.S. EPA, 2026b](#)). The acute consumer exposure was one event for 1 day without wash-off for 5 hours.

Step 4: Interpret HEDs Within Context

Non-Cancer: Non-cancer dermal HEDs are defined as the retained dermal doses to which an adult human must be exposed in order to reach the same animal non-cancer internal doses for certain exposure conditions and over some duration and frequency.

Cancer: The HED corresponding to the benchmark tumor response is considered the POD for cancer potency. This value is converted to a CSF as described in Section 2.4.7 below.

2.3 Non-Cancer Hazard Assessment

The sections below describe adverse outcomes and mechanistic data available, evidence integration, and weight of scientific evidence conclusions for relevant human health hazard outcomes for ethylene dibromide. Full details on all evaluated health outcomes from all key studies are in *Draft Data Extraction Information for Human Health Hazard Animal Toxicology and Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026c](#)).

Evidence integration judgments were determined based on considerations described in Section 7 of the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)). In brief, strength of the evidence judgments (robust, moderate, slight, indeterminate, or compelling evidence of no effect) for individual evidence streams (*i.e.*, human, animal, mechanistic) were determined by expert judgment based on the considerations described in the protocol. These considerations include quality of the database, consistency, magnitude and precision, dose-response, and biological significance. These were then integrated into an overall summary classification.

EPA used results from systematic review and previous assessments to independently evaluate the weight of scientific evidence for each hazard outcome. Hazard outcomes with sufficient confidence and quantitative study data then underwent dose-response analysis for both non-cancer (Section 2.3.2.2) and cancer (Section 2.4.7) assessments.

2.3.1 Critical Human Health Hazard Outcomes

The sections below summarize the human health hazard identification and evidence integration of acute dermal and ocular toxicity, reproductive/developmental toxicity, hepatic toxicity, gastrointestinal toxicity, lung/respiratory toxicity, and adrenal toxicity, which are the endpoints for ethylene dibromide for which the most critical and best scientific data are available. In determination of best available data, all data yielded from EPA's literature search was considered. All health outcomes identified in the literature search were characterized and the findings are organized by exposure duration. Critical health outcomes used in dose-response analysis were data considered for PODs and are organized below by critical health outcome in Sections 2.3.1.1 through 2.3.1.4.4; the remaining non-cancer data identified for critical health outcomes are further described in 0. Non-critical health outcomes are further characterized in Appendix B. Complete data extraction of all the relevant studies is provided in the *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026c](#)). Details on the data quality evaluations are provided in the *Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology for Ethylene Dibromide* ([U.S. EPA, 2026e](#)) and the *Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026f](#)).

The evidence integration for each hazard section summarizes the strength of the available human and laboratory animal health effect evidence. Mechanistic information relevant to evidence integration judgements, cross-evidence stream coherence, biological plausibility, and mode of action (MOA) understanding or potential susceptibility was considered. EPA identified mechanistic information to support several non-cancer and cancer hazards for most health outcomes except for diabetes outcomes, mortality, adrenal, and gastrointestinal toxicity sections of this draft assessment/TSD.

Oral and inhalation studies provide a consistent pattern of toxicities. Adverse health outcomes are observed with acute exposure; however, outcomes increased in severity with extended exposure durations. This trend is observed and described by other assessing agencies, including ([ATSDR, 2018](#)) and ([U.S. EPA, 2004b](#)). These agencies determined chronic PODs for inhalation and oral exposure routes for ethylene dibromide only, citing lack of sufficient evidence for determination of acute or intermediate PODs.

EPA determined there is insufficient dermal evidence to directly calculate dermal PODs for acute, intermediate, and chronic timepoints, as described in Section 2.3.2.5. However, the strong evidence of systemic toxicity provides confidence in applicability of a PBPK model based on available oral and inhalation data, to complete route-to-route extrapolation.

2.3.1.1 Reproductive/Developmental Toxicity

2.3.1.1.1 Human Evidence

EPA identified several epidemiology studies that assessed the association between ethylene dibromide exposure in male workers and reproductive toxicity outcomes, including changes in semen and sperm parameters ([Schrader et al., 1988](#); [Ratcliffe et al., 1987](#); [Schrader et al., 1987](#); [Takahashi et al., 1981](#)) or birth rates ([Turner and Barry, 1979](#); [Wong et al., 1979](#); [Equitable Environmental Health Inc, 1977](#)).

These studies provide moderate evidence of adverse male reproductive system outcomes following

occupational inhalation and dermal exposure to ethylene dibromide. Additionally, one study assessed the association between maternal ethylene dibromide exposure and low birth weight in offspring and found a statistically significant association, with an odds ratio (OR) of 1.97 (95% confidence interval [CI]: 1.24–3.15) ([Gong and Zhan, 2022](#)). The main analyses in these studies compared outcomes between two levels of exposure: exposed and unexposed. Although these studies did not provide sufficient data for dose-response assessment, increased adverse semen and sperm outcomes compared to unexposed groups were observed in medium-quality studies with exposed groups with relatively low geometric mean time-weighted average (TWA) exposure levels of 88 ppb (peak 262 ppb) ethylene dibromide in a cross-sectional study of papaya workers and 60 ppb (peak 2,165 ppb) ethylene dibromide in a longitudinal study of forestry workers. These studies are described in Appendix A.2, whereas Table_Apx A-3 characterizes all reproductive/developmental outcomes observed in identified human studies.

2.3.1.1.2 Laboratory Animal Evidence

EPA identified six animal studies (3 short-term, 2 subchronic, and 1 chronic) that evaluated the effects of ethylene dibromide inhalation on reproductive and developmental outcomes. Additionally, two short-term and one chronic animal oral gavage study were identified. In this section, the studies considered for POD selection are characterized. Appendix A.2.2 characterizes all other reproductive/developmental data identified by EPA that were not considered for POD. Table_Apx A-4 and Table_Apx A-5 in Appendix A.2.2 also provide a brief study description, PODs, and critical effects resulting from inhalation and oral exposure to ethylene dibromide, respectively, for all studies identified with reproductive and developmental data. Although this reference was not utilized for hazard identification, evidence includes a study on ethylene dibromide exposure and reproductive outcomes in male rats reported significant decreases in absolute weight of testes ([Rowe et al., 1952](#)).

Short-Term Inhalation

Pregnant mice were exposed to ethylene dibromide in an inhalation chamber for 23 hours/day for 10 days, starting on gestational day six. Exposure groups were 0 ppm (n = 18), 20 ppm (n = 20), 38 ppm (n = 20), 80 ppm (n = 22), and 0 ppm with feed restriction (n = 18) ([Short et al., 1978](#)). Mice were sacrificed on gestational day (GD) 18 for fetal assessment of soft tissue and skeletal abnormalities. Significant dam body weight change was observed during exposure at 20 ppm, but feed-restricted controls received similar amounts of food as that consumed by the 80-ppm group (significantly less than the consumption of the 20-ppm group). Late resorptions were significantly increased at 20-ppm exposure. Fetal weight was significantly decreased at 20-ppm exposure, and fetal skeletal abnormalities including incomplete supraoccipital and incus ossification were observed. Significant mortality in dams was reported at 38 ppm. The percentage viable fetuses were significantly decreased at 38-ppm exposure, and the number of runts significantly increased. An increased variety of skeletal abnormalities in fetuses was observed at 38 ppm (e.g., enlarged fontanel occipital; unossified phalanges; incompletely ossified or split sternebrae; and an unossified or incompletely ossified hyoid bone, supraoccipital, or incus), compared to those observed at 20 ppm. An LOAEC of 20 ppm was assigned for maternal and developmental effects. EPA assigned this study a high overall quality determination rating.

Subchronic Inhalation

Male CD rats (18–20/group) were exposed to 0, 19, 39, or 89 ppm ethylene dibromide 7 hours/day, 5 days/week for 10 weeks via inhalation chamber ([Short et al., 1979](#)). Following exposure, 9 or 10 rats per group were sacrificed for reproductive histopathology, and the remaining 9 or 10 rats were housed with unexposed females for 2 weeks prior to sacrifice for reproductive histopathology. Mated females were sacrificed mid-gestation to assess implants, viable implants, and resorptions. No effects were observed at the two lowest doses. Males exposed to 89 ppm consumed less food, gained less weight, and had higher mortality (21%) than controls. Males exposed to 39 ppm gained less weight than controls. Testis weight

and testosterone serum concentration were significantly lower in the 89-ppm group. Males from the 89-ppm group had significantly lower fertility, resulting in zero impregnations. Histological examination of the males from the 89-ppm group found atrophy of the testis, epididymis, prostate, and seminal vesicles. A reproductive lowest-observed-adverse-effect level (LOAEL) of 89 ppm was assigned, though this dose also resulted in significant mortality. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

2.3.1.1.3 Mechanistic Evidence

EPA considered available mechanistic evidence in humans and animals that may contribute to the weight of scientific evidence for reproductive or developmental effects. *In vitro* exposure to 100 and 1,000 μ M of ethylene dibromide resulted in significant DNA damage (*i.e.*, single-strand DNA breaks) in both rat and human testicular germ cells (Björge et al., 1996), which is consistent with damage induced by reactive oxygen species (ROS), which is distinct from episulfonium ion-induced damage. Additional human *in vitro* assays have shown ethylene dibromide exposure to result in high mutagenic efficiency, as well as significant covalent bonding of ethylene dibromide to DNA and bioactivation of ethylene dibromide (Datta et al., 1994; Ferreri et al., 1983). Animal studies *in vitro* studies have also similarly shown that ethylene dibromide exposure resulted in the covalent bonding of ethylene dibromide to DNA and protein in GST isozymes in exposed rat embryos, where the bioactivation by the GST isozymes resulted statistically significant decreases of crown rump length, yolk sac diameter, and the composite score of morphological parameters were observed (Mitra et al., 1992a). Significant adverse effects in the central nervous system, optic and olfactory systems, and the hind limb were also observed (Mitra et al., 1992a). Kowalshi et al. (1985) examined metabolism and binding of ethylene dibromide in several target tissues in rats and mice, where autoradiographic results demonstrated that the metabolism of ethylene dibromide to reactive products is highly tissue selective and most marked in several tissues, including the epithelial linings of the vagina. Mechanistic evidence identified further supports the mutagenic MOA further described below in Section 2.4.5, which may also induce reproductive and developmental toxicity in humans.

2.3.1.1.4 Evidence Integration and Summary

Male Reproductive Outcomes

The evidence from the epidemiologic literature is moderate for male reproductive toxicity from ethylene dibromide exposure. Two medium-quality studies reported statistically significant adverse semen and sperm outcomes in exposed workers (Ratcliffe et al., 1987; Schrader et al., 1987). A lower quality study also found a statistically significant decrease in sperm count in exposed workers (Takahashi et al., 1981). Additionally, lower quality epidemiologic studies assessed the less-specific outcome of birth rates among the partners of male workers exposed to ethylene dibromide (Larsen et al., 1998; Turner and Barry, 1979; Wong et al., 1979; Equitable Environmental Health Inc, 1977) and generally did not find statistically significant associations, with the exception of one cohort that had a statistically significant lower birth rate among the partners of male workers exposed to ethylene dibromide (Wong et al., 1979).

The database is not large, but it includes medium- and low-quality studies that found consistent results for male reproductive biomarkers. The lack of consistency in findings for birth rate somewhat decreases the strength of the evidence, but the birth rate studies received lower overall quality determination ratings. The magnitude and precision of the observed differences in sperm and semen parameters somewhat increase the strength of the evidence. These studies did not report sufficient data for quantitative dose-response analyses.

The evidence in laboratory animals is robust for male reproductive outcomes. Two studies with high overall quality determination ratings reported findings that are relevant to human health risk assessment. In male rats, ethylene dibromide in the highest exposed group was statistically significantly associated with lower fertility, resulting in zero impregnations. Also, testes weight and testosterone serum concentrations were significantly lower. Histological examination found atrophy of the testes, epididymis, prostate, seminal vesicles ([Short et al., 1979](#)), and testicular degeneration ([NTP, 1982](#)). An additional medium-quality study on ethylene dibromide exposure and reproductive outcomes in male rats reported significant increased incidences of atrophy in the testes ([NCI, 1978](#)). Additionally, significant increases in mortality were observed ([NTP, 1982](#); [Short et al., 1979](#); [NCI, 1978](#); [Rowe et al., 1952](#)). Furthermore, other clinical signs observed included reddened ears and hunched appearance, large abdomen, and changes in body weight ([NCI, 1978](#)). Overall, the observed evidence indicates that there were strong associations between ethylene dibromide exposure and male reproductive-related outcomes, based on findings in rats. The quality of the database substantially increases the strength of the evidence as four relevant studies were available, one of which had substantial limitations. Consistency between study findings can be determined with respect to atrophy in the testes and changes in testes weight as both outcomes were observed in two studies, with no substantial inconsistencies identified. There was sufficient availability of data to assess dose-response, with statistically significant associations found between exposure and male reproductive toxicity outcomes, which increases the strength of the evidence.

Evidence on male reproductive outcomes based on mechanistic data is slight. A mechanistic study suggests that increases in single-strand DNA breaks in human and rat testicular cells results from ethylene dibromide exposure, which may be related to adverse male reproductive outcomes ([Bjorge et al., 1996](#)).

Female Reproductive Outcomes

Epidemiologic evidence for female reproductive outcomes is indeterminate due to lack of available epidemiology studies.

Animal evidence for female reproductive outcomes is robust. Two studies with high overall quality determination ratings were identified. Mice exposed to 38 ppm of ethylene dibromide during GDs 6 to 16 were observed to have a statistically significant decrease in the percentage of viable fetuses, increases in late resorptions, and increases in the number of runts ([Short et al., 1978](#)). Female rats exposed to 80 ppm for this same duration had reduced implantation and no viable fetuses ([Short et al., 1978](#)), experienced diestrus and did not cycle normally for 3 to 4 days following exposure. Additionally, statistically significant changes in weight and increased mortality in dams were observed in both studies across different species ([Short et al., 1979](#); [Short et al., 1978](#)). Overall, the quality of the database on female reproductive associations resulting from ethylene dibromide exposure were comprehensive and increases the strength of the evidence, with no substantial limitations. There was consistency between study findings for several adverse female reproductive outcomes in two different species. Additionally, there was sufficient availability of data to assess dose-response, with findings of statistically significant associations between exposure and female reproductive toxicity outcomes, which increases the strength of the evidence.

Developmental Outcomes

The evidence for developmental outcomes in humans is slight. There is some indication of a potential association between maternal ethylene dibromide exposure and low birth weight in offspring. However, only one epidemiological study of the association between ethylene dibromide exposure and this outcome was identified ([Gong and Zhan, 2022](#)). Although the study was medium quality and found a

positive association between maternal ethylene dibromide exposure and low birth weight in offspring, the lack of additional studies assessing this association substantially decreases the strength of the evidence. Additionally, consistency between study findings cannot be determined because only one epidemiologic study was identified that specifically assessed the association between maternal ethylene dibromide exposure and low birth weight in offspring. The magnitude and precision of the observed associations are neither extremely large nor extremely small as indicated by the odds ratio and the 95% confidence intervals.

Evidence for laboratory animals with developmental outcomes is robust. Two high-quality studies in rodents reported developmental outcomes that are relevant to human health risk assessment. Pregnant mice exposed to ethylene dibromide showed statistically significant decreases in fetal weight. Additionally, fetal skeletal abnormalities including incomplete supraoccipital and incus ossification were observed ([Short et al., 1978](#)). In rats, statistically significant fewer fetuses had normally ossified centra and lower fetal weight ([Short et al., 1978](#)). In addition to these results, significant mortality was observed in mice and rat dams ([Short et al., 1978](#)). The quality of the database on developmental outcomes following exposure to ethylene dibromide are comprehensive and substantially increases the strength of the evidence with no substantial limitations. Consistency between study findings can be determined as adverse developmental outcomes in two different species observed include lower fetal weight and skeletal abnormalities. Mortality in mice and rat dams was also associated with exposure. Furthermore, there was sufficient availability of data to assess dose-response as developmental toxicity found statistically significant associations between exposure and outcomes assessed, which increases the strength of the evidence. The interactive web-based evidence integration tables for [male](#) and [female reproductive](#), and [developmental](#) (both accessed June 18, 2026) effects are available in the Health Assessment Workspace Collaborative (HAWC) ([Shapiro et al., 2018](#)).

Evidence on developmental outcomes based on mechanistic data suggest that increases in mutagenicity in embryonic epithelial cells resulting from ethylene dibromide exposure may be related to the adverse developmental outcome also observed in humans ([Ferreri et al., 1983](#)). Nonetheless, the exact mechanism by which this occurs is not known. There was a limited number of mechanistic studies assessing ethylene dibromide and developmental outcomes and the evidence is slight.

Reproductive and Developmental Outcomes

The currently available evidence indicates that ethylene dibromide likely causes adverse reproductive/developmental outcomes in humans under relevant exposure circumstances. This conclusion is based on human, animal, and mechanistic evidence streams, including epidemiology studies that found associations with adverse male reproductive biomarker outcomes for workers with 8-hour TWA ethylene dibromide exposure levels as low as 60 ppb. The 60 ppb TWA was based on breathing zone air sampling for ethylene dibromide in an exposed group of temporary forestry workers, with peak breathing zone exposures of 2,165 ppb and “extensive” dermal exposure ([Schrader et al., 1988](#)).

2.3.1.2 Hepatic Toxicity

2.3.1.2.1 Human Evidence

Several case reports and case series have reported hepatic toxicity occurring after acute ethylene dibromide exposure, including in cases where exposed individuals died and cases where individuals survived ([Singh et al., 2007](#); [Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Prakash et al., 1999](#); [Osterloh, 1986](#); [Saraswat et al., 1986](#); [Letz et al., 1984a, b](#)). These references did not undergo data quality evaluation because they were screened as Supplemental based on the PECO screening criteria described

in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)). Although some case reports noted adverse hepatic outcomes occurring after ingestion of 3 mL of ethylene dibromide ([Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Prakash et al., 1999](#)), the data are insufficient to compare different dose levels. Additionally, potential inferences from case studies and case series are limited due to the lack of an unexposed comparison group. Thus, these references did not contain sufficient data for dose-response assessment. Therefore, these references are discussed in Appendix A.3.1, where Table_Apx A-3 characterizes all hepatic outcomes observed in identified human studies.

2.3.1.2.2 Laboratory Animal Evidence

EPA identified one acute, two short-term, five subchronic, and one chronic animal study that evaluated the effects of ethylene dibromide inhalation on hepatic outcomes. Additionally, 19 oral gavage studies in various animal species were identified: 12 acute, 5 short-term, and 1 chronic. In this section, the studies considered for POD selection are characterized. Appendix A.3.2 characterizes all other hepatic data identified by EPA that were not considered for POD. Table_Apx A-7 and Table_Apx A-8 in Appendix A.3.2 provides a brief study description, PODs, and critical effects resulting from inhalation and oral exposure to ethylene dibromide, respectively, for all studies identified with hepatic data. While these references were not utilized for human health hazard identification, evidence includes short-term inhalation studies in rabbits and rats, which resulted in increased organ weight and cloudy swelling of hepatocytes at 100 ppm ([Rowe et al., 1952](#)). Subchronic inhalation studies in rats and guinea pigs that yielded slight fatty degeneration of livers with edema and interstitial congestion at 50 ppm exposure ([Rowe et al., 1952](#)) as well as increased relative organ weight at 10 ppm ([Nitschke et al., 1981](#)). A different study observed significant centrilobular hepatic necrosis in male rats chronically exposed to 10 ppm ([NTP, 1982](#)). Oral acute and short-term studies yielded similar results to what was observed in inhalation studies, including increased organ weights, swelling of hepatocytes ([Nii et al., 1993](#)), increased cell proliferation, and increased serum and liver alkaline phosphatase ([Nachtomí, 1980](#)) in rats exposed to 110 mg/kg/day. Rats exposed to 10 mg/kg/day showed granular degeneration of hepatocyte cytoplasm and marked sinusoidal dilation, partly or completely degenerated nuclei, and centrilobular necrosis ([Broda et al., 1976](#)). Serum chemistries, including increased sorbital dehydrogenase (SDH), were seen at exposures as low as 10 mg/kg/day ([Nachtomí, 1980](#)). In a singular chronic study, male rats exposed to 38 mg/kg/day had significantly increased incidence of hepatic peliosis—an uncommon condition characterized by blood-filled cavities in the liver ([NCL, 1978](#)).

Chronic Inhalation

F344 rats (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide for 6 hours/day, 5 days/week for 2 years ([NTP, 1982](#)). Inhalation chambers were monitored constantly to detect fluctuations in inhaled concentration. Animals were observed twice daily for signs of toxicity and mortality. At the end of the 2-year exposure, animals were sacrificed for microscopic examination of representative tissues, including liver. Moribund animals were sacrificed for tissue examination prior to completion of the 2-year exposure. Throughout the study, mean body weights of high-dose rats of either sex were lower than those of the corresponding untreated controls. Survival of the high-dose rats of either sex was significantly shorter than that in the corresponding controls. General hepatic necrosis was observed in males (2 control, 6 low-dose, 19 high-dose) and females (2 control, 3 low-dose, 13 high-dose), with significant occurrence seen in high-dose animals. Localized centrilobular hepatic necrosis was significant in low-dose males (1/50 controls, 5/50 low-dose, 13/50 high-dose). A LOAEC of 10 ppm was determined based on centrilobular liver necrosis in males. EPA assigned this study a high overall quality determination rating.

Chronic Oral

Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/groups receiving treatment) ([NCI, 1978](#)). Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group were 0, 38, and 41 mg/kg/day for male rats, 0, 37, and 39 mg/kg/day for female rats (target doses 40 and 80 mg/kg/day). High-doses were suspended at 17 weeks due to deaths of 18 high-dose males and 20 high-dose females; at week 30, treatments resumed at the for the remaining rats in high-dose groups at the same dose the low-dose rats were receiving. At week 42, all treatments in rats were paused for a week then resumed for an additional 4 weeks. The study was discontinued at 49 weeks in male rats due to excessive deaths in both treatment groups. The study was discontinued for female rats at week 61. In the corn oil gavage vehicle group, male gavage doses were stopped at week 49 and animals were observed for an additional 14-week recovery period; females gavage doses were stopped at week 61 followed by a 2-week observation period (vehicle controls sacrificed at week 63). In the untreated control group, 5 males were sacrificed in week 59 and the remaining 4 in week 107. Endpoints evaluated included mortality (daily); clinical signs of toxicity, body weight, food consumption and palpation for tissue masses (weekly); and histopathological examination of the liver.

Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included reddened ears and hunched appearance in all treated groups by week five, and firm distended abdomens and abdominal urine stains in all treated groups by week 38 (incidence data not reported). Body weights were decreased in males and females after 10 weeks of treatment; however, the study authors note that this decrease in mean weight may reflect maybe due to mortality. In male rats, liver peliosis was observed in 0/40 control, 10/50 low-dose, and 9/50 high-dose groups. In females, peliosis was observed in 0/40 control, 1/47 low-dose, and 5/48 high-dose groups. A POD was not reported by study authors. A LOAEL of 38 mg/kg/day was determined in males for increased incidence of liver peliosis. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a medium overall quality determination rating.

2.3.1.2.3 Mechanistic Evidence

EPA considered available mechanistic evidence that may contribute to the weight of scientific evidence for hepatic effects. EPA identified three mechanistic studies that examined ethylene dibromide ability to induce hepatic effects in human liver cells or tissue ([Cmarik et al., 1990](#); [Wiersma et al., 1986](#); [Moody et al., 1981](#)). Cmarik et al. (1990) demonstrated the ability of ethylene dibromide to mediate unscheduled DNA synthesis in human hepatocytes following a 2-hour exposure to ethylene dibromide. In separate experiments, Moody et al. (1981) exposed male Sprague-Dawley rats (3/group) to 625 mg/kg or 220 mg/kg of ethylene dibromide via gavage and consistently reported that the recovery of diene conjugates and concentration of CYP were significantly lower in exposed animals regardless of exposure duration. Other factors reported were the increase of NADPH cytochrome C reductase, percentage of palmitic (16:0), oleic (18:1), and linoleic (18:2) acids and the decrease in arachidonic (20:4) and docosahexanoic (22:6) acids. The authors indicated that the decrease in CYP may be associated with lipid peroxidation, and that the decreased arachidonic acid in turn may be a sequela to that peroxidation or it may be associated with inhibition of CYP synthesis from linoleic acid. Wiersman et al. (1986) conducted *in vitro* experiments (enzyme assays) and used human liver tissue obtained from three patients. After 20 minutes incubation and in the presence of NADPH and GSH, compared to controls, ethylene dibromide was metabolized by human liver cytosolic, microsomal GST, and microsomal MFO. Furthermore, compared with controls, microsomes and cytosol resulted in a greater amount of DNA adducts when incubated in the presence of NADPH or GSH. Overall, these findings provide some mechanistic support for ethylene dibromide-induced liver toxicity.

2.3.1.2.4 Evidence Integration and Summary

Epidemiology studies provide slight evidence that acute ethylene dibromide exposure is associated with adverse liver outcomes. The quality of the database somewhat decreases the strength of the evidence. The available studies were case studies and case series, which generally are less informative for causal inference due to their lack of a control or comparison group. The consistency of the findings somewhat increases the strength of the evidence, as adverse hepatic outcomes were found in some, but not all, of the cases. The lack of precision of the findings somewhat decreases the strength of the evidence. The data were not adequate to evaluate a dose-response pattern, which neither increases nor decreases the strength of the evidence. This moderate epidemiologic evidence of hepatic toxicity is specific to acute exposure, as epidemiologic data were not available to assess hepatic outcomes potentially associated with chronic exposure.

Laboratory animal studies provide robust evidence of liver effects in relation to ethylene dibromide oral and inhalation exposure. A total of 27 experiments were identified, 19 of which are assigned medium- or high-quality ratings.

Mechanistic evidence for hepatic relationships based on inhibition of DNA repair and DNA damage in human hepatocytes following exposure to ethylene dibromide supports the toxicity observed in humans and likely observed in whole animals or cells derived from animals. Thus, evidence was considered slight for hepatic outcomes.

The currently available evidence indicates that ethylene dibromide likely causes hepatic effects in humans under relevant exposure circumstances, based on moderate human evidence of adverse hepatic outcomes following acute exposure, robust animal toxicology evidence of adverse hepatic outcomes following acute, short-term, and subchronic exposure, and slight mechanistic evidence. The interactive web-based evidence integration table for [hepatic effects](#) (accessed June 18, 2026) is available in HAWC.

2.3.1.3 Gastrointestinal Toxicity

2.3.1.3.1 Human Evidence

Several case reports and case series have reported adverse gastrointestinal outcomes occurring after acute ethylene dibromide exposure ([Singh et al., 2007](#); [Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Prakash et al., 1999](#); [Saraswat et al., 1986](#); [Peoples et al., 1978](#)). These references did not undergo data quality evaluation because they were screened as Supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)). Although many of the references reported adverse gastrointestinal outcomes in all of the individuals with acute ethylene dibromide exposure, including case reports that noted adverse gastrointestinal outcomes occurring after ingestion of 3 mL of ethylene dibromide ([Mehrotra et al., 2001](#); [Prakash et al., 1999](#)), the data are insufficient to compare different dose levels. Additionally, potential inferences from case studies and case series are limited due to the lack of an unexposed comparison group. Thus, these references did not contain sufficient data for dose-response assessment. Therefore, these references are discussed in Appendix A.4.1, where Table_Apx A-9 characterizes all gastrointestinal outcomes observed in identified human studies.

2.3.1.3.2 Laboratory Animal Evidence

EPA identified one short-term and two chronic animal studies that evaluated the effects of oral ethylene dibromide on gastrointestinal outcomes. In this section, the studies considered for POD selection are characterized. Appendix A.4.2 characterizes all other gastrointestinal data identified by EPA that were not considered for POD. Table_Apx A-10 in Appendix A.4.2 provide a brief study description,

candidate PODs, and critical effects relevant to the gastrointestinal system resulting from oral exposure to ethylene dibromide. The available evidence includes two chronic oral studies, where hyperkeratosis and acanthosis in the forestomach were significantly increased in male and female rats and mice ([NCI, 1978](#)). In male rats, 12/50 animals had both hyperkeratosis and acanthosis at 41 mg/kg/day, but no animals showed these lesions at 38 mg/kg/day or in the controls. In female rats, 18/50 animals had hyperkeratosis and acanthosis at 39 mg/kg/day, only 4 had them at 37 mg/kg/day, and 1/40 of the control animals showed these lesions. In male mice, 13/49 animals had hyperkeratosis and 5/49 had acanthosis at the high dose of 107 mg/kg/day, while only 1/50 animals had acanthosis (no hyperkeratosis) at 62 mg/kg/day, and no animals showed these lesions in the controls. In female mice, 12/50 had hyperkeratosis and 9/50 had acanthosis at 107 mg/kg/day, 1/49 had hyperkeratosis (no acanthosis) at 62 mg/kg/day, and no animals in the control group had these lesions. Due to early attrition, doses were adjusted mid-study; these doses represent TWAs. These results show that the forestomach is a target for non-cancer toxicity in rats and mice of both sexes for chronic exposures.

Short-Term Oral

Male F344 rats (8-16/group) were exposed to 0, 40, or 80 mg/kg/day of ethylene dibromide in corn oil vehicle 5 days/week for 2 weeks ([Ghanayem et al., 1986](#)). At the end of the experiment, the forestomach was harvested and processed for histopathology. While effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case it was examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. The only endpoint available for dose-response analysis for oral exposure that was of sufficient quality was cell proliferation and hyperkeratosis in the forestomach ([Ghanayem et al., 1986](#)). The forestomach is a rodent-specific structure lined with squamous epithelium and is not present in humans, rodents also possess a glandular stomach, which is more closely comparable to the human stomach due to its specialized mucosal epithelium involved in secretion of gastric enzymes and acid. The incidences of forestomach epithelial cell proliferation and hyperkeratosis were determined. Increased cell proliferation was observed in 0/16 controls, 0/8 animals at 40 mg/kg/day, and 4/8 animals at 80 mg/kg/day. Hyperkeratosis was observed in 0/16 controls, 1/8 animals at 40 mg/kg/day, and 6/8 animals at 80 mg/kg/day. A no-observed-adverse-effect level (NOAEL) of 40 mg/kg/day and a LOAEL of 80 mg/kg-day were determined for gastrointestinal effects, based on increased cell proliferation and hyperkeratosis. EPA assigned this study a high overall quality determination rating.

2.3.1.3.3 Evidence Integration and Summary

There is slight evidence that acute exposure to ethylene dibromide is associated with adverse gastrointestinal outcomes in epidemiology studies. The quality of the database decreases the strength of the evidence. There were few available studies, and the studies were case studies and case series, which generally are less informative for causal inference due to their lack of a control or comparison group. The consistency of findings within and across studies, with many of the studies reporting adverse gastrointestinal outcomes in 100% of the individuals with acute ethylene dibromide exposure, increases the strength of the evidence. This slight epidemiologic evidence of gastrointestinal toxicity is specific to acute exposure, as epidemiologic data were not available to assess gastrointestinal outcomes potentially associated with chronic exposure.

In a high quality short-term study, oral exposure resulted in forestomach epithelial cell proliferation and hyperkeratosis in rats starting at 80 mg/kg/day ([Ghanayem et al., 1986](#)).

The currently available evidence suggests but is not sufficient to conclude that ethylene dibromide might cause adverse gastrointestinal outcomes in humans under relevant exposure circumstances, based on slight human evidence of adverse gastrointestinal outcomes following acute exposure. There was

relatively little evidence of gastrointestinal effects of ethylene dibromide in laboratory animal studies yielded by EPA's literature search, but these data are supported by effects seen in exposure to other alkylating agents. Although there were no mechanistic studies flagged for gastrointestinal outcomes related to ethylene dibromide exposure per our literature search, alkylating agents as a class are known to cause gastrointestinal effects via multiple mechanisms: mutagenesis through a pathway mediated by the chemoreceptor trigger zone (O'Brien, 2008) as well as breakdown of the gastrointestinal mucosa due to differential cytotoxicity of alkylating agents on rapidly dividing cells, such as those lining the intestinal tract (Mustian et al., 2008). Alkylating agents, such as drugs used to treat cancer (*i.e.*, chemotherapy), have been associated with nausea and vomiting (NIDDK, 2015; Mustian et al., 2008). As mentioned previously, forestomach effects observed in rodents as a result of exposure to ethylene dibromide are relevant to humans. This finding is supported by ethylene dibromide's well-established genotoxic effects and mutagenic MOA and the formation of tumors at multiple sites across multiple doses without the observation of forestomach irritation, demonstrating that the forestomach effects resulting from the genotoxicity of ethylene dibromide are human-relevant (despite the anatomical difference). Proctor et al. (2007) suggests that forestomach effects observed in rodents, resulting from exposure to alkylating agents that are genotoxic (such as ethylene dibromide) are relevant to humans. Additionally, adverse gastrointestinal outcomes have been reported in several cases of acute oral and inhalation exposure to ethylene dibromide in humans (Singh et al., 2007; Saraswat et al., 1986; Peoples et al., 1978). Together, this evidence supports moderate confidence in the identified gastrointestinal data. The interactive web-based evidence integration table for [gastrointestinal](#) (accessed June 18, 2026) effects is available in HAWC.

2.3.1.4 Lung/Respiratory Toxicity

2.3.1.4.1 Human Evidence

EPA identified one medium-quality epidemiology study that evaluated the association between exposure to ethylene dibromide and adult-onset asthma (Hoppin et al., 2009). This cross-sectional analysis of enrollment data from the Agricultural Health Study found that ever use of ethylene dibromide was associated with a higher prevalence of allergic asthma compared to never use of ethylene dibromide (OR = 2.07; 95% CI: 1.02–4.20). Although the analyses included comparisons between an unexposed referent group and two exposure levels, and a statistically significant exposure-response trend was found ($p < 0.05$), the exposure levels for these comparisons were defined based on the median of intensity-adjusted lifetime days of ethylene dibromide use, which is not sufficient to determine the dose of ethylene dibromide. Furthermore, the cross-sectional design of the study precludes determination of temporality. Therefore, this study/reference was not used for POD determination; however, it is discussed further in Appendix A.5.1 where Table_Apx A-11 characterizes all respiratory outcomes observed in identified human studies.

2.3.1.4.2 Laboratory Animal Evidence

EPA identified nine animal studies (2 acute, 3 short-term, 3 subchronic, and 1 chronic) that evaluate the respiratory effects resulting from exposure to ethylene dibromide via inhalation. Additionally, one acute animal gavage study was identified. In this section, the studies considered for POD selection are characterized. Appendix A.5.2 characterizes all other respiratory data identified by EPA that were not considered for POD. Table_Apx A-10 in Appendix A.5.2 provides a brief study description, PODs, and critical effects resulting from inhalation exposure to ethylene dibromide for all studies identified with respiratory data. While these references were not utilized for human health hazard identification, evidence includes acute and short-term inhalation studies reporting significantly increased lung weight (Rowe et al., 1952), nasal respiratory epithelium hyperplasia (Nitschke et al., 1981), and tracheal epithelial damage (Koptagel and Bulut, 1998) with LOAELs around 10 ppm. Also, focal necrosis of the

nasal epithelium was seen in some animals—especially in the high dose groups but these lesions were almost completely absent in the recovery animals, appearing in only one female animal at the high dose. Furthermore, none of the male animals in the recovery arm had this lesion at any exposure level (Nitschke et al., 1981). Subchronic and chronic inhalation studies both report these same changes to the nasal cavity and lungs before ultimately progressing to tumor development. A single oral study also provides evidence of pulmonary edema in exposed animals; however, a POD was not determined due to vague reporting (Kettering Laboratory, 1943).

Subchronic Inhalation

CDF (F344) rats (9 weeks old) were exposed via inhalation to 0, 3, 10, or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 13 weeks (10/sex/group), or for 13 weeks plus an 88- to 89-day recovery to evaluate lesion reversibility (10/sex/group) (Nitschke et al., 1981). In animals that were exposed for 13 weeks without the recovery period, significantly decreased body weights were observed in male rats at 40 ppm ethylene dibromide dose. By the end of the recovery period, weights returned to control levels. Males and females exposed to 10 ppm had isolated to multifocal hyperplasia of the nasal respiratory epithelium. One female also had epithelial cell necrosis of the nasal respiratory epithelium. However, animals that underwent the recovery period following 13-week exposure to 10 ppm showed no nasal epithelium changes. Males and females exposed to 40 ppm had diffuse or focal nonkeratinizing squamous metaplasia, hyperplasia of the respiratory epithelium, and focal necrosis of the respiratory epithelium. Only one female rat in the 40 ppm group that underwent the recovery period had histological abnormalities—an isolated focus of epithelial hyperplasia in the respiratory epithelium of the nasal turbinates. A LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia in animals that did not undergo the recovery period. EPA assigned this study a high overall quality determination rating.

2.3.1.4.3 Mechanistic Evidence

EPA considered available mechanistic evidence in humans and animals that may contribute to the weight of scientific evidence for respiratory effects. Holzer et al. (2008) reported that ethylene dibromide exposure in human nasal mucosa cells and rat nasal turbinate and ethmoidal mucosa cells resulted in significant DNA damage, with differences in same sensitivity observed between human sources, suggesting potential interindividual variation in susceptibility (Hölzer et al., 2008). Although DNA damage was reported after three hours of exposure to ethylene dibromide in various mouse organs by Sasaki et al. (1998), significant DNA damage was not reported at 24 hours of exposure. Similar to the findings reported in Section 2.3.1.1.3, ethylene dibromide was observed to metabolize and bind in rat and mice tissues, where autoradiographic results demonstrated that metabolism of ethylene dibromide to reactive products is highly tissue selective and most marked in several tissues including the epithelial linings of the lung. Although DNA damage was reported after three hours of exposure to ethylene dibromide in various mouse organs, significant DNA damage was not reported at 24 hours of exposure. Mechanistic evidence identified further supports the mutagenic MOA further described below in Section 2.4.5, which may also induce respiratory toxicity in humans.

2.3.1.4.4 Evidence Integration and Summary

Epidemiologic literature provides slight evidence of adverse respiratory outcomes associated with ethylene dibromide exposure. A single study assessed the association between ever use of ethylene dibromide and the prevalence of adult-onset asthma in a cohort of farm workers using pesticides and found a significant association for allergic asthma but not non-allergic asthma (Hoppin et al., 2009). Thus, the adverse respiratory outcome might be due to adverse immune modulation. The study was medium quality, which increases the strength of the evidence. However, the strength of the evidence is substantially decreased by the lack of additional studies. A statistically significant trend was found in an exposure-response model, which increases the strength of the evidence.

Inhalation studies in laboratory animals provide slight evidence of respiratory effects in relation to ethylene dibromide exposure.

Evidence on respiratory outcomes based on mechanistic data reported damage to DNA human nasal mucosa cells resulting from ethylene dibromide exposure *in vitro* may be associated with adverse respiratory outcomes (Hölzer et al., 2008). However, the exact mechanism by which this occurs is not known. Thus, evidence was considered slight for respiratory outcomes. The available evidence indicates that ethylene dibromide likely causes respiratory endpoints in humans under relevant exposure circumstances. The interactive web-based evidence integration table for [respiratory](#) (accessed June 18, 2026) effects is available in HAWC.

2.3.2 Non-Cancer Dose-Response Assessment

2.3.2.1 Integration of Human Health Hazard Data Across Organ Systems

Examination of the non-cancer effects of ethylene dibromide across routes of exposure (oral, dermal, and inhalation) and durations of exposure (acute, intermediate, and chronic) shows portal-of-entry and systemic effects for all durations and routes that are consistent with the MOA for this chemical.

First, portal of entry effects are consistent and route-dependent. In inhalation studies in animals, pre-neoplastic changes to the nasal epithelium and lung are observed. In oral studies in animals, pre-neoplastic changes to the oral cavity, esophagus, and forestomach have been observed. While effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case it was being examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. The only endpoint available for dose-response analysis for oral exposure that was of sufficient quality was hyperkeratosis in the forestomach (Ghanayem et al., 1986). The forestomach is a rodent-specific structure lined with squamous epithelium and is not present in humans; however, rodents also possess a glandular stomach that is more closely comparable to the human stomach due to its specialized mucosal epithelium involved in secretion of gastric enzymes and acid.

There are portal-of-entry effects observed and also non-cancer degenerative effects consistent with DNA-damaging agents. This MOA is relevant for non-cancer as these effects at point of contact/portal of entry sites would be expected to occur first and can lead to generation of cancer precursor lesions (among other effects). Any consistency seen in effects across the database can plausibly be connected by this DNA damage MOA are further described below in Section 2.4.5.4.

Alkylating agents like ethylene dibromide (Section 2.2.3) are known to be cytotoxic, teratogenic, and carcinogenic (IARC, 2000). Cytotoxicity is often seen at the portal of entry where doses are highest, whereas carcinogenic effects require time to manifest and can only be observed in studies where the animals are kept alive long enough to develop histopathologically-visible tumors. Teratogenicity can only be detected in studies where offspring are examined. The database for ethylene dibromide contains all of these study types and the effects seen in each one are consistent with an underlying MOA that involves one or more DNA alkylating agents.

For non-cancer effects, the database shows hyperplasia and metaplasia in acute, short-term, and subchronic studies. The database also shows embryo- or feto-toxicity and teratogenicity at intermediate exposures that may be relevant to acute exposure scenarios. At chronic exposure durations, the most consistent and sensitive effect is on the liver, which is consistent with the liver having the greatest

metabolic capacity for biotransformation of ethylene dibromide. However, other organs have significant toxicity. These organs map neatly onto the metabolic capacity for biotransformation as shown in the PBPK model (liver >> kidney > lungs >> testes $\approx$ skeletal muscle > stomach $\approx$ intestines).

The following sections describe the dose-response assessment for ethylene dibromide for non-cancer health effects based on animal toxicology results. This assessment describes the selection of critical studies, selection of critical endpoints, dose-response assessment (including benchmark dose modeling, where appropriate), route-to-route extrapolation, and application of uncertainty factors. It integrates information on routes, durations, effects, dose-response, and mechanistic support to derive health-protective PODs for risk calculation.

2.3.2.2 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 and individual adverse health effects for which sufficient data were available to support dose-response analysis. From among the database supporting those outcomes, EPA selected studies and relevant health effects based on the following considerations:

- overall quality determination ratings;
- 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 ratings;
- endpoint sensitivity; and
- uncertainty and sensitivity of benchmark response 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).

2.3.2.3 Inhalation Route of Exposure for Acute, Intermediate, and Chronic Durations

Intermediate Durations

EPA identified three references that examined inhalation exposure for intermediate durations (at least two exposures up to 10% of lifespan; 13 weeks for rats and mice) and were assigned medium or high overall quality determinations ([Nitschke et al., 1981](#); [Short et al., 1979](#); [Short et al., 1978](#)). These studies are summarized in Table 2-1. Nitschke et al. ([1981](#)) describes respiratory cell hyperplasia at 10 ppm exposure for 6 hours/day for 5 days per week, where these effects are found to be reversible after up to 13 weeks of exposure. Instead, mouse fetal developmental abnormalities and increased late resorptions reported in Short et al. ([1978](#)) were selected as the basis for the POD (LOAEL of 20 ppm) used for characterizing risk from exposure to ethylene dibromide. While it may be expected for maternal effects to be reversible, per the effects reported by Nitschke et al. ([1981](#)), the developmental effects seen in Short et al. ([1978](#)) are permanent. In addition, while the effects in Short et al. ([1979](#)) study were at slightly lower concentrations than those reported by Short et al. ([1978](#)) when adjusted for continuous exposure (*i.e.*, HEC), the LOAEC for Short, et al. ([1979](#)) was lower and the effects were more severe. Both studies were used in later analysis, particularly for route-to-route extrapolation from inhalation-to-dermal.

EPA identified robust laboratory animal toxicology data available for developmental outcomes. Although identified reproductive/developmental mechanistic data was considered slight, ethylene dibromide is known to have a mutagenic MOA, which involves modification of cellular macromolecules such as DNA, RNA, proteins, and lipids ([Godschalk et al., 2025](#)). This MOA is often described in

reference to cancer endpoints but also applies to developmental effects. Modification of cellular macromolecules during critical developmental periods can disrupt normal fetal development, leading to effects such as those described in Short (1978). EPA has moderate confidence in the consideration of dose response presented in Short (1978), as three dose groups were utilized in addition to a control group, but excessive mortality in the highest dose group made BMD modeling infeasible. Ultimately, data for two dose groups in addition to the control was included in the dose-response analysis, which is sufficient for consideration of dose effects. There is robust confidence in this POD's relevance to exposure, as inhalation exposure is relevant to occupational, consumer, and general population scenarios, in which ethylene dibromide is released into air. This may occur in manufacturing scenarios or can be related to use of ethylene dibromide-containing products or air pollution. The significant effects on reproductive endpoints reported in (Short et al., 1978) are supported by additional studies (Short et al., 1979), (NTP, 1982), and (NCI, 1978), which show similar effects at doses ranging from 10 to 89 ppm.

Table 2-1. Summary of Candidate Acute ^a and Intermediate Inhalation, Non-Cancer PODs for Ethylene Dibromide

Target Organ/System	Species/Exposure	NOAEC	LOAEC	Endpoint	Candidate POD	Reference (OQD)
Reproductive/Developmental	Mouse Inhalation exposure 24 hours/day 10 days (starting GD 6)	Adverse effects at lowest dose tested	150 mg/m ³ [20 ppm]	fetal developmental abnormalities and increased late resorptions	150 mg/m³ [20 ppm] (HEC/LOAEC)	Short et al. (1978) (High)
Reproductive/Developmental	Rat Inhalation exposure 7 hours/day 5 days/week 10 weeks	Adverse effects at lowest dose tested	680 mg/m ³ [89 ppm]	testicular atrophy, lowered fertility	140 mg/m³ [18 ppm] (HEC/LOAEC)	Short et al. (1979) (High)
Lung/Respiratory	Rat Inhalation exposure 6 hours/day 5 days/week 13 weeks	23 mg/m ³ [3 ppm]	77 mg/m ³ [10 ppm]	hyperplasia of the nasal epithelium ^b	4.1 mg/m ³ [0.53 ppm] (HEC/NOAEC)	Nitschke et al. (1981) (High)
GD = gestational day; HEC = human equivalent concentration; LOAEC = lowest-observed-adverse-effect concentration; OQD = overall quality determination; POD = point of departure ^a These candidate values were considered for acute PODs because of the lack of endpoints observed in acute studies suitable for POD derivation ^b Effects were almost fully reversible following a 3 month recovery period Bolded value = identified POD for ethylene dibromide acute/intermediate inhalation exposures						

Exposure in (Short et al., 1978) took place from gestational day 6 through 16. Because exposure in Short et al. (1978) took place over several days during gestation, this dosing regimen falls under the “intermediate” duration for toxicity studies. However, without highly specialized studies to probe the “window of susceptibility” of the developing fetus to the toxic effect, it cannot be ruled out that a single dose (*i.e.*, a single, acute exposure) would have been sufficient for the adverse effects seen in the study. Because of this uncertainty, a single value is used for both acute and intermediate exposures for inhalation. The acute and intermediate inhalation PODs were set at 150 mg/m³ (20 ppm) based on skeletal malformations and increased resorptions in mice exposed to ethylene dibromide as shown in

([Short et al., 1978](#)). The choice of UFs is discussed in Section 2.3.2.6.2 below. A NOAEC could not be identified given the adverse effects at the lowest dose tested. The data could not be modeled using benchmark dose (BMD) modeling due to issues with the dataset. Specifically, all pregnant dams in the high dose group died prior to parturition, so that dose group could not be plotted on the dose-response curve. At the mid-dose, the bars were quite wide because of excess attrition and high variability in the measured endpoints. As a result, the software could not find a model that met the viability criteria. The model outputs showing a lack of viable fits may be found in Appendix D.2. The critical study was performed in male and female CD rats and CD-1 mice, with pups born to CD-1 mice selected as the basis for the POD.

The acute and intermediate dermal PODs were extrapolated from the inhalation data in ([Short et al., 1978](#)). Using the default approach, the POD was determined to be 28 mg/kg/day. Using the PBPK approach, the POD differed based on the exposure scenario. Factors like exposure magnitude, frequency, and duration; concentration of ethylene dibromide in the mixture/product, and exposed skin surface area affect the values. The PODs ranged from 38 to 42 mg/kg/day (in volumes of 9.4–32 mL) for high-end estimates and 40 to 45 mg/kg/day (in volumes ranging from 40–230 mL) for central tendency estimates. The choice of UFs is discussed in Section 2.3.2.6.2 below.

Acute Durations

EPA considered all reasonably available acute (exposure for 24 hours or less) inhalation studies. None of the identified references reported dose-response data for non-mortality outcomes, nor did they have a medium or high overall quality determination. While mortality effects were observed following inhalation exposure to ethylene dibromide (LC50 values in rats and guinea pigs ranging from approximately 200 to 400 ppm ([Short et al., 1978](#); [Rowe et al., 1952](#))) mortality is not considered a sensitive or appropriate outcome for the POD. Mortality typically occurs at much higher exposure levels than those associated with the onset of adverse, but non-lethal effects. Furthermore, mortality endpoints lack the granularity needed for dose-response modeling of sublethal effects. Additional acute inhalation studies were also not used for quantitative analysis due to various experimental design and/or outcome limitations, including lack of adequate reporting of non-lethal endpoints, insufficient dose groups or inappropriate controls, and only one animal per dose group ([Nitschke et al., 1981](#); [Rowe et al., 1952](#); [Kettering Laboratory, 1943](#)). Another study included inhalation exposures in rats was designed to assess reproductive endpoints over a subchronic duration and did not provide acute, non-lethal endpoints suitable for quantitative analysis ([Short et al., 1979](#)).

Due to the lack of acute studies of sufficient quality to be used for quantitative analysis, EPA used the developmental effects observed in Short et al. ([1978](#)) as the basis for an acute POD. This study is described in detail under “Intermediate Durations” above and is captured in Table 2-1. Although the Short et al. ([1978](#)) study was designed as a short-term (intermediate duration) developmental toxicity study, it provides the most sensitive and well-characterized endpoint available—fetal developmental abnormalities and increased late resorptions in mice—at the lowest exposure tested (LOAEC = 20 ppm). In the absence of acute studies with suitable non-lethal endpoints, and without information on the precise window of susceptibility for developmental toxicity, it is scientifically reasonable and health-protective to assume that a single exposure during the critical period of development could result in the observed adverse effects. This approach is consistent with EPA research that found that “developmental effects occurring under single-day exposure scenarios do not appear to be qualitatively different or discernable from those occurring under multiple-day exposure scenarios” ([Davis et al., 2009](#)). Specifically, the authors found that the incidence of fused sternebrae was associated with the magnitude of exposure (the dose in mg/kg) but not with the number of exposures (*i.e.*, the POD did not change between acute and repeated dose scenarios, only with dose level) ([Davis et al., 2009](#)). These effects are

directly comparable to those seen with ethylene dibromide, where the incidence of skeletal anomalies of the sternebrae in pups exposed *in utero* during GDs 6 to 15 was 24.8% in the control group (0 ppm), 35.5% in the low dose group (20 ppm), and 100% in the high dose group (38 ppm) ([Short et al., 1978](#)). Given these observations, the LOAEC of 20 ppm is expected to be relevant to single exposure scenarios in humans during pregnancy and is appropriate to use as an acute POD. This approach also meets the requirement to consider PESS including the time period during pregnancy and gestation.

Chronic Durations

EPA considered all reasonably available chronic inhalation data and identified the study with the best available science from the small pool of references that had dosing levels appropriate for dose response assessment and were assigned medium or high overall quality determinations ([NTP, 1982](#)). This study is summarized in Table 2-2 below. This reference was also selected by U.S. EPA ([2004b](#)). ATSDR ([2018](#)) considered this study but decided against deriving an inhalation MRL based on their conclusion that “the limited available data do not provide adequate information to identify the most sensitive effects of 1,2-dibromoethane, with adverse effects occurring at the lowest concentrations tested. Because mortality or serious adverse health effects were observed at the lowest concentrations tested, this precludes identification derivation of MRLs” ([ATSDR, 2018](#)). The lack of an identifiable NOAEC was overcome using BMD modeling, which allowed extrapolation to a NOAEC-equivalent using concentration-response data from animal studies. At 10 ppm exposure in rats, National Toxicology Program ([1982](#)) reported a critical outcome of liver necrosis. Additionally, adrenal cortex degradation and testicular degradation were significant, as were retinal atrophy, nasal cavity inflammation, and splenic hematopoiesis. Although there is limited mechanistic evidence for liver effects for ethylene dibromide directly, the fact that the liver bioactivates ethylene dibromide to an alkylating agent supports the liver being a target ([NIDDK, 2015](#)).

EPA has moderate confidence in this study’s consideration of dose response, as two dose groups were utilized in addition to a control group, which is sufficient for consideration of dose effects. There is high confidence in this POD’s relevance to exposure, as inhalation exposure is relevant to occupational, consumer, and general population scenarios, in which ethylene dibromide is released into air. This may occur in manufacturing scenarios or can be related to use of ethylene dibromide-containing products or air pollution. The chronic inhalation POD was calculated to be 11 mg/m³ (1.5 ppm) based on benchmark dose modeling of the liver effects data in ([NTP, 1982](#)) with a total UF = 30. The choice of UFs is discussed in Section 2.3.2.6.2 below. The critical study was performed in male F344 rats. The critical effect was centrilobular necrosis not otherwise specified of the liver.

Table 2-2. Summary of Candidate Chronic Inhalation, Non-Cancer PODs for Ethylene Dibromide

Target Organ/System	Species/Exposure	NOAEC	LOAEC	Endpoint	Candidate POD	Reference (OQD)
Liver	Rat Inhalation exposure 6 hours/day 5 days/week 88–106 weeks (depending on dose group)	Adverse effects at lowest dose tested	77 mg/m ³ [10 ppm]	Liver, centrilobular necrosis	11 mg/m³ [1.5 ppm] (HEC/BMCL ₁₀)	NTP (1982) (High)
BMCL ₁₀ = benchmark concentration lower 95% confidence limit with a benchmark response of 10% extra risk; HEC = human equivalent concentration; LOAEC = lowest-observed-adverse-effect concentration; NOAEC = no-observed-adverse-effect concentration; OQD = overall quality determination; POD = point of departure Bolded value = identified POD for ethylene dibromide chronic inhalation exposures						

Benchmark dose modeling for inhalation exposure for the chronic duration was found to be acceptable based on the *Benchmark Dose Technical Guidance* (for more detail see Figure 4, “BMD decision tree” on page 42) ([U.S. EPA, 2012b](#)). The Benchmark Dose Software produced eight viable models (Gamma, Log-Logistic, Multistage 1, Multistage 2, Weibull, Logistic, Probit, and Quantal Linear). Five models gave near-identical fits (Gamma, Multistage 1, Multistage 2, Weibull, and Quantal Linear). The Benchmark Dose Software recommended the Log-Logistic model based on having the lowest AIC value with a viable fit, and this is the model that was selected. A plot of the selected model versus the data is shown in Figure_Apx D-4. The BMC was 19 mg/m³ and the BMCL was 11 mg/m³. More information on EPA’s benchmark dose modeling of this study can be found in Appendix D.4.

To estimate the dermal chronic non-cancer POD, the inhalation POD as described above, along with the oral chronic non-cancer POD (further described below in 2.3.2.4) were used for route-to-route extrapolation to the dermal route of exposure. In the case of the critical effects for the chronic endpoints, both the oral and inhalation studies used systemic effects, specifically adverse histopathological changes of the liver. Both were considered to be suitable choices for extrapolation. The acute and intermediate dermal PODs were extrapolated from the inhalation data in ([NTP, 1982](#)). Using the default approach, the POD was determined to be 2.2 mg/kg/day. Using the PBPK approach, the POD differed based on the exposure scenario. Factors like exposure magnitude, frequency, and duration; concentration of ethylene dibromide in the mixture/product, and exposed skin surface area affect the values. The PODs ranged from 3.3 to 3.4 mg/kg/day (in volumes of 0.83–2.7 mL) for high-end estimates and 3.4 to 3.6 mg/kg/day (in volumes ranging from 3.9–7.0 mL) for central tendency estimates. The total UF was 30. The choice of UFs is discussed in Section 2.3.2.6.2 below. For risk calculations, the exposure scenario-specific PODs derived using the PBPK model were selected for use because the PBPK model represents a refinement over the default approach, more details and the rationale for selecting the PODs are included in Section 2.5.2.

2.3.2.4 Oral Route of Exposure for Acute, Intermediate, and Chronic Durations

Intermediate Duration

EPA considered all reasonably available intermediate oral data and identified one study that had dosing levels appropriate for dose response assessment and was assigned medium or high overall quality determinations ([Ghanayem et al., 1986](#)). This study is summarized in Table 2-3 below. Ghanayem, et al. (1986) assessed exposure to ethylene dibromide in male rats, evaluating histopathological changes to organs. Forestomach epithelial cell proliferation and hyperkeratosis was selected as the basis for the POD used for characterizing risk from exposure to ethylene dibromide due to its LOAEL of 80 mg/kg/day and the severity of outcomes. This study was designed and intended to measure precursor events in the pathway for alkylating agents. Although effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case it was being examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. The only endpoint available for dose-response analysis for oral exposure that was of sufficient quality was cell proliferation and hyperkeratosis in the forestomach ([Ghanayem et al., 1986](#)). The HED from benchmark dose modeling was calculated to be 2.7 mg/kg/day. Again, the forestomach is a rodent-specific structure lined with squamous epithelium and is not present in humans, rodents also possess a glandular stomach, which is more closely comparable to the human stomach due to its specialized mucosal epithelium involved in secretion of gastric enzymes and acid. Although effects observed in the rodent forestomach are not assumed to be directly relevant to humans, this may be reconsidered when supported by MOA evidence.

Proctor et al. (2007) provides three criteria that determine human health relevance of forestomach tumors observed in rodent studies. Those criteria are well-established genotoxicity, its ability to induce

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tumors at multiple sites across a range of doses, and the observation that these effects occur in the absence of forestomach irritation. The non-cancer effects observed in Ghanayem (1986) were selected by the study authors because they are precursor effects to the tumors seen at longer durations; these effects represent non-cancerous histopathological changes at an earlier stage of the adverse outcome pathway for ethylene dibromide. Ethylene dibromide meets the criteria in Proctor et al. (2007), which suggests forestomach effects are relevant, despite the anatomical difference between humans and rodents.

Table 2-3. Summary of Candidate Intermediate Oral, Non-Cancer PODs for Ethylene Dibromide

Target Organ/System	Species/Exposure	NOAEL	LOAEL	Endpoint	Candidate POD	Reference (OQD)
Gastrointestinal	Rat Oral gavage 5 days/week 2 weeks	Adverse effects at lowest dose tested	80 mg/kg/day	forestomach epithelial cell proliferation and hyperkeratosis	2.7 mg/kg/day (HED/BMD0L₁₀)	Ghanayem et al. (1986) (High)
BMDL ₁₀ = benchmark dose lower 95% confidence limit with a benchmark response of 10% extra risk; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; OQD = overall quality determination; POD = point of departure Bolded value = identified POD for ethylene dibromide intermediate oral exposures						

Although there were no mechanistic studies flagged for gastrointestinal outcomes related to ethylene dibromide exposure per se, alkylating agents as a class are known to cause gastrointestinal effects via multiple mechanisms: emetogenesis through a pathway mediated by the chemoreceptor trigger zone (O'Brien, 2008) as well as breakdown of the gastrointestinal mucosa due to differential cytotoxicity of alkylating agents on rapidly dividing cells, such as those lining the intestinal tract (Mustian et al., 2008). EPA has moderate confidence in the Ghanayem, et al. (1986) study's consideration of dose response, as two dose groups were utilized in addition to a control group, which is sufficient for consideration of dose effects. There is moderate confidence in this POD's relevance to exposure, as oral exposure is relevant to general population scenarios related to consumption through polluted water and fish from polluted waterways. However, the POD utilizes gavage experimentally rather than food or drink to expose animals. Effects are expected to be similar but may not directly capture all factors associated with oral exposure.

Although relatively little evidence in animal studies is available for gastrointestinal outcomes, (NCI, 1978) supports the findings described in (Ghanayem et al., 1986) at a chronic exposure duration, as the histological lesions in the former are more advanced and severe versions of the same histopathological changes from the latter, linked by the adverse outcome pathway for this chemical. Additionally, adverse gastrointestinal outcomes have been reported in several cases of acute oral and inhalation exposure in humans (Singh et al., 2007; Saraswat et al., 1986; Peoples et al., 1978), resulting in moderate confidence in the available data. The intermediate oral HED was calculated to be 2.7 mg/kg/day with a benchmark MOE of 30 (UF_A 3 since using an HED, UF_H 10) based on benchmark dose modeling of the data in (Ghanayem et al., 1986). The critical effect was hyperkeratosis of the epithelium of the stomach; the co-critical effect was cellular proliferation of the epithelium of the stomach. Benchmark dose modeling for oral exposure for the intermediate duration was found to be acceptable based on Ghanayem, et al. (1986) and the decision tree logic in U.S. EPA (2012b). The Benchmark Dose Software produced eight viable models (Gamma, Log-Logistic, Multistage 1, Weibull, Logistic, Log-Probit, and Quantal Linear). Two models gave identical fits (Multistage 1 and Quantal Linear). The Benchmark Dose Software recommended the Multistage 1 model based on having the lowest BMDL, but it was tied (with the Quantal Linear model) as the viable model with the highest AIC, so it was not selected. The Weibull model was selected instead based on having the lowest AIC value with a viable fit. A plot of the selected

model versus the data is shown in Figure_Apx D-2. The benchmark dose was 8.6 mg/kg/day, the BMDL was 2.7 mg/kg/day. More information on EPA's benchmark dose modeling of this study can be found in Appendix D.3. Oral-to-dermal extrapolation was determined to be invalid as a potential route-to-route extrapolation as the adverse effects seen in the oral study were at the portal of entry. Route-to-route extrapolation should generally be for systemic, not local, effects.

Acute Duration

EPA considered all reasonably available acute (exposure for ≤ 24 hours) oral studies. While several animal studies were identified with medium overall quality determinations ([Ledda-Columbano et al., 1987](#); [Nachtomí, 1980](#); [Broda et al., 1976](#); [Nachtomí et al., 1968](#)), none of the identified acute references tested more than one exposure level, making these references unusable for dose response. Ghanayem, et al. ([1986](#)) exposed test animals to ethylene dibromide five times per week, for 2 weeks. For oral studies, the available study for dose-response had multiple oral exposures. This dosing regimen falls under the "intermediate" duration for toxicity studies because there was more than one exposure to the same dosing groups. Because of the low number of exposures (10 exposures over 2 weeks) and because there were no high-quality acute studies for dose response, this study was used to derive both an acute and intermediate POD for oral exposures.

Human studies show that gastrointestinal symptoms are a common finding after acute oral exposure to ethylene dibromide but were not suitable for dose-response due to study design. In a case series describing 64 cases of acute exposure to ethylene dibromide, all cases had symptoms of nausea, vomiting, and abdominal pain ([Singh et al., 2007](#)). In a case series describing six cases of ethylene dibromide ingestion, there was stomach wall congestion in the first case; vomiting, nausea, and burning throat in cases two through five; and vomiting in the sixth case ([Saraswat et al., 1986](#)). In a report on two cases of ingestion of three mL of ethylene dibromide, one case showed generalized abdominal pain and the other case showed vomiting and diarrhea ([Mehrotra et al., 2001](#)). In a case report of a 20 year old who consumed 3 mL of ethylene dibromide, the individual developed recurring vomiting over the course of 5 days ([Prakash et al., 1999](#)). In this case, because the mass of ethylene dibromide was known and the weight of the individual was included in the report, a rough estimate of the dose could be made, giving 116 mg/kg. Finally, in another case report of ethylene dibromide ingestion, there was noted vomiting ([Singh et al., 2000](#)). This indicates that the initial symptoms of acute ethylene dibromide ingestion are in the gastrointestinal tract. Rats and mice physiologically lack the ability to vomit; it is possible that these symptoms might have appeared at lower levels than hyperkeratosis and cell proliferation in the forestomach had they been possible. Nausea and vomiting can also be triggered by stimulation of the chemoreceptor trigger zone in the brain separately from tissue damage in the gastrointestinal tract, this is known to be the principal contributor to chemotherapy-induced nausea and vomiting from alkylating chemotherapy agents, which are typically administered intravenously ([NIDDK, 2015](#); [Mustian et al., 2008](#)). Taken together, the available human and animal evidence indicates that adverse effects on the gastrointestinal tract are a sensitive endpoint for acute oral exposures to ethylene dibromide and supports basing the acute oral POD on these effects in rats.

Chronic Duration

EPA considered all reasonably available chronic oral data and identified one study that had dosing levels appropriate for dose response assessment and was assigned a medium or high overall quality determination ([NCI, 1978](#)). This reference is summarized in Table 2-4 below. This reference was also selected by U.S. EPA ([2004b](#)) for calculation of chronic inhalation RfC. National Cancer Institute ([1978](#)) reports co-critical liver, reproductive, and adrenal endpoints. At 38 mg/kg/day, liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy were identified in rats. While not related specifically to ethylene dibromide, there is strong mechanistic evidence linking alkylating agents, as a

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class, with male reproductive effects including testicular atrophy ([Sriram et al., 2024](#); [Lazowski et al., 1982](#)). EPA has moderate confidence in National Cancer Institute (1978) consideration of dose response, as two dose groups were utilized in addition to a control group, which is sufficient for consideration of dose effects. There is moderate confidence in this POD's relevance to exposure, as oral exposure is relevant to general population scenarios related to consumption of impacted water and fish. However, the study for which the POD was derived included animals dosed via gavage rather than via diet or drinking water, which would have been more relevant to the general population than gavage. Effects are expected to be similar but may not directly capture all factors associated with oral exposure. The chronic oral POD was calculated to be 3.3 mg/kg/day based on benchmark dose modeling of the liver effects data in ([NCL, 1978](#)). Adrenal cortex degenerative lesions were not suitable for benchmark dose modeling due to a non-monotonic dose response. Testicular atrophy was not chosen for two reasons: (1) it is not relevant to females, and (2) there was a high background level in the control group decreasing the sensitivity of this endpoint when compared to the liver effects.

Table 2-4. Summary of Candidate Chronic Oral, Non-Cancer PODs for Ethylene Dibromide

Target Organ/System	Species/ Exposure	NOAEL	LOAEL	Endpoint	Candidate POD	Reference (OQD)
Liver	Rat Oral gavage 5 days/week ^a	Adverse effects at lowest dose tested	38 mg/kg/day	Liver necrosis, focal and liver peliosis hepatis	3.3 mg/kg/day (HED/BMDL₁₀)	NCI (1978) (Medium)
BMDL ₁₀ = benchmark dose lower 95% confidence limit with a benchmark response of 10% extra risk; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; OQD = overall quality determination; POD = point of departure ^a Untreated control animals were on test for 107 weeks. Vehicle control animals were on test for 63 weeks, with vehicle administered by gavage for 49 of those weeks. Low-dose animals were on test for 49 weeks, with the chemical being administered for 47 of those weeks. High-dose animals were on test for 49 weeks, with the chemical being administered for 34 of those weeks. Bolded value = identified POD for ethylene dibromide chronic oral exposures						

Benchmark dose modeling for oral exposure for the chronic duration was found to be acceptable according to the decision logic in EPA's Benchmark Dose Technical Guidance ([U.S. EPA, 2012b](#)). The Benchmark Dose Software produced seven viable models (Gamma, Log-Logistic, Multistage 1, Weibull, Logistic, Probit, and Quantal Linear). Two models gave identical fits (Multistage 1 and Quantal Linear). The Benchmark Dose Software recommended the Multistage 1 model based on having the lowest AIC value with a viable fit, and this is the model that was selected. A plot of the selected model versus the data is shown in Figure Apx D-6. The BMD was 4.6 mg/kg/day and the BMDL was 3.3 mg/kg/day. More information on EPA's benchmark dose modeling of this study can be found in 3.4.3D.5 Appendix D.5. The choice of UFs is discussed in Section 2.3.2.6.2 below, with a total UF of 30. The critical study was performed in male Osbourne-Mendel rats. The critical effects were focal necrosis and peliosis hepatis in the liver.

As mentioned above in Section 2.3.2.3, to estimate the dermal chronic non-cancer POD, the inhalation POD, along with the oral chronic non-cancer POD were used for route-to-route extrapolation to the dermal route of exposure. In the case of the critical effects for the chronic endpoints, both the oral and inhalation studies used systemic effects, specifically adverse histopathological changes of the liver. Both were considered to be suitable choices for extrapolation. The chronic dermal POD was extrapolated from the oral data in ([NCL, 1978](#)). Using the default approach, the POD was determined to be 3.3 mg/kg/day. Using the PBPK approach, the POD differed based on the exposure scenario. Factors like exposure magnitude, frequency, and duration; concentration of ethylene dibromide in the mixture/product, and exposed skin surface area affect the values. The PODs ranged from 5.4 to 5.7

mg/kg/day (in volumes ranging between 1–5 mL) for high-end estimates and 5.6 to 6.0 mg/kg/day (in volumes of 6.6–14 mL) for central tendency estimates. The choice of UFs is discussed in Section 2.3.2.6.2 below.

2.3.2.5 Dermal Route-to-Route Extrapolation Approach

To characterize human health hazards from dermal exposure to ethylene dibromide, EPA used a tiered, route-to-route extrapolation approach, applying both default screening methods and then refinements through PBPK-based methods, to derive dermal HEDs for non-cancer and cancer endpoints. At the screening tier, the default approach translated animal toxicity values from oral and inhalation toxicity studies to HEDs using allometric scaling, which assumes that many physiological processes scale with body size. This approach has been widely used in risk evaluations because it is straightforward and provides a consistent approach for when chemical-specific data are limited. However, it primarily relies on addressing interspecies differences through body size relationships.

At the refinement tier, PBPK-based route-to-route extrapolation was applied. PBPK models mechanistically represent time-varying ADME of a substance and incorporate species-specific physiological and biochemical parameters. The PBPK model simulates the chemical kinetics in both animal and humans and identifies the human exposure that would produce the same internal dose metric associated with toxicity in the critical animal study of concern. Because the model is mechanistic, it provides a context-specific basis for dermal risk evaluation. The incorporation of systemic and time-course kinetics furnishes additional tiered support and confidence in extrapolation methods that go beyond the sole reliance of body weight scaling. Toxicokinetic data were evaluated to inform route-to-route and interspecies extrapolation of animal oral and inhalation PODs to dermal HEDs. The consistent evidence of observed toxicological effects resulting from both oral and inhalation routes of exposure and systemic toxicity provides confidence in performing route-to-route extrapolation of available oral and inhalation data using a PBPK model to derive dermal PODs for non-cancer.

POD Selection

For a POD to be relevant for route-to-route extrapolation, it must be associated with systemic effects. The PODs from animal studies were identified as reported in Section 2.3.1. A chronic inhalation LOEC was identified from (NTP, 1982) as the basis for POD determination because it evaluates sensitive dose levels and the endpoints reported reflect patterns seen in acute, intermediate, and chronic studies. At 38 mg/kg/day, co-critical effects of liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy are identified in rats. At 10 ppm exposure in rats, a critical outcome of liver necrosis is identified. Additionally, adrenal cortex degradation and testicular degradation are significant, as well as retinal atrophy, nasal cavity inflammation, and splenic hematopoiesis. The liver, adrenal, and testicular endpoints are mirrored in many non-cancer studies described in Section 2.3.1. A chronic oral LOAEL was identified from NCI (1978) and converted to a BMDL of 11 mg/kg/d. Both the inhalation and oral chronic studies describe similar effects, notably on the liver. For acute/intermediate inhalation exposure, there was a difference between the default and PBPK approaches described below.

For the default approach, the same critical study in mice (Short et al., 1978) was used to select the POD, as described in Section 2.3.2.3. For the PBPK approach, (Short et al., 1979) was selected, which is a rat study that evaluated the effects of ethylene dibromide exposure on male and female reproductive endpoints including implantations and resorptions. EPA did not have a mouse PBPK model available so this rat study was chosen as an alternative critical study. Males or females were exposed, then mated with non-exposed controls. A male LOAEL of 89 ppm was determined for decreased fertility and testicular atrophy. Note that in the Short et al. (1979) intermediate inhalation study, both male and female rats were exposed to ethylene dibromide, but male rats were given higher daily concentrations

(89 ppm) than female rats (80 ppm), but for a shorter duration, resulting in a lower internal dose metric in male rats (2,080 $\mu\text{M}/\text{d}$) compared to female rats (2,550 $\mu\text{M}/\text{d}$). Both concentrations resulted in mortality for each sex. Thus, the 89-ppm endpoint is used for the PBPK route-to-route extrapolation, as it is more protective. The PODs and corresponding BMDL or BMCL reported in Table 2-5.

2.3.2.5.1 Default Approach

The “default approach” for route-to-route extrapolation can be broken down into three distinct components: (1) adjusting for interspecies differences in toxicokinetics by deriving an HED or HEC; (2) modeling the dose-response relationship from the experimental data in the critical study (benchmark dose modeling) using the HED/HEC values; and (3) adjusting for differences in absorption between the original route of exposure (oral or inhalation) and the extrapolated route of exposure (dermal).

For the default approach, data were taken from four critical studies. For the two oral studies, an HED was calculated using body weight to the three-quarters power allometric scaling ($\text{BW}^{3/4}$). This aligns with EPA’s guidance on $\text{BW}^{3/4}$ -scaling. For the two inhalation studies, an HEC was calculated by adjusting for continuous exposure (24 hours/day, 7 days/week) using Haber’s Law ([Haber, 1924](#)) and applying an RGDR specific to ethylene dibromide. Because ethylene dibromide is a category 3 gas, an RGDR of 1 was found to be appropriate. All doses/concentrations in the critical study were converted in this way, as they are inputs to the next step in the process. This adjustment allows the TK portion of the interspecies uncertainty factor (UF_A) to be reduced from 3 to 1; the overall UF_A is therefore reduced from 10 to 3.

Benchmark dose modeling allows for estimation of a benchmark dose (the dose corresponding to the benchmark response [BMR], which is taken as the cut point for adversity for a given endpoint), and the confidence interval around the benchmark dose. The POD is commonly taken as the BMDL or the lower 95th percentile confidence limit on the benchmark dose (BMDL). HED/HEC values are entered as the doses/concentrations, and response levels are entered as continuous (*e.g.*, body weight) or dichotomous (*e.g.*, incidence) variables. The software (BMDS Online build 491f764a) finds the best curve to describe the dose-response relationship given particular statistical constraints and then calculates the BMD and BMDL for a given response threshold (*i.e.*, the BMR). For cancer calculations, it also calculates the slope factor in the low-dose region assuming low-dose-linear extrapolation. Benchmark dose modeling was performed for all routes and durations except for intermediate inhalation, where the data were found to be unsuitable for modeling (this value was also used as the acute POD for inhalation). Where benchmark dose modeling is performed, the LOAEL-to-NOAEL uncertainty factor (UF_L) can be reduced from 10 to 1 because the BMDL is a statistically-rigorous estimate of the NOEL. Because the LOAEL for the intermediate inhalation study was based on a reproductive and developmental toxicity (DART) study, and the study was not amenable to BMD modeling, UF_L was reduced from 10 to 3, which is recommended in this situation ([U.S. EPA, 2002a](#)) and peer-reviewed literature ([Dourson et al., 1996](#)) where a NOAEL cannot be identified but the database includes a developmental and/or reproductive toxicity study.

Adjustment for absorption is performed last to account for differences in bioavailability by different routes of exposure. Bioavailability is defined as the fraction of a dose that is absorbed into the systemic circulation. For example, if a chemical has an oral bioavailability of 0.5, one possibility is that half of the dose is absorbed into the bloodstream while the other half passes unchanged through the digestive tract and is eliminated in the feces unabsorbed. For ethylene dibromide, given its physical-chemical properties, absorption via oral or inhalation exposure is expected to be effective, so the assessment team assumed bioavailability of 1 (*i.e.*, 100% absorption). For dermal exposures, EPA had a choice of adjusting the point of departure (*i.e.*, hazard) values for less than complete absorption, or adjusting the

dermal dose (*i.e.*, exposure) values to account for absorption, evaporation, and other processes that affect the level of absorption. The Agency decided to account for dermal absorption on the exposure side. Therefore, the absorbed dose used in the dermal risk calculators is less than the applied dose; that is, the difference between the absorbed dose and applied dose constitutes the amount unavailable to the systemic circulation.

2.3.2.5.2 Default Assumptions

Oral and inhalation PODs were developed independently from critical studies identified through EPA's systematic review process. When considering the suitability of route-to-route extrapolation, a number of considerations need to be accounted for. The Interdepartmental Group on Health Risks from Chemicals has published "Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals" (IGHRC, 2006). Section 4 of these guidelines lays out five criteria to consider when performing route-to-route extrapolation:

1. Absorption is the same between routes, or the difference is known and can be quantified.
2. The critical target tissue is not at the portal of entry of the compound (*i.e.*, the concern is with systemic toxicity and not local effects).
3. There is no significant metabolism of the chemical by oral, gut or skin enzymes or in pulmonary macrophages, or transformation by other processes in the gut or lung.
4. First-pass effects are minimal.
5. The chemical is relatively soluble in body fluids.

Going through each criterion in turn:

1. For ethylene dibromide, the difference in absorption is known and can be quantified; specifically, absorption via oral or inhalation exposure is taken as 100% and absorption via dermal exposure is adjusted for by mathematically adjusting the applied dose to get an absorbed dose.
2. Consideration #2 is specific to the endpoint, duration, and route of exposure (see more below for details).
3. There is metabolism in the liver, kidneys, lungs, testes, stomach, small intestines, and skeletal muscle. However, rate in extrahepatic tissues is a small fraction of the hepatic metabolism, so this is still considered reasonable ($V_{\max}$ liver = 413.8, $V_{\max}$ kidneys = 0.15, and $V_{\max}$ lungs = 0.04 $\mu\text{mol/h/kg}$).
4. First-pass effects are moderately important for oral-to-dermal extrapolation and negligible for inhalation-to-dermal extrapolation. The liver is the target organ for non-cancer effects for oral and inhalation studies, so this is still considered reasonable.
5. Ethylene dibromide is sufficiently soluble in body fluids to allow for systemic exposure following oral, dermal, and/or inhalation administration.

2.3.2.5.3 PBPK – Non-Cancer Oral/Inhalation to Dermal Extrapolation

Dermal HEDs were calculated using the following steps, as described in Section 2.2.5.2.

Step 1: Identify Animal PODs Associated with Toxicity Studies

Animal PODs are described in the introduction of Section 2.3.2.5

Step 2: Estimate Internal Doses from Animal PODs

EPA considered the amount of ethylene dibromide metabolized by the GST pathway in the liver per liver volume (weight) per day ($\mu\text{M-d}$) as the most appropriate dose metric considering its mutagenic MOA discussed in Section 2.4.6. For each POD that is relevant for route-to-route extrapolation (*i.e.*, PODs for systemic effects), the external exposure was translated into an internal dose metric using the

PBPK model. The PODs, corresponding BMDL or BMCL, and associated PBPK-predicted internal dose are reported in Table 2-5; justifications for using these PODs are provided in Section 2.3.2.2.

Table 2-5. Rodent Internal Doses for Inhalation and Oral Exposures for Amount Metabolized in Liver (per L Liver) per Day (μM/d) for Each Rat POD and Exposure

Internal Dose (μM-d)	POD _{Rat}	POD Type	Route of Exposure	Exposure Scenario	Species	Endpoint	Source
105	9 ppm	BMDL (from LOEC of 10 ppm)	Inhalation	6 h/day, 5 days/week, 103 weeks	Mixed sex F344 rats	Chronic, non-cancer	NTP (1982)
183	11 mg/kg/d	BMDL (from LOEL of 38 mg/kg/d)	Oral	Daily gavage in corn oil, 5 days/ week for 365 days	Male Osborne-Mendel rats	Chronic, non-cancer	NCI (1978)
2,080	89 ppm	Dose seen with effects (highest dose in the study, ~20% mortality)	Inhalation	7 h/day, 5 days/week for 10 weeks	Male CD rats	Acute, non-cancer	Short et al. (1979)
BMDL = benchmark dose lower 95% confidence limit; LOEC = lowest-observed-effect concentration; LOEL = lowest-observed-effect level; POD = point of departure							

Step 3: Calculate Dermal HEDs to Reach Target Internal Dose Metrics

For each scenario, PBPK model predicted a corresponding volume of ethylene dibromide solution at the scenario-specific concentration (wt %) allowing to calculate an HED in mass unit (mg/kg/day). See Section 2.6.3 for the HEDs generated for each COU and the applicable exposure context. The HED values reported in Table 2-21 include the volumes of ethylene dibromide solution across various solute/vehicle compositions needed to achieve skin-surface effective concentrations that produces the internal doses equivalent to the rodent PODs under the relevant human exposure scenarios. These volumes are derived from the PBPK model using the scenario-specific ethylene dibromide concentration at the skin surface (expressed as % in the carrying vehicle), given the specified contact area and duration. Using the estimated volumes and scenarios-specific exposure concentrations, mass-based HEDs were calculated using the formulation molar density derived from component densities ([EAG, 1992](#)).

Step 4: Interpret HEDs Within Context

Non-cancer dermal HEDs are defined as the retained dermal doses to which an adult human must be exposed in order to reach the same animal non-cancer internal doses (reported in Table 2-21 for certain exposure conditions and over some duration and frequency. See Table 2-21 for a list of HEDs for each of COU and exposure conditions.

Note that in some cases, PBPK results indicated that exposures to formulations of 0.085 to 0.1 wt % were unable to reach the internal dose metric of concern. As discussed earlier, surface concentration is critical to achieving the target internal dose; exposure to a diluted solution would not be able to yield a comparable internal dose, even if a larger volume is applied. In simulations reflecting surface concentrations consistent with fueling COUs (0.1% ethylene dibromide), chronic and acute exposure scenarios did not achieve the target internal concentration. Reverse dosimetry results indicate that, under expected human exposure conditions as defined in *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)), achieving the target internal dose would require high concentrations (e.g., neat ethylene dibromide) and/or large applied volumes. The following

provides an example of how to interpret the results within context: for the occupational import COUs and exposure scenarios, where high-end exposures involve two hands (1070 cm²) being exposed to 60% ethylene dibromide, route-to-route extrapolation (chronic inhalation-to-dermal) predicted that the dermal exposure necessary to reach the hazardous internal dose was an HED of 3.38 mg/kg/day ethylene dibromide in a 3 mL solution; conversely, acute and intermediate inhalation-to-dermal extrapolation predicted an HED of 42 mg/kg/day ethylene dibromide in a 35 mL volume solution.

2.3.2.6 Dose-Response Derivation for Non-Cancer Hazard Values

As described in Section 2.3.2, EPA identified the best available studies for ethylene dibromide for quantitative dose-response analysis. The sections below describe the steps used to derive the hazard values used to calculate risks for ethylene dibromide. Hazard values were derived for both the oral and inhalation routes and route-to-route extrapolation was used to derive dermal values from these oral and inhalation values, where appropriate. EPA conducted BMD modeling in accordance with guidance ([U.S. EPA, 2012b](#)) to refine PODs for the endpoints and studies described in Section 2.3.2. EPA decisions on modeling of specific datasets and results are described below. For each hazard outcome see Appendix D for a summary of all BMD modeling results, including model selection, alternative endpoint options, statistical tests, results from all models, and any associated graphs. Studies not listed were not possible to model by the BMD software or were uninformative for dose-response analysis.

2.3.2.6.1 Duration, Dosimetric, and Unit Adjustments

Dosimetric Adjustments

Ethylene dibromide is a liquid under standard conditions. However, due to its volatility, inhalation exposure to the vapor is expected. When inhaled, ethylene dibromide is expected to act as a category 3 gas as defined in the “Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry” ([U.S. EPA, 1994](#)). Category 3 gases are water insoluble/perfusion limited, where absorption predominantly occurs in the pulmonary region.

Duration Adjustments

The studies selected for dose-response assessment utilized differing exposure durations and frequencies. 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 based on Haber’s Law ([Haber, 1924](#)) using the Equation 2-1 below:

Equation 2-1. Adjusting Average Exposure Concentration or Inhalation POD for Differences in Days and Hours of Exposure Across Scenarios

$$Concentration_{continuous} = Concentration_{study} \times \left(\frac{D_s}{7}\right) \times \left(\frac{H_s}{24}\right)$$

Where:

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

Unit Conversion

It is often necessary to convert between ppm and mg/m³ due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all inhalation hazard values throughout this document in both units. Equation 2-2 presents the conversion of the HEC from mg/m³ to ppm.

Equation 2-2. Converting ppm to mg/m³

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

Dose-response information that meets EPA's quality criteria from dermal exposure studies was not available. As a result, route-to-route extrapolation was performed from inhalation to dermal as described in Section 2.4.7.4. The "default" method of route-to-route extrapolation uses Equation 2-3 to convert inhalation HEC values to dermal HED values. A PBPK model was also used, as described elsewhere in this document.

Equation 2-3. Converting Inhalation HEC to Dermal HED

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

Where:

Daily inhalation rate	=	14.7 m ³ for a continuous exposure (equivalent to 0.6125 m ³ /hour)
Body weight	=	80 kg for an average adult

The acute and intermediate inhalation PODs were set at 150 mg/m³ (20 ppm) based on skeletal malformations and increased resorptions in mice exposed to ethylene dibromide as shown in Short (1978) with a total UF of 100. The choice of UFs is discussed in Section 2.3.2.6.2 below. The critical study was performed in male and female CD rats and CD-1 mice, with pups born to CD-1 mice selected as the basis for the POD.

Dosimetric Adjustments

EPA reviewed the PBPK model on ethylene dibromide and a discussion is found elsewhere in this document.

For comparison to the PBPK model results, 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 2-4.

Equation 2-4. Dosimetric Adjustment Factor (DAF)

$$\text{DAF} = \left(\frac{\text{BW}_A}{\text{BW}_H} \right)^{1/4}$$

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)

The acute and intermediate oral HEDs adjusted for duration (5–7 day extrapolation) and BW^{3/4} were calculated to be 2.7 mg/kg/day based on benchmark dose modeling of the data in (Ghanayem et al.,

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

1986). The critical effect was hyperkeratosis of the epithelium of the stomach, the co-critical effect was cellular proliferation of the epithelium of the stomach

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 draft assessment (U.S. EPA, 2011a). The Agency used the body weights of 0.025 and 0.25 kg for mice and rats, respectively, as presented in (U.S. EPA, 2011b). The resulting DAFs for mice and rats are 0.13 and 0.24, respectively. Doses were adjusted to HEDs prior to benchmark dose modeling (BMD).

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 2-4.

Equation 2-5. Adjusting Average Exposure Concentration or Inhalation POD for Differences in Days and Hours of Exposure Across Scenarios

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

Where:

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

2.3.2.6.2 Uncertainty Factors Used for Non-Cancer Endpoints

EPA commonly uses extrapolation and uncertainty factors in risk assessment to extrapolate between species, across the diverse human population, and to account for other uncertainties in the available toxicology data. For interspecies and intraspecies extrapolation factors EPA has developed guidance documents (e.g., DDEF guidance and reference concentration [RfC] guidance) that describe tiered processes for evaluating the available data and determining the most appropriate extrapolation approach. These approaches have been followed in this draft risk evaluation.

The EPA *Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation* (also called “DDEF guidance”) recommends a “data first, defaults second” approach (U.S. EPA, 2014b). Although the DDEF guidance specifically focuses on the interspecies and intraspecies extrapolation factors, this recommendation is also more broadly applicable to other uncertainty factors. When developing risk evaluations, EPA makes chemical-specific determinations on the appropriate uncertainty factors using the available toxicology studies along with information on pharmacokinetics and mechanistic understanding. For purposes of transparency, as shown below, it is important for the Agency to explain and justify the application and magnitude when applying uncertainty factors.

In general, the higher the total, composite uncertainty factor, the higher the uncertainty in the hazard value. The following text describes the appropriate interspecies, intraspecies, and LOAEC-to-NOAEC uncertainty factors appropriate for ethylene dibromide.

For the non-cancer health effects, EPA used a total UF of 30 for the benchmark MOEs for acute, intermediate, and chronic exposure durations for all exposure routes among studies that are used to

estimate risks—with the exception of the acute and intermediate values for inhalation (and the inhalation-to-dermal route-to-route extrapolations based on these values). For acute and intermediate inhalation, benchmark dose modeling did not produce any usable model fits, and EPA selected a LOAEC as the point of departure. An NOAEC could not be derived based on the data. Given this, EPA used a LOAEC-to-NOAEC UF of 3 with a total benchmark MOE of 100. EPA guidance further discusses considerations for application of UFs in human health hazard dose-response assessment ([U.S. EPA, 2014b, 2012a, 2002a, 1993a](#)).

1. Interspecies Uncertainty Factor (UF_A) of 3

- a. 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 dermal HED values because these values are derived from the oral HED.

2. Intraspecies Uncertainty Factor (UF_H) of 10

- a. 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 ethylene dibromide.

3. LOAEC-to-NOAEC Uncertainty Factor (UF_L) of 1 or 3

- a. The PODs chosen to calculate acute, intermediate, and chronic risks for oral exposures, chronic inhalation exposures, and the dermal PODs based on these values using route-to-route extrapolation, were BMDL/BMCL values and therefore, EPA used a UF_L of 1. For acute and intermediate inhalation exposures and the inhalation-to-dermal route-to-route extrapolations based on these values, a BMCL could not be derived and a LOAEC was used instead, and for this case EPA used a UF_L of 3. In studies where a no-observed adverse effect level cannot be identified, a UF_L of 3 or 10 is applied to account for extrapolation down to the dose where no effects would be expected. In this case, a value of 3 was used because the LOAEC was based on a reproductive/developmental toxicity study, which was considered adequate for reducing the UF_L based on Agency policy.

2.3.2.7 Summary of Non-Cancer PODs

Past assessments have evaluated non-cancer effects for ethylene dibromide, where PODs from past assessments are summarized in Table Apx C-1. The decisions around cancer slope factors (CSFs) are discussed in detail in Section 2.4.7.5. In this assessment, EPA selected non-cancer PODs for acute, intermediate, and chronic oral exposures, acute, intermediate, and chronic inhalation exposures. ATSDR considered non-cancer studies but did not derive any MRLs for acute, intermediate, or chronic durations. NICNAS selected PODs for acute oral exposure, acute inhalation exposure, and chronic inhalation exposure. EPA's IRIS Program selected PODs for subchronic inhalation exposure, chronic oral exposure, and chronic inhalation exposure ([U.S. EPA, 2004b](#)). California's Office of Environmental Health Hazard Assessment and Air Resources Board (OEHHA/ARB) selected a POD for chronic inhalation exposure ([CalEPA, 2001](#)). Overall, there was a high degree of concordance among assessments, when agencies chose to quantify values for their specific program needs.

In regard to conducting route-to-route extrapolation to estimate dermal PODs based on both oral and inhalation empirical toxicity data, EPA presents potential dermal PODs below (Table 2-6); however, the inhalation-to-dermal extrapolation was selected for risk characterization resulting from dermal exposure to ethylene dibromide. Best available science supports choosing inhalation as the basis for extrapolation

by choosing the route of exposure that results in effects most similar to those resulting from dermal exposure; since both inhalation and dermal exposures bypass the “first-pass effect” in the liver, they result in similar liver exposures. Given the centrality of metabolism to the bioactivation of ethylene dibromide as well as the choice of liver effects as the critical effect for both oral and inhalation PODs support the decision to estimate PODs extrapolation from inhalation studies. Oral exposures will lead to different liver concentrations due to the first pass effect. The PBPK approach represents a refinement over the default approach. The high-end scenarios reported in Table 2-21 were used for the POD since there was not much difference between high-end and central tendency (*i.e.*, CT values range from 3.4 mg/kg/day in 7.9 mL to 3.6 mg/kg/day in 3.3 mL while HE values range from 3.3 mg/kg/day in 0.83 mL to 3.4 mg/kg/day in 2.7 mL), and these scenarios match those for the risk calculations. As a result, the chronic dermal POD was selected to be a range from 3.3 to 3.4 mg/kg/day with a total UF of 30. These values are HEDs from the HE scenario; the doses range from 3.3 to 3.4 mg/kg/d across each HE COU for formulations that contain 60 to 100% ethylene dibromide. The volumes of each HED range from 0.83 to 2.7 mL, depending on the formulation concentration. Note that this does not apply for the HE Avgas COU of 0.1%, for which no dermal HED could be calculated due to the concentration (0.1% ethylene dibromide) being too low to reach a hazard value.

2855 **Table 2-6. Non-Cancer PODs for All Routes of Exposure for Ethylene Dibromide**

Target Organ System	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Reference	OQD ^c	POD Selection Confidence ^d
Acute and intermediate inhalation POD									
Reproductive/developmental	Mouse	24 hours/day, 10 days (starting GD=6)	LOAEC = 20 ppm/day	Fetal developmental abnormalities and increased late resorptions	HEC = 150 mg/m ³ (20 ppm)	100 [UF _A = 3, UF _H = 10, UF _L = 3]	Short et al. (1978)	High	Slight (acute duration) Moderate (intermediate duration)
Acute and intermediate oral POD									
Gastrointestinal	Rat	5 days/week, 2 weeks	LOAEL = 80 mg/kg/day	Forestomach epithelial cell proliferation and hyperkeratosis	HED = 2.7 mg/kg-bw/day	30 [UF _A = 3, UF _H = 10]	Ghanayem et al. (1986)	High	Slight (acute duration) Moderate (intermediate duration)
Acute and intermediate dermal POD									
Reproductive/developmental	Mouse	24 hours/day, 10 days (starting GD=6)	LOAEC = 20 ppm/day	Fetal developmental abnormalities and increased late resorptions	HED = 28 mg/kg/day (This is the default route-to-route extrapolation from the acute and intermediate inhalation POD)	100 [UF _A = 3, UF _H = 10, UF _L = 3]	Short et al. (1978)	High	Slight (acute duration) Moderate (intermediate duration)
Reproductive/developmental	Rat	7 hours/day, 5 days/week, 10 weeks	LOAEC = 89 ppm/day	Testicular atrophy, lowered fertility	HE = 38–40 mg/kg/d (9–33 mL) CT = 43–45 mg/kg/d (24–100 mL) (This is a PBPK route-to-route extrapolation from the acute and intermediate inhalation POD)	100 [UF _A = 3, UF _H = 10, UF _L = 3]	Short et al. (1979)	High	Slight (acute duration) Moderate (intermediate duration)
Chronic inhalation POD									

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Target Organ System	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Reference	OQD ^c	POD Selection Confidence ^d
Liver	Rat	6 hours/day, 5 days/week, 2 years	LOAEC = 10 ppm	Liver necrosis	HEC = 11 mg/m ³ (1.5 ppm)	30 [UF _A = 3, UF _H = 10]	NTP (1982)	High	Robust
Chronic oral POD									
Liver, adrenal, reproductive	Rat	5 days/week, 49 weeks	LOAEL = 38 mg/kg/day	Liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy	HED = 3.3 mg/kg-bw/day	30 [UF _A = 3, UF _H = 10]	NCI (1978)	Medium	Robust
Chronic dermal POD									
Liver	Rat	6 hours/day, 5 days/week, 2 years	LOAEC = 10 ppm	Liver necrosis	BMDL = 2.2 mg/kg/day (This is the default route-to-route extrapolation from the chronic inhalation POD)	30 [UF _A = 3, UF _H = 10]	NTP (1982)	Medium	Robust
Liver	Rat	6 hours/day, 5 days/week, 2 years	BMDL = 9 ppm from LOEC = 10 ppm	Liver necrosis	HE = 3.3–3.8 (1–3 mL) – selected value for risk calculation CT = 3.4–3.6 mg/kg/d (3-8mL) (This is a PBPK route-to-route extrapolation from the chronic inhalation POD)	30 [UF _A = 3, UF _H = 10]	NTP (1982)	Medium	Robust
Liver, adrenal, reproductive	Rat	5 days/week, 49 weeks	LOAEL = 38 mg/kg/day	liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy	BMDL = 3.3 mg/kg/day (This is the default route-to-route extrapolation from the chronic oral POD)	30 [UF _A = 3, UF _H = 10]	NCI (1978)	Medium	Robust

Target Organ System	Species	Duration	POD	Effect	HEC/HED ^a	Benchmark MOE ^b	Reference	OQD ^c	POD Selection Confidence ^d
Liver, adrenal, reproductive	Rat	5 days/week, 49 weeks	BMDL = 11 mg/kg/day From LOAEL = 11 mg/kg/d	Liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy	HE = 5.5–5.7 mg/kg/d (1–5mL) CT = 5.6–6 mg/kg/d (1–7 mL) (This is the PBPK route-to-route extrapolation from the chronic oral POD)	30 [UF _A = 3, UF _H = 10]	NCI (1978)	Medium	Robust

BMDL = benchmark dose lower 95% confidence limit; CT = central tendency; HEC = human equivalent concentration; HED = human equivalent dose; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level; MOE = margin of exposure; NOAEL = no-observed-adverse-effect level; PBPK = physiologically-based pharmacokinetic; POD = point of departure; UF = uncertainty factor

^a HED/HEC values were derived in accordance with the appropriate guidance (HED ([U.S. EPA, 2011b](#)), HEC ([U.S. EPA, 1994](#))). Exposure values used in the critical study were converted to HED/HEC values and benchmark dose modeling (BMD) was performed for all endpoints except for acute and intermediate inhalation, where BMD modeling was not possible. More details on non-cancer HEC/HED derivation and BMD modeling in Section 2.3.2.5, More details on cancer HEC/HED derivation and BMD modeling in Section 2.4.7.2.

^b UF = uncertainty factor; UFA = extrapolation from animal to human (interspecies); UFH = potential variation in sensitivity among members of the human population (intraspecies); UFL = LOAEC-to-NOAEC extrapolation; UFS = subchronic-to-chronic duration extrapolation

^c Overall quality determination (OQD) is a rating that is reported for each health outcome per study that undergoes data quality evaluation. Section 2.1.1 provides a brief overview and lists the data quality evaluation and extraction supplemental files relevant for studies identified for the characterization of environmental and human health hazard. Full details regarding the systematic review process for all the identified studies are described in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)).

^d POD selection confidence is based on an evaluation of the identified POD and the confidence in the alignment of this POD with the assigned route/duration and any uncertainties associated with the POD being used for risk estimates (*e.g.*, route-to-route extrapolation, duration adjustment). These considerations are summarized in Section 2.5.1.

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2.4 Cancer Hazard Assessment

2.4.1 Hazard Identification

This section summarizes the available human and animal carcinogenicity evidence resulting from ethylene dibromide exposure. Previous assessments have identified sufficient evidence to support a quantitative cancer risk assessment, which refers to the weight of scientific evidence conclusion based on integration of human, animal, and mechanistic data. Across assessment bodies, the criteria for cancer hazard designations (*e.g.*, likely, probable) are generally consistent and are typically supported by reproducible, dose-related tumor findings in animal studies, together with plausible mechanistic evidence when human data are limited. For ethylene dibromide, both the ([ATSDR, 2018](#)) and ([U.S. EPA, 2004b](#)) identified multisite tumor formation across species and exposure routes supported by robust mutagenicity as the key evidence supporting cancer classifications. Although these assessments were published years apart, the evidence relied upon establishing PODs remain consistent, with no newer data identified in the reviewed assessments that altered the current understanding of ethylene dibromide's mutagenic MOA for cancer. Appendix B contains additional information regarding specific evidence utilized by previous assessments to support cancer designations.

Ethylene dibromide has been extensively studied for its carcinogenic potential in both inhalation and oral animal studies, consistently demonstrating its ability to induce tumors at multiple sites in mice and rats. The following sections provide a detailed overview of the findings from these studies, which are critical for risk evaluation.

The summary of all studies identified containing cancer data resulting from inhalation, oral and dermal exposure, including overall quality determination ratings and limitations are presented in Table_Apx A-15, Table_Apx A-16, Table_Apx A-17, respectively. Tumor incidence endpoints considered for dose-response are characterized in Table 2-11 and Table 2-12, resulting from inhalation and oral exposure, respectively. The interactive web-based evidence integration table for [carcinogenic](#) (accessed June 18, 2026) effects is available in HAWC.

2.4.2 Human Evidence

Few epidemiology studies have assessed potential associations between ethylene dibromide exposure and cancer. The available epidemiology data on their own are insufficient to draw conclusions on potential associations between ethylene dibromide and carcinogenesis, and therefore, the epidemiology evidence is indeterminate for the potential carcinogenicity of ethylene dibromide. A description of the cancer epidemiology studies for ethylene dibromide is in Appendix A.7.1.

2.4.3 Laboratory Animal Evidence

EPA identified three chronic toxicity and cancer bioassays that evaluated the carcinogenicity of ethylene dibromide via inhalation ([U.S. EPA, 2026i](#)). These studies revealed that ethylene dibromide exposure induces a variety of tumor types across different anatomical sites in both mice and rats. Specifically, the studies documented the occurrence of carcinomas, adenocarcinomas, and adenomas in the nasal cavity; adenomatous polyps of the nasal cavity; alveolar/bronchiolar adenomas and carcinomas fibroadenomas and adenocarcinomas of the mammary gland; and hemangiosarcoma of the circulatory system ([Adkins et al., 1986](#); [NTP, 1982](#); [Wong et al., 1982](#)). Consistent carcinogenic effects were observed in animal exposed to ethylene dibromide via inhalation ([Adkins et al., 1986](#); [NTP, 1982](#); [Wong et al., 1982](#)).

Additionally, EPA identified five chronic toxicity and cancer bioassays that evaluated the carcinogenic potential of ethylene dibromide resulting from oral exposure. Similar to the findings resulting from the

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inhalation exposure, mice and rats exposed to ethylene dibromide were observed to have consistently developed tumors at multiple sites. The tumor types observed included squamous-cell carcinomas of the forestomach, hemangiosarcoma, hepatocellular carcinoma, and tumors of the liver and esophagus. The studies varied in terms of exposure durations and concentrations, providing a robust evaluation of ethylene dibromide's carcinogenic potential ([Stoner et al., 1986](#); [Van Duuren et al., 1986](#); [Van Duuren et al., 1985](#); [NCI, 1978](#)).

EPA identified one dermal by Van Duuren ([1979](#)). Skin papilloma and lung tumors were evaluated following the dermal application of ethylene dibromide. An increased incidence of papillomas and lung tumors was reported as a result of dermal exposure to 50 mg of ethylene dibromide/application (0.2 mL of acetone vehicle) ([Van Duuren et al., 1979](#)). A brief study description, PODs, and critical effects resulting from inhalation, oral, and dermal exposure to ethylene dibromide, respectively described in Appendix A.7.2.

Inhalation Studies

The carcinogenic potential of ethylene dibromide has been rigorously evaluated through a series of inhalation studies, providing valuable insights into its effects on both respiratory and systemic health. A summary of inhalation carcinogenic studies, including brief study description, PODs, and critical effects, is presented in Table_Apx A-15.

In a comprehensive study involving F344 rats, both male and female groups (50 of each per dose) were exposed to ethylene dibromide via inhalation at concentrations of 0, 10, or 40 ppm for 6 hours daily, 5 days per week, for a study duration of 2 years ([NTP, 1982](#)). Despite some limitations, such as the presence of only two dose groups and high mortality in the high-dose group (40 ppm), this study received an overall quality determination rating of high due to its adherence to established guidelines, including accurate chemical measurements, randomized animal grouping, and comprehensive result reporting. The study revealed significantly shorter lifespans for both male and female rats exposed to the highest dose of ethylene dibromide compared to controls. There was a marked increase in the incidence of carcinomas and adenocarcinomas in the nasal cavities ($p < 0.001$) in high-dose rats. Similarly, low-dose rats showed significant increases in nasal cavity adenocarcinomas and adenomas ($p < 0.001$), and low-dose male rats exhibited more adenomatous polyps ($p < 0.001$). High-dose female rats had a significant increase in combined alveolar/bronchiolar adenomas and carcinomas ($p = 0.024$). High-dose male rats showed increased incidences of hemangiosarcomas and mesotheliomas ($p < 0.001$), while dosed female rats had a significant rise in mammary gland fibroadenomas ($p < 0.001$). Notably, the mean body weights of high-dose rats were lower than those of untreated controls. The study concluded that ethylene dibromide was carcinogenic in both sexes of F344 rats, leading to increased occurrences of various tumors across different organs at all doses.

In a related study with B6C3F1 mice (50 animals per sex per dose), the study authors further explored the effects of ethylene dibromide exposure at the same concentrations as those used in the rat study described above (0, 10, and 40 ppm) for 6 hours daily, 5 days per week, over 78 weeks to 2 years ([NTP, 1982](#)). The study reported significantly increased incidences of alveolar/bronchiolar carcinomas and adenomas in high-dose male mice ($p < 0.001$). High-dose female mice also exhibited increased tumor incidences ($p = 0.007$ for adenomas and $p < 0.001$ for carcinomas). Hemangiosarcomas were significantly more frequent at both dose levels in female mice ($p < 0.001$) and low-dose females showed a significant increase in mammary gland adenocarcinomas ($p < 0.001$). The primary cause of early death in male mice was urinary tract infections, and high-dose mice had lower body weights compared to controls ([NTP, 1982](#)). Histopathologic evaluation was performed and survival-adjusted statistical

analyses were used to ensure that early deaths unrelated to ethylene dibromide exposure and did not confound interpretation of tumor incidence ([NTP, 1982](#)).

Oral Studies

In a series of studies evaluating the carcinogenic potential of ethylene dibromide, various animal models and methodologies were used to understand toxicological effects resulting from oral exposure.

EPA identified two studies ([Van Duuren et al., 1986](#); [Van Duuren et al., 1985](#)) that were rated as uninformative and are further characterized in Table_Apx A-16 and Appendix A.7.2. A summary of oral carcinogenic studies, including brief study descriptions, PODs, and critical effects, are presented in Table_Apx A-16.

The first study involved Osborne-Mendel rats (50 animals per sex of each group) were exposed to ethylene dibromide via gavage in corn oil, administered 5 days a week as part of a chronic cancer bioassay. Control groups received either corn oil or no treatment. The TWA doses achieved were 0, 38, and 41 mg/kg/day for male rats, and 0, 37, and 39 mg/kg/day for female rats. The study identified a LOAEL of 38 mg/kg/day, with observed carcinogenic effects including squamous cell carcinoma of the stomach, degenerative lesions in the adrenal cortex, and testicular atrophy. Because the study included limitations such as inconsistent timing and dosing, the overall quality determination rating assessed as medium ([NCI, 1978](#)).

2.4.4 Mechanistic and Supporting Evidence

Mechanistic studies have provided substantial evidence regarding the mutagenic and carcinogenic properties of ethylene dibromide. A detailed discussion of the mutagenicity and genotoxicity is provided in Section 2.4.5. The bioactivation of ethylene dibromide into DNA reactive metabolite is a critical step in its carcinogenic MOA, leading to DNA adduct formation, DNA damage, and mutations. These effects have been observed in both human and rodent cells. The evidence shows that ethylene dibromide exposure causes genotoxicity through DNA adduct formation and mutations in cancer-related genes, correlating with species-specific metabolism.

2.4.5 Genotoxicity Hazard Identification and Evidence Integration

Extensive evidence has demonstrated the genotoxic potential of ethylene dibromide across various biological systems. In brief, ethylene dibromide has been found to induce genotoxic effects in a wide range of *in vivo* and *in vitro* test systems. Ethylene dibromide genotoxicity is attributed to its metabolic activation into DNA reactive intermediates. Studies have shown that these reactive metabolites cause various types of genetic damage, including DNA adducts. Moreover, this genotoxic effect has been consistently observed in various experimental models, including bacterial mutagenicity assays, mammalian cell cultures, and *in vivo* studies. The genotoxic effects of ethylene dibromide presented here have been consistently observed in various experimental models including *in vivo* studies, mammalian cell cultures, and bacterial mutagenicity assays ([ATSDR, 2018](#); [U.S. EPA, 2004b](#)). Although EPA did not evaluate these studies using formal data quality criteria, studies were reviewed by comparing against current OECD or EPA test guidelines.

2.4.5.1 Evidence from Epidemiology Studies

EPA identified two epidemiology studies that assessed genotoxic outcomes following exposure to ethylene dibromide ([Steenland et al., 1986](#); [Steenland et al., 1985](#)). Outcomes evaluated include frequencies of sister-chromatid exchanges (SCE) and chromosomal aberrations (CA).

NIOSH assessed genotoxicity in a longitudinal study of forestry workers in Colorado ([Steenland et al., 1985](#)), which appears to be the same cohort of forestry workers that NIOSH studied for reproductive

toxicity ([Schrader et al., 1988](#)), which was discussed previously in this draft hazard assessment for ethylene dibromide. The genotoxicity study assessed the association between ethylene dibromide exposure and frequencies of SCE and CA in peripheral blood lymphocytes. Blood samples were collected from 14 workers before and after they sprayed felled pine trees with an emulsion that contained 4% ethylene dibromide by volume. The other compounds and chemicals present in the emulsion were not specified by Steenland ([1985](#)). Blood samples were also collected from six non-exposed controls at the same time points as the exposed workers. For the exposed workers, the 8-hour TWA ethylene dibromide exposure level was 60 ppb, with a range of 5 to 281 ppb, based on 44 full-shift personal exposure breathing zone samples. Additionally, 19 short-term breathing-zone samples were collected over 4 to 15 minutes during peak exposures; these samples had an average of 463 ppb with a range of 8 to 2,165 ppb ethylene dibromide. After accounting for the potential confounders of smoking and taking prescription medicine, no statistically significant associations were found between ethylene dibromide exposure and the frequency of SCE or CAs. Strengths of the study include the use of breathing zone air sampling and the prospective study design, but the small sample size is a limitation. This study assessed short-term exposure durations as the 14 exposed individuals sprayed ethylene dibromide for an average of 2 weeks during the summer with a range of 5 to 26 days.

NIOSH also assessed genotoxicity in a cross-sectional study ([Steenland et al., 1986](#)), which appears to include workers from the same six papaya packing plants that were assessed for reproductive toxicity ([Schrader et al., 1988](#); [Ratcliffe et al., 1987](#); [Schrader et al., 1987](#)), as discussed above in Section 2.3.1.1.1. The genotoxicity study investigated whether ethylene dibromide exposure was associated with SCE and CA in peripheral blood lymphocytes ([Steenland et al., 1986](#)). Blood samples from 60 exposed men were compared to samples from a control group of 42 men who worked at a nearby sugar mill. There is some potential for residual confounding due to differences in characteristics or differences in co-exposures between the exposed group and the comparison group. The 8-hour TWA geometric mean exposure level based on full-shift personal sampling was 88 ppb among the papaya workers, with peak levels up to 262 ppb. In t-tests that compared frequencies between exposed and unexposed groups, the only statistically significant association observed was a higher frequency of chromatid exchanges per 100 cells in the exposed group ($p = 0.03$), which persisted after adjustment for age ($p = 0.004$). The authors noted that this finding was based on “only 9 individuals (out of 102)” with chromatid exchanges, of which 8 were exposed and 1 was unexposed and that “caution is needed in interpreting this result.” The study authors noted that chromatid exchanges were the least frequent of four types of aberrations studied and that there were no statistically significant differences between exposed and unexposed groups when different types of aberrations were grouped together. The authors also noted the limitations of multiple comparisons but did not perform statistical analyses to adjust for multiple comparisons (such as Bonferroni correction). No other statistically significant associations were found between exposure to ethylene dibromide and CA or SCE in t-tests or in regression analyses that adjusted for potential confounders.

Neither study demonstrated that ethylene dibromide was associated with genotoxicity based on evaluation of SCE and CA in peripheral blood lymphocytes.

2.4.5.2 Evidence from *In Vitro* Studies of Human Cells

Several *in vitro* studies assessed genotoxic and mutagenic outcomes following treatment with ethylene dibromide in a variety of human cell lines. Outcomes assessed include SCE, DNA adduct formation, DNA damage, and gene mutation. Table 2-7 lists the findings from *in vitro* studies on DNA damage in human cells, whereas Table 2-8 outlines the results regarding chromosome aberrations and SCE.

Tucker et al. (1984) examined changes in the frequency of SCE in lymphocytes exposed to ethylene dibromide *in vitro*. Human peripheral lymphocyte cultures were treated with phytohemagglutinin to stimulate proliferation and exposed to ethylene dibromide in the presence or absence of air for up to 8 hours. Cells were then harvested 75 hours after culture initiation, and second-division. Overall, SCE frequency was approximately doubled in cultures treated with ethylene dibromide. Also, Channarayappa and Nath (1992) evaluated micronuclei kinetics and persistence in mononucleated cells and binucleated human peripheral lymphocytes following 4 hours and continuous (until harvest) exposure to ethylene dibromide. Compared to the controls, a statistically significant higher incidence of micronuclei in binucleated cells, whereas in mononucleated cells higher micronucleus frequencies were observed only in cultures treated continuously.

Bjørge et al. (1996) assessed the potential for ethylene dibromide to induce single-strand DNA breaks (ssDNA breaks) in rat and human testicular germ cells. Cells isolated from rats or human organ transplant donors were exposed for 30 minutes to several concentrations of ethylene dibromide (0, 10, 30, 100, 300, and 1,000 μM). Rat testicular cells treated with at least 100 μM of ethylene dibromide, and human testicular germ cells treated with 1,000 μM of ethylene dibromide had statistically significant higher levels of ssDNA breaks compared to controls. Cells treated with lower concentrations of ethylene dibromide did not result in statistically significant higher levels of ssDNA breaks.

Likewise, Perocco and Prodi (1981) evaluated effects of ethylene dibromide on the inhibition of scheduled (duplicative) and unscheduled (reparative) DNA syntheses seen as tritiated thymidine uptake in human lymphocytes. Lymphocytes were collected from healthy blood donors and cultured for a 4-hour period in the presence of 10 mM hydroxyurea and 3 doses of ethylene dibromide (2.5, 5, 10 $\mu\text{L/mL}$) in the presence or absence of S-9 mix metabolizing system. Compared to controls, ethylene dibromide elicited significant DNA damage by inhibiting scheduled and unscheduled DNA synthesis.

Cmarik et al., (1990) measured the ability of ethylene dibromide to mediate unscheduled DNA synthesis in hepatocytes *in vitro*. Human hepatocytes were exposed for 2 hours to several doses of ethylene dibromide with or without thiol depletion by diethylmaleate, and with thymidine incorporation measured after 10 hours. Compared to controls, ethylene dibromide-dependent unscheduled DNA synthesis was demonstrated in hepatocytes, and when concurrently treated with diethylmaleate to deplete intracellular glutathione inhibited ethylene dibromide-induced unscheduled DNA synthesis.

Additionally, Holzer et al. (2008) assessed DNA damage using an *in vitro* comet assay on rat and human nasal mucosa cells. The human cells were obtained from tissue samples of 10 patients (3 females and 7 males), who underwent surgery for treatment of nasal airway obstruction. Several chemicals, including ethylene dibromide were assessed individually, and each chemical was assessed in mucosa cells from at least 3 different human donors (from amongst the 10 patients) and 3 male Sprague-Dawley rats. Mucosa cells were treated with ethylene dibromide (0, 0.048, 0.195, 0.78, and 1.56 mM) for 1 hour. A statistically significant increase in DNA damage was reported after ethylene dibromide exposure compared to controls. The lowest effective concentration of ethylene dibromide associated with significant DNA damage compared to the respective control differed between patient sources for the human mucosa cells, with values of 0.048, 0.195, and 0.78 mM ethylene dibromide for each of three human cell donors. These differences in sample sensitivity to ethylene dibromide-induced DNA damage between patient sources suggest that interindividual variation in susceptibility may exist.

Crespi et al. (1985) tested the ability of ethylene dibromide to induce gene mutations in two human lymphoblastoid cell lines, designated as AHH-1 and TK6. AHH-1 and TK6 human lymphoblasts were exposed with several doses of ethylene dibromide *in vitro*. In AHH-1 cells, statistically significant

mutagenic responses were observed at or above 5 µg/mL of ethylene dibromide compared to controls. Additionally, statistically significant mutagenic responses in TK6 cells were observed at or above 20 µg/mL of ethylene dibromide compared to controls.

Additionally, Ferreri et al. (1983) assessed the potential mutagenicity of ethylene dibromide in EUE cells, which are a line of epithelial-like cells from human embryo skin and muscle explants. Cells were exposed to media containing 10^{-4} , 10^{-3} , or 10^{-2} M concentrations of ethylene dibromide for 24 hours and were assessed for induction of diphtheria-toxin (DT)-resistant mutants. Cells exposed to ethylene dibromide had a higher frequency of DT mutations compared to controls and compared to other halogenated compounds tested. There was a linear dose-response relationship, with the mutation frequency increasing with increasing concentrations of ethylene dibromide.

2.4.5.3 Evidence from Bacterial Mutagenicity Assays

In vitro studies examining the conjugation of ethylene dibromide with glutathione further emphasizes the critical role of glutathione dependent bioactivation in mediating mutagenicity. Studies using *Salmonella typhimurium* strain TA100 demonstrated that glutathione conjugation was associated with increased mutagenic responses following exposure to ethylene dibromide, with the glutathione adduct identified as a key contributor to the observed mutagenic effects (van Bladeren et al., 1980).

2.4.5.4 DNA Adducts and DNA Damage

Several studies focus on the formation and stability of DNA adducts following the metabolic bioactivation of ethylene dibromide, providing insight into the role of reactive intermediates in pathways leading to DNA damage and potential carcinogenicity. These studies elucidate the toxic mechanisms of ethylene dibromide, which involve biotransformation through oxidation to 2-bromoacetaldehyde, a highly reactive metabolite, as well as an alternative pathway involving direct conjugation with glutathione to form a reactive *S*-(2-bromoethyl) half-mustard intermediate, discussed further in Section 2.4.6.

Results of *in vivo* studies in rats and mice show that ethylene dibromide induces DNA adduct formation and DNA damage. *S*-[2-(*N*⁷-guany)ethyl]glutathione has been identified as the major DNA adduct in rats following treatment with ethylene dibromide (Kim et al., 1990). *In vitro* studies have shown that ethylene dibromide can cause DNA damage both in the presence and absence of S9 enzyme activation (refer to as with or without activation in Table 2-7).

Results of DNA adducts formation and DNA damage assays are summarized together in Table 2-7. This table includes all data compiled in (ATSDR, 2018). Positive studies are bolded. A formal evaluation of mutagenicity as the primary MOA of carcinogenicity follows in Section 2.4.6.

Table 2-7. Studies Summary of Ethylene Dibromide-Induced DNA Adduct and DNA Damage

Assay Type	Test System (Species/Exposure)	Results	Reference(s)
DNA adducts and DNA damage – <i>in vivo</i> animal studies			
DNA adducts	Rat (intraperitoneal)	Positive	Liu et al. (2007) ; Humphreys et al. (1990)
DNA adducts	Mouse (intraperitoneal)	Positive	Cho and Guengerich (2013) ; Liu et al. (2007) ; Sasaki et al. (1998) ; Humphreys et al. (1990)
DNA adduct and DNA damage – <i>in vitro</i>			
DNA adducts (DNA binding)	Rat (hepatocytes)	Positive (without activation)	Cmarik et al. (1990)
DNA adducts (DNA binding)	Human (hepatocytes)	Positive (without activation)	Cmarik et al. (1990)
DNA damage (single strand breaks)	Rat (testicular germ cells)	Positive (without activation)	Bjerge et al. (1996)
DNA damage (double strand breaks)	Rat (hepatocytes)	Negative	Storer et al. (1996)
DNA damage (single strand breaks)	Human (testicular germ cells)	Positive (without activation)	Bjerge et al. (1996)
DNA damage (SOS uma test)	<i>Salmonella typhimurium</i>	Positive (with and without activation)	Oda et al. (1996)
DNA damage (SOS chromotest)	<i>Escherichia coli</i>	Negative	Mersch-Sundermann et al. (1994)
DNA damage (SOS chromotest)	<i>Escherichia coli</i>	Positive (without activation)	Venkat et al. (1995)
DNA damage (spot test)	<i>Escherichia coli</i>	Positive (without activation)	Rosenkranz (1977) ; Brem et al. (1974)
DNA damage (spot test)	<i>B. subtilis</i>	Negative	Shiau et al. (1980)

2.4.5.5 Chromosomal Aberration and SCE

Several studies have evaluated the induction of chromosomal aberrations and SCE following exposure to ethylene dibromide, providing further evidence of its genotoxic potential. In cultured Chinese Hamster Ovary cells (CHO), treatment with ethylene dibromide resulted in increased frequencies of chromosomal aberrations and SCE, indicating structural chromosomal damage.

Results from chromosomal aberration and SCE assays are summarized below in Table 2-8. This table is adapted from ATSDR and includes all data summarized in ATSDR ([2018](#)).

In a study by Tezuka et al. ([1980](#)), the induction of SCE and chromosomal aberrations was investigated in CHO cells. The results of this study demonstrated a statistically significant and dose-dependent increase in both SCE and chromosomal aberrations compared with control cultures ([Tezuka et al., 1980](#)).

Similarly, Ivett et al. ([1989](#)) evaluated *in vitro* cytogenetic damage using SCE and chromosome aberration assays in CHO cells. Predominantly positive responses were observed both in the presence

and absence of exogenous metabolic activation, supporting the conclusion that ethylene dibromide induces structural chromosomal damage through direct and metabolically-mediated mechanisms ([Ivett et al., 1989](#)).

The presence of chromosomal aberrations indicates that ethylene dibromide can cause significant damage to the genetic material within cells. Positive results for SCE induction by ethylene dibromide suggest that the compound can interfere with normal DNA replication and repair mechanisms, leading to genomic instability and increasing the risk of mutations and cancer development ([ATSDR, 2018](#)).

Table 2-8. Study Summary of *In Vivo* and *In Vitro* Ethylene Dibromide-Induced Chromosomal Aberration and SCE Reported by ATSDR (2018)

Assay Type	Test System (Species/Exposure)	Results	Reference(s)
Chromosome aberrations	Mouse (intraperitoneal)	Negative	Krishna et al. (1985)
SCE	Human (occupational)	Negative	Steenland et al. (1986) ; Steenland et al. (1985)
SCE	Mouse (intraperitoneal)	Negative	Tucker et al. (1993) ; Krishna et al. (1985)
Chromosome aberrations	Chinese hamster (V79 cells)	Positive (with activation)	National Toxicology Program (NTP) (1989)
SCE	Human (skin fibroblasts)	Positive (not determined)	Deleve (1997)
SCE	Human (peripheral lymphocytes) Sister	Positive (not determined)	Tucker et al. (1993) ; Tucker et al. (1984)
SCE	Chinese hamster (V79 cells)	Positive (positive with activation)	Tucker et al. (1993) ; National Toxicology Program (NTP) (1989) ; Tezuka et al. (1980)
SCE = sister-chromatid exchanges			

2.4.5.6 Gene Mutation, Sex-Linked Recessive Mutation, and Somatic Mutation

Results from gene mutation and sex-linked recessive and somatic mutation assays are summarized together in Table 2-9. This table includes all data summarized in ([ATSDR, 2018](#)).

A few *in vivo* studies reported that ethylene dibromide did not induce gene mutations, although other studies have observed gene mutation. For example, Cho et al. ([2013](#)) reported gene mutation in mice following intraperitoneal injections ([Cho and Guengerich, 2013](#)). *In vitro* studies in mouse and rats cell lines ([National Toxicology Program \(NTP\), 1989](#); [Clive et al., 1979](#)), reported mutagenic effects with and without S9 fraction activation ([Ballering L et al., 1998](#); [Graves et al., 1996](#); [Brimer et al., 1982](#); [Tan and Hsie, 1981](#)) and without activation in human cell lines (epithelial and lymphoblasts TK6 and AAH-1) ([Crespi et al., 1985](#); [Ferreri et al., 1983](#)). There is sufficient data in prokaryotic organisms (e.g., *S typhimurium* and *E-coli*) where changes in the DNA, gene function and inactivate gene mutation assays with and without S9 activation were detected (see Table 2-9 below). Ethylene dibromide exposure has been shown to result in positive mutations *in vivo* assays. These mutations include sex-linked mutations, which are associated with genes on the sex chromosomes, and somatic mutations, which occur in non-reproductive cells. Kale et al. ([1979b](#)) reported sex-linked recessive lethal mutations in spermatozoa of *Drosophila melanogaster* resulting from ethylene dibromide exposure. These gene mutation data

suggest that exposure to ethylene dibromide can potentially affect reproductive health and may lead to inherited genetic disorders ([ATSDR, 2018](#)).

Table 2-9. Studies Summary of Ethylene Dibromide-Induced Gene Mutation and Sex-Linked Mutation

Assay Type	Test System (Species/Exposure)	Results	Reference
Gene mutation – <i>in vivo</i>			
Rodent data			
Gene mutation	Mouse (inhalation)	Negative	Schmezer et al. (1998)
Gene mutation	Mouse (intraperitoneal)	Positive	Cho and Guengerich (2013)
Gene mutation (dominant lethal)	Rat (oral)	Negative	Teramoto et al. (1980)
Gene mutation (urine extracts)	Rat (intraperitoneal)	Negative	Novotná, B and Duverger-Van Bogaert (1994)
Invertebrates			
Sex-linked recessive lethal mutation	<i>Drosophila melanogaster</i> (inhalation)	Positive	Ballering et al. (1993)
Sex-linked recessive lethal mutation	<i>D. melanogaster</i> (dietary)	Positive	Foureman et al. (1994) ; Vogel and Nivard (1993) ; National Toxicology Program (NTP) (1989) ; Vogel and Chandler (1974)
Sex-linked recessive lethal mutation	<i>Drosophila melanogaster</i> (inhalation)	Positive	Kale and Kale (1995) ; Kramers et al. (1991) ; Kale and Baum (1983) ; Kale and Baum (1982) ; Kale and Baum (1980, 1979b)
Somatic mutation and recombination (wing spot test)	<i>Drosophila melanogaster</i> (inhalation)	Positive	Vogel et al. (1996) ; Ballering et al. (1993) ; Vogel and Nivard (1993) ; Kramers et al. (1991)
Gene mutation - <i>in vitro</i>			
Gene mutation (forward)	Human (epithelial cells) gene	Positive (without activation)	Ferreri et al. (1983)
Gene mutation (forward)	Human (lymphoblasts; Tk6, AAH-1)	Positive (without activation)	Crespi et al. (1985)
Gene mutation (forward mutation)	Mouse (L5178Y lymphoma cells)	Positive (with and without activation)	National Toxicology Program (NTP) (1989) ; Clive et al. (1979)
Gene mutation	Chinese Hamster Ovary cells (CHO)	Positive (without activation)	Ballering et al. (1998) ; Graves et al. (1996)
Gene mutation (forward mutation)	CHO cells	Positive (with and without activation)	Brimer et al. (1982) ; Tan and Hsie (1981)
Gene mutation	<i>Salmonella typhimurium</i>	Positive (with and without activation)	Bogen (1994) ; Novotn?A and Duverger-Van Bogaert (1994) ; Simula et al. (1993) ; Bakale and McCreary (1992) ; Zeiger et al. (1992)
Gene mutation	<i>Salmonella typhimurium</i>	Positive (without activation)	Kawakami et al. (1998) ; Thier et al. (1996) ; Mersch-Sundermann et al. (1994) ; Thier et al. (1993)

Assay Type	Test System (Species/Exposure)	Results	Reference
Gene mutation (vapor phase)	<i>Salmonella typhimurium</i>	Positive (with and without activation)	Kado et al. (1992)
Gene mutation (reverse mutation)	<i>Salmonella typhimurium</i>	Positive (without activation)	Ames (1971)
Gene mutation (reverse mutation)	<i>Salmonella typhimurium</i>	Positive (with and without activation)	National Toxicology Program (NTP) (1989) ; Zoetemelk et al. (1987) ; Moriya et al. (1983) ; Barber et al. (1981) ; Principe et al. (1981) ; Stolzenberg and Hine (1980) ; McCann et al. (1975)
Gene mutation (reverse mutation)	<i>Salmonella typhimurium</i>	Positive (without activation)	Hughes et al. (1987) ; Kerklaan et al. (1985)
Gene mutation (reverse mutation)	<i>Salmonella typhimurium</i>	Negative (without activation)	Shiau et al. (1980)
Gene mutation (reverse mutation; spot test)	<i>Salmonella typhimurium</i>	Positive (with activation), Negative (without activation)	Shiau et al. (1980)
Gene mutation (Ara test)	<i>Salmonella typhimurium</i>	Positive (with and without activation)	Oda et al. (1996)
Gene mutation	<i>Escherichia coli</i>	Positive (without activation)	Watanabe et al. (1998)
Gene mutation (reverse mutation)	<i>Escherichia coli</i>	Positive (without activation)	Hemminki et al. (1980)
Gene mutation (reverse mutation)	<i>Escherichia coli</i>	Positive (with activation)	Moriya et al. (1983)
Gene mutation (forward mutation; spot test)	<i>Bacillus subtilis</i>	Positive (without activation)	Izutani et al. (1980)
Gene mutation (forward mutation; spot test)	<i>Bacillus subtilis</i>	Positive (with activation), Negative (without activation)	Shiau et al. (1980)
Gene mutation (forward mutation; spot test)	<i>Aspergillus nidulans</i>	Positive (without activation)	Principe et al. (1981)
Gene mutation (reverse mutation; host mediated)	<i>Serratia marcescens</i> (strain a21)	Negative	Buselmaier et al. (1973, 1972)
Gene mutation (recessive lethal)	<i>Neurospora crassa</i>	Positive (without activation)	Malling (1969)
Gene mutation (forward mutation)	<i>Streptomyces coelicolor</i>	Negative	Principe et al. (1981)
Gene mutation (forward mutation, spot test)	<i>Streptomyces coelicolor</i>	Positive (without activation)	Principe et al. (1981)

2.4.5.7 **Unscheduled DNA Synthesis (UDS), DNA Repair and Micronuclei**

Results from unscheduled DNA synthesis, DNA repair and micronuclei assays are summarized together in Table 2-10. This table includes all data summarized in ([ATSDR, 2018](#)).

The results of studies on unscheduled DNA synthesis are mixed. UDS was observed in rats following gavage exposure, indicating that ethylene dibromide can induce DNA repair synthesis in response to

damage when administered orally ([Coni et al., 1992](#)). However, no UDS was observed following intraperitoneal exposure ([Bentley and Working, 1988](#)).

The micronucleus assay results also show variability. *In vivo* studies in mice did not show positive results, indicating a lack of chromosomal damage under these conditions. However, positive results were obtained in human lymphocyte cell lines, suggesting that ethylene dibromide can cause chromosomal damage leading to the formation of micronuclei in cells ([ATSDR, 2018](#)).

Positive results in DNA repair assays indicate that ethylene dibromide can cause DNA damage that necessitates repair. This suggests that ethylene dibromide has the potential to induce genotoxic effects by damaging DNA, which triggers cellular repair mechanisms ([ATSDR, 2018](#)).

Table 2-10. Studies Summary of (*In Vivo* and *In Vitro*) Ethylene Dibromide-Induced Unscheduled DNA Synthesis, DNA Repair and Micronuclei

Assay Type	Test System (Species/Exposure)	Results	Reference(s)
Unscheduled DNA synthesis	Rat (gavage)	Positive	Coni et al. (1992)
Unscheduled DNA synthesis	Rat (intraperitoneal)	Negative	Bentley and Working (1988)
Micronucleus assay	Mouse (intraperitoneal)	Negative	Kawakami et al. (1998) ; Tucker et al. (1993) ; Krishna et al. (1985)
<i>In vitro</i>			
Unscheduled DNA synthesis	Human (hepatocytes)	Positive (without activation), Not determined with activation	Cmarik et al. (1990)
Unscheduled DNA synthesis	Rat (hepatocytes)	Positive (without activation), Not determined with activation	Cmarik et al. (1990)
Unscheduled DNA synthesis	Opossum (lymphocytes)	Positive (without activation), Not Determined with activation	Meneghini (1974)
DNA repair	Human (lymphocytes)	Positive (with activation), Negative (without activation)	Perocco and Prodi (1981)
DNA repair	Rat (primary hepatocytes)	Positive (without activation), Not Determined with activation	Working et al. (1986) ; Williams et al. (1982)
Micronucleus assay	Human (peripheral lymphocytes)	Positive (without activation)	Channarayappa and Nath (1992)

2.4.5.8 Evidence Integration for Genotoxicity

Epidemiologic evidence for genotoxicity in humans is indeterminate due to lack of sufficient data. The evidence base was small and consisted of two studies, which decreases the strength of the evidence. Although the two studies assessed a consistent outcome, they generally did not find statistically significant associations. The lack of precision of the findings decreases the strength of the evidence. The evidence for genotoxicity in laboratory animals provides strong support for an association between ethylene dibromide exposure and the induction of genetic damage, consistent with a metabolic genotoxic mode of action. The genotoxicity database for ethylene dibromide was evaluated using a weight of scientific evidence approach that integrates findings from *in vitro* genotoxicity assays, *in vivo* studies,

and mechanistic investigations. These data were examined to assess the potential for ethylene dibromide to induce genetic damage and to determine the relevance of observed effects to humans. Overall, the available evidence indicated that ethylene dibromide exhibits genotoxic activity that is dependent on metabolic activation, supporting a genotoxic mode of action.

In vitro genotoxicity studies provide strong evidence that ethylene dibromide induces genetic damage across multiple assay systems, including gene mutation, chromosomal damage (chromosomal aberrations and sister chromatid exchange), micronucleus formation, and DNA damage and repair endpoints. These effects have been observed in the presence of metabolic activation, although positive results have also been reported in the absence of metabolic activation in some assay systems.

Positive gene mutation results have been reported in bacterial (*Salmonella typhimurium*) reverse mutation assays, mammalian cell gene assays, mouse lymphoma cells and CHO are summarized in Table 2-9. Chromosomal damage including chromosomal aberrations and SCE has been observed in CHO cells in the presence of metabolic activation ([Conard et al., 2009](#); [National Toxicology Program \(NTP\), 1989](#); [Tezuka et al., 1980](#)). These findings indicate that the bioactivation of ethylene dibromide to reactive intermediates leads to genotoxic effects, while also suggesting that the parent compound may exhibit limited intrinsic genotoxic activity under certain experimental conditions ([Working et al., 1986](#); [Williams et al., 1982](#)).

The evidence for genotoxicity *in vivo* further supports the genotoxic potential of ethylene dibromide following systemic exposure. Positive genotoxic responses have been observed in experimental animals following multiple exposure routes. Gene mutation has been reported in mice following intraperitoneal injection ([Cho and Guengerich, 2013](#)), and unscheduled DNA synthesis, indicative of DNA damage and repair has been observed in rats following oral gavage exposure ([Arora et al., 2005](#)). These findings demonstrate that ethylene dibromide, following systemic absorption and metabolic activation, can induce genetic damage *in vivo*.

Mechanistic studies provide strong support for genotoxic MOA for ethylene dibromide. Metabolism of ethylene dibromide occurs primarily through CYP-dependent oxidation and glutathione conjugation pathways, resulting in the formation of electrophilic intermediates capable of covalently binding to DNA ([Cmarik et al., 1990](#); [Kim et al., 1990](#); [Inskeep et al., 1986](#); [Inskeep and Guengerich, 1984](#)).

Experimental studies have identified the formation of DNA adducts, including *S*-[2-(*N*⁷-guanyl)ethyl]glutathione, following ethylene dibromide exposure ([Thomas et al., 2001](#); [Cmarik et al., 1990](#); [Kim et al., 1990](#); [Inskeep et al., 1986](#); [Inskeep and Guengerich, 1984](#)). The presence of the adducts provides molecular evidence linking metabolic activation of ethylene dibromide to DNA damage and supports a mutagenic mechanism.

In summary, the available evidence provides strong support for genotoxicity of ethylene dibromide in laboratory animals. The consistency of mutagenic effects across *vitro* and *in vivo* systems, combined with evidence of DNA adduct formation and a well characterized metabolic activation pathway supports a metabolically mediated genotoxic mode of action. Ethylene dibromide is metabolized through CYP and glutathione conjugation (GST). The GST pathway can generate a reactive episulfonium ion capable of forming DNA adducts, providing a mechanistic basis for the observed genotoxic effects. Although the relative contributions of CYP and GST pathways under low-dose conditions are not fully characterized, the demonstrated formation of DNA reactive intermediates supports the potential for genetic damage. The observation of mutagenic effects *in vitro*, confirmation of genetic damage *in vivo*, and direct evidence of DNA adduct formation indicate that ethylene dibromide has the potential to induce genetic

damage. These findings support consideration of genotoxic mode of action contributing to the carcinogenicity of ethylene dibromide.

2.4.6 Carcinogenic Mode of Action Analysis

Ethylene dibromide exerts carcinogenic effects primarily through direct covalent modification (alkylation) of macromolecules following metabolic activation, predominantly via GSH conjugation and to a lesser extent, via CYP-mediated oxidation. Disturbances in GSH homeostasis, including depletion and oxidative stress, contribute to cytotoxicity and may promote tumor development through increased cellular proliferation and inflammation. This mechanistic framework is consistent with observed toxicity outcomes across test systems and species ([ATSDR, 2018](#); [U.S. EPA, 2004b](#)).

As discussed in Section 3.3, the formation of glutathione derived metabolites is associated with generation of reactive electrophilic intermediates, representing key upstream events for both cytotoxicity and mutagenic mode of action. Following exposure, metabolic activation via CYP and glutathione S-transferase (GST) pathways generate reactive intermediates that conjugate with GSH, leading to its depletion. This depletion contributed to cytotoxicity and cell proliferation, as well as covalent binding to DNA. This processes support both a cytotoxicity and mutagenic MOA, where systemic cytotoxicity (in addition to portal-of-entry effects in respiratory and gastrointestinal tissues) may contribute to regenerative cell proliferation and tumor formation, which underlie observed liver toxicity and carcinogenic outcomes ([ATSDR, 2018](#); [U.S. EPA, 2004b](#)).

Genotoxicity is central to the mutagenic mode of action for ethylene dibromide, which contextualizes the positive findings for carcinogenicity, developmental toxicity (teratogenicity and fetotoxicity), reproductive toxicity (effects on testes and sperm), and liver toxicity (site of bioactivation). Collectively, these interconnected processes contribute to systemic, genotoxic, and carcinogenic potential effects.

2.4.6.1 Mutagenic Mode of Action

Ethylene dibromide is a bifunctional alkylating agent that readily reacts with nucleophilic sites in biological macromolecules, including DNA and proteins ([ATSDR, 2018](#); [IARC, 1999](#)). Following exposure, ethylene dibromide undergoes biotransformation through two primary metabolic pathways (see Section 2.2.3). The conjugation pathway, with glutathione forming S-(2-bromoethyl)glutathione, produces highly reactive episulfonium or bis-sulfonium ions. These short-lived electrophilic intermediates are capable of covalently binding to a nucleophilic site on molecules such as DNA and protein. Through this mechanism, ethylene dibromide-specific metabolites then produce specific DNA adducts which are well characterized for direct DNA alkylation ([ATSDR, 2018](#); [U.S. EPA, 2004b](#)). This can result in base mispairing, strand breaks, and chromosomal aberrations. Protein alkylation also occurs and may contribute to enzyme inactivation and cellular toxicity ([ATSDR, 2018](#)).

The evidence for this pathway is robust, and *in vitro* and *in vivo* studies have identified a GSH-derived conjugate resulting in DNA adducts formation. As described in Section 2.4.6.1.1, this direct alkylation process represents the molecular initiating event for ethylene dibromide's genotoxic and carcinogenic effects.

The mutagenic MOA can be understood through a series of molecular initiation events, and adverse outcomes that contribute to its genotoxic effects. This section provides a detailed examination of the MOA of ethylene dibromide, focusing on the key mechanistic steps that contribute to its carcinogenic effects. Figure 2-6 proposed mutagenic MOA for ethylene dibromide, organized as a sequence of key events and adverse outcome framework.

Building on the understanding of ethylene dibromide's mutagenic MOA, specific molecular events contribute to its carcinogenic effects. These events are part of an ordered sequence of steps that involve bioactivation, DNA damage, and subsequent genetic alterations:

- MIE:** Bioactivation of ethylene dibromide to DNA-reactive metabolites (DNA alkylation)
- KE1:** DNA adduct formation
- KE2:** Inadequate DNA repair
- KE3:** Induction of mutation
- AO:** Development of tumors from ethylene dibromide-induced mutations

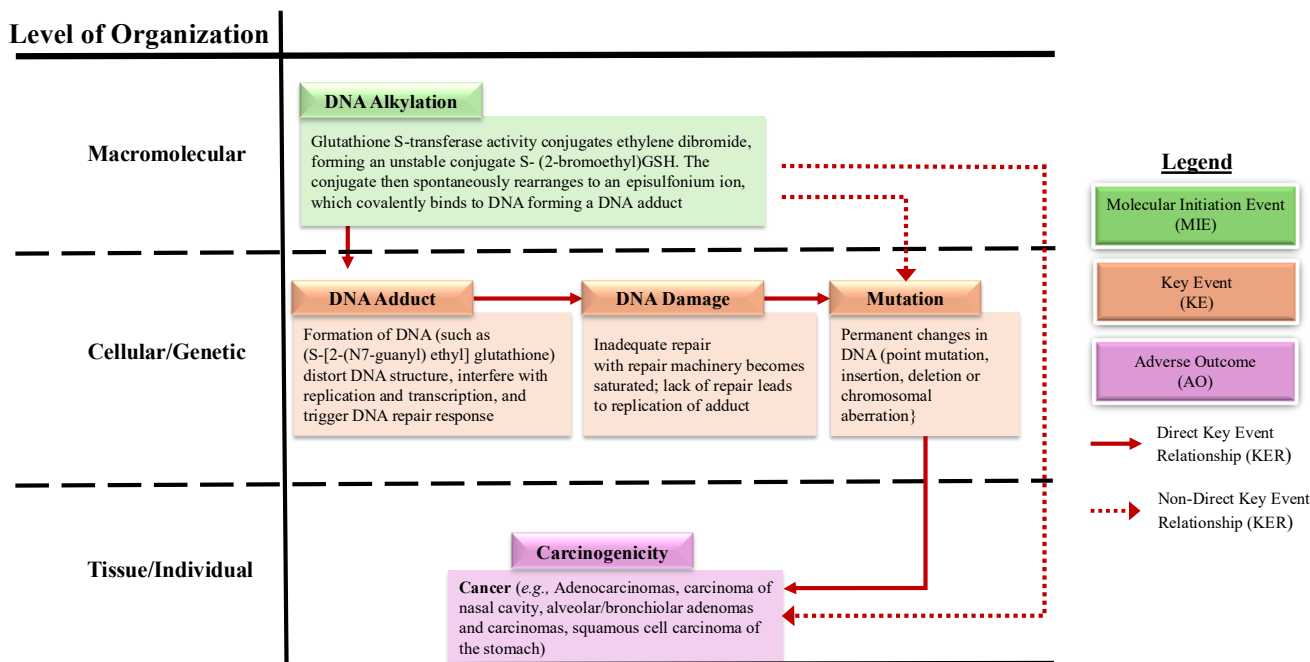


Figure 2-6. Adverse Outcome Pathway: MOA of Ethylene Dibromide
Ethylene dibromide's mutagenic mode of action (MOA) is illustrated in this adverse outcome pathway (AOP). Image was adopted and modified from AOP 15, which describes the AOP for DNA alkylation: <https://aopwiki.org/aops/15> (accessed June 18, 2026), with effects specific to ethylene dibromide. AOP 15 is endorsed by the OECD Working Group of National Coordinators of the Test Guidelines Programme (WNT) and Working Party of Hazard Assessment (WPHA).

2.4.6.1.1 Molecular Initiation Event: Bioactivation of Ethylene Dibromide to DNA-Reactive Metabolites (DNA Alkylation)

The molecular initiating event involves metabolic activation of ethylene dibromide to a DNA-reactive intermediate. Metabolism plays a crucial role in determining the carcinogenicity of ethylene dibromide as detailed in the metabolism section. Following exposure, ethylene dibromide undergoes bioactivation primarily through conjugation with GSH, catalyzed by GST. This reaction produces an unstable electrophilic episulfonium ion. The episulfonium ion reacts with nucleophilic sites in cellular macromolecules, particularly DNA, resulting in the formation of DNA adducts (Cmarik et al., 1990). Formation of these DNA reactive metabolites represents the molecular initiating event, and the formation of DNA adducts constitutes a key event in the mutagenic mode of action, which may lead to genotoxicity, genetic instability, and subsequent tumor development (Cmarik et al., 1990; Vanbladeren et al., 1982; van Bladeren et al., 1980).

2.4.6.1.2 Key Event 1: DNA Adducts Formation

The episulfonium ion generated during ethylene dibromide's bioactivation can alkylate DNA, primarily targeting the N^7 position of guanine bases. This alkylation results in the formation of DNA adducts, such as *S*-[2-(N^7 -guanyl)ethyl]glutathione. These adducts disrupt the normal structure and function of DNA, interfering with replication and repair processes ([U.S. EPA, 2004b](#)). The presence of DNA adducts is a critical indicator of genotoxicity mutagenic potential.

2.4.6.1.3 Key Event 2: Inadequate DNA Repair

Following DNA adduct formation, the efficiency of DNA repair mechanisms plays a crucial role in determining the extent of genetic damage. Inadequate DNA repair can lead to the persistence of DNA adducts, or mispairing during repair processes, increasing the likelihood of mutations. In addition, unrepaired DNA adducts may interfere with DNA replication, acting as structural impairment to replication machinery and potentially resulting in strand breaks and genomic instability. This step is directly linked to DNA alkylation, as the repair processes directly address the damage caused by alkylation. The failure to adequately repair DNA adducts can result in a fixation of genomic mutations ([Cmarik et al., 1990](#)).

Experimental data on the mode of action of ethylene dibromide implicate several cellular DNA damage repair pathways ([IARC, 1999](#)). After the body metabolically activates ethylene dibromide (often via glutathione *S*-transferase [GST] enzymes), ethylene dibromide forms "adducts," which are like chemical attachments on DNA bases that alter the canonical double-helix structure of genomic DNA (MIE) ([IARC, 1999](#)). These adducts occur mostly on guanine at the N^7 position, which is the most reactive site in DNA, and sometimes on adenine at the N^3 position, plus some hydroxyethyl and "etheno" adducts, and even occasional crosslinks ([IARC, 1999](#)). Cells try to repair these: many N^7/N^3 adducts fall off and leave abasic sites (sites without a DNA base) that BER can repair, but if the cell proliferates prior to these lesions being repaired, error prone polymerases often insert the wrong base, fixing these mutations within the daughter cell population ([Gates, 2009](#)). DNA polymerases have error rates spanning from 10^0 to 10^9 ([McCulloch and Kunkel, 2008](#)). Figure 2-7, below, shows how unrepaired adducts can lead to base pair changes on the complementary strand of DNA as another mechanism by which mutations can become fixed.

An O^6 -guanine adduct can be directly repaired by methylated-DNA-protein-cysteine methyltransferase (MGMT); if not, it tends to cause guanine-to-adenine mutations ([Fu et al., 2012](#)). Etheno adducts have their own repair enzymes and are usually handled well unless they build up ([Gros et al., 2003](#)). Crosslinks are difficult to repair as they represent physical bonds between base-paired DNA strands and can lead to more errors and even large-scale chromosomal rearrangements ([Deans and West, 2011](#)). Put together, ethylene dibromide can increase both single strand and double strand DNA damage resulting in the fixation of small-scale (single base substitutions) and large-scale (chromosomal rearrangements) DNA changes.

While use of the different DNA damage repair pathways can result in different sources contributing to genomic instability, tumorigenesis, and tumor progression, it is appreciated that once mutations are fixed within a genome, regardless of the mechanism by which they were induced, these fixed mutations are not detected as further targets of DNA damage repair pathways, but still contribute to an increased risk of tumor formation and an overall increase in genomic instability.

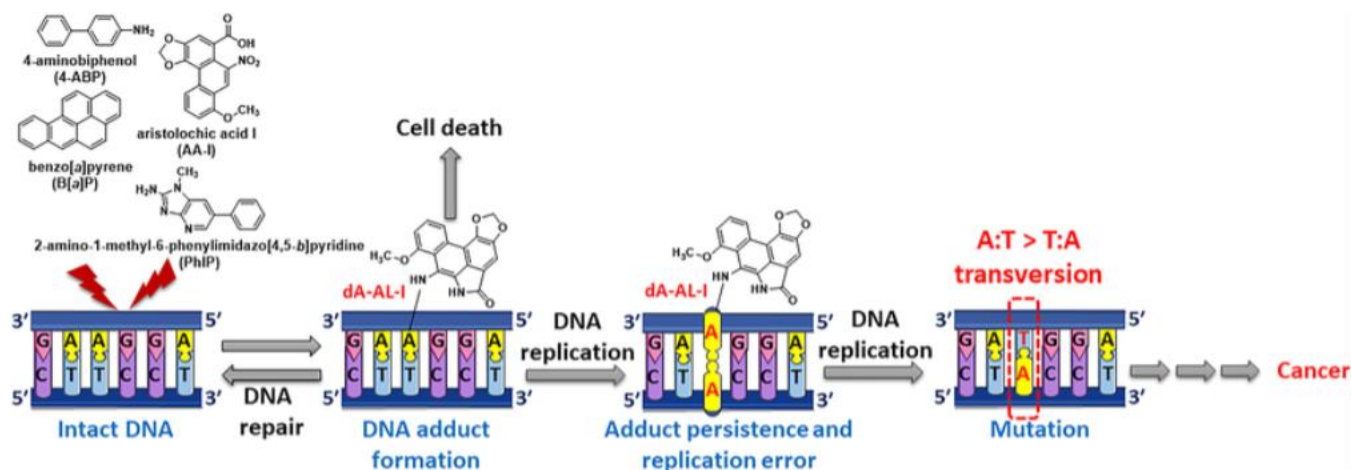


Figure 2-7. Example Pathway from DNA Adduct Formation Through Mutation to Cancer (from (Yun et al., 2020))

From left to right: (1) **Intact DNA:** A mutagenic agent interacts with intact DNA to form an adduct (right arrow); (2) **DNA adduct formation:** The adduct can be sensed by the cell and lead to cell death (up arrow), or it can be repaired (left arrow), or the DNA can be replicated and paired with the wrong base (right arrow); (3) **Adduct persistence and replication error:** If the adduct persists, this can also lead to cell death (not shown), or the complementary strand can be used as a template causing a transition or transversion (right arrow); and (4) **Mutation:** This mutation is no longer sensed by the cell as DNA damage, because the adduct is gone and the bases are paired correctly, though the sequence has changed from the original. When a mutation causes a change in a critical protein, it can lead to cell death (not shown) or cancer (right arrow) (Yun et al., 2020)

2.4.6.1.4 Key Event 3: Induction of Mutation

If the DNA adducts resulting from ethylene dibromide exposure are not efficiently repaired (KE 2), they can lead to fixed genomic mutations. These mutations may manifest as point mutations, insertions, deletions, or chromosomal aberrations. The persistence of DNA adducts during cell division can result in errors in DNA replication, leading to permanent genetic alterations (Cmarik et al., 1990). Such mutations are a driving force in the carcinogenic process, as they can activate oncogenes or inactivate tumor suppressor genes, promoting uncontrolled cell proliferation. This process can be directly linked to DNA alkylation, as they may occur later in the process, influenced by several factors (e.g., cell cycle dynamics, DNA repair capacity).

2.4.6.1.5 Adverse Outcome: Tumor Formation

The outcome of these molecular events is the accumulation of genomic mutations leading to the development of tumors. Ethylene dibromide's ability to form DNA adducts and induce mutations ultimately leads to cancer in exposed tissues. Animal studies consistently demonstrate increased tumor incidences following ethylene dibromide exposure via multiple exposure routes and in different organ systems (see Section 2.4.3), supporting its classification as a genotoxic carcinogen (ATSDR, 2018; U.S. EPA, 2004b; Van Duuren et al., 1985).

In summary, the MOA of ethylene dibromide involves its metabolic activation to DNA-reactive intermediates, leading to DNA adduct formation and subsequent mutations. These genetic alterations drive the carcinogenic process, resulting in systemic tumor development.

2.4.6.2 Cancer Classification and Evidence Integration Conclusions

Overall, the epidemiology evidence for carcinogenicity in humans is indeterminate due to lack of sufficient data. The evidence base was small and included some low-quality studies, which decreases the strength of the evidence. The strength of the evidence is neither increased nor decreased based on

consistency because other than two studies that assessed breast cancer incidence, the studies did not assess a consistent outcome but generally did not find statistically significant associations. Increased odds of some cancers and increased mortality for some cancers were observed in groups exposed to ethylene dibromide compared to unexposed groups, but these findings were not statistically significant; the p-values for these findings were greater than 0.05 and the 95% confidence intervals for the odds ratios or standardized mortality ratios included ratios of one, indicating no statistically significant difference between groups. Thus, the small magnitude and lack of precision (relatively wide confidence intervals) of the findings decreases the strength of the evidence. The data were not amenable to assess the dose-response relationship, so the strength of the evidence is neither increased nor decreased by the dose-response relationship. Overall, the small size and low quality of the database, along with the lack of statistically significant findings, resulted in evidence that is indeterminate.

The evidence is robust for the carcinogenic potential effects of ethylene dibromide based on multiple chronic animal bioassays. Across these studies, ethylene dibromide consistently induced tumors at multiple sites, including the nasal cavity, lung liver, and forestomach. The occurrence of tumors across multiple tissues supports a systemic carcinogenic effect. The forestomach is a rodent-specific structure lined with squamous epithelium and is not present in humans, rodents also possess a glandular stomach, which is more closely comparable to the human stomach due to its specialized mucosal epithelium involved in secretion of gastric enzymes and acid. Although effects observed in the rodent forestomach are not assumed to be directly relevant to humans, this may be reconsidered when supported by mode of action evidence. Proctor et al. (2007) provides three criteria that determine human health relevance of forestomach tumors observed in rodent studies. Ethylene dibromide meets these criteria which suggests forestomach effects are relevant to the cancer assessment because it is likely to cause cancer via oral exposure in humans, despite the anatomical difference.

Carcinogenic effects were observed in both rats and mice, in males and females, and following both inhalation and oral exposure. The chronic bioassays were of adequate duration and dose selections to elicit tumorigenic responses. This concordance across species, sexes, and exposure routes, and study designs strengthens confidence in the animal evidence.

In two high-quality chronic inhalation studies, exposure to ethylene dibromide resulted in increased tumor incidence in both male and female F344 rats and male and female B6C3F1 mice. These studies demonstrated increased incidence of adenoma and carcinoma at multiple sites, including nasal cavity adenocarcinomas, hemangiosarcoma, mesotheliomas, and alveolar/bronchiolar adenomas and carcinomas of the lung. Tumor responses were observed regardless of sex or strain, indicating a consistent carcinogenic response across rodent model (NTP, 1982). Additional evidence was provided by studies conducted in other rodent strains. In female A/J mice, ethylene dibromide exposure was associated with a statistically significant increase in pulmonary adenomas (Adkins et al., 1986). In Sprague-Dawley rats, mammary gland tumors in females were observed, further supporting the carcinogenic potential of ethylene dibromide across tissues and strains (Wong et al., 1982).

Although oral studies have limitations for quantitative dose-response analysis, they provided qualitative evidence of carcinogenicity. In Osborne-Mendel rats, oral exposure to ethylene dibromide has been associated with squamous cell carcinoma of the forestomach (NCI, 1978). In a drinking water study in female B6C3F1 mice by Van Duuren and colleagues, tumor development was observed in the forestomach, liver, and esophagus in females, and the forestomach, glandular stomach, and liver in male (Van Duuren et al., 1986; Van Duuren et al., 1985). These data reflect the available oral carcinogenicity database for oral studies.

Dose-response relationships were evident in several studies, with increasing tumor incidence observed with increasing exposure concentration. In some studies, tumors occur at relatively low exposure levels and with early onset, supporting the carcinogenic potency of ethylene dibromide. In NTP (1982) inhalation study, high-dose male rats exhibited significant increases in nasal cavity adenocarcinomas and adenomas and increased incidences of hemangiosarcoma and mesotheliomas. Low-dose male rats also showed significant increase in nasal cavity adenocarcinomas and adenomas, with increased incidences of adenomatous polyps. High-dose female rats demonstrated significant increase in combined alveolar/bronchiolar adenomas and carcinoma, while high-dose male rats exhibited increased incidences of hemangiosarcoma and mesotheliomas (NTP, 1982).

In mice from NTP (1982) study, high-dose males exhibited increased incidences of alveolar/bronchiolar carcinomas, and high-dose females similarly showed increased tumor incidence for both adenomas and carcinomas (NTP, 1982).

Hemangiosarcomas were significantly increased in both low- and high-dose female mice, and low dose females also exhibited a significant increase in mammary gland adenomas and carcinomas. Overall, tumor findings were observed consistently across independent bioassays, providing reproducible evidence of carcinogenic activity in experimental animals (NTP, 1982).

In summary, the animal studies database provides robust evidence of carcinogenicity for ethylene dibromide, characterized by consistent, dose related tumors at multiple sites across multiple species and exposure routes, providing a strong foundation for subsequent consideration of MOA and cancer response.

Based on the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), EPA determined that ethylene dibromide is “Likely to be Carcinogenic to Humans” based on the adequate evidence demonstrating ethylene dibromide’s carcinogenic potential in animals across multiple species and tumor types. These findings are consistent with a previous EPA assessment, from the IRIS program (U.S. EPA, 2004b), and equivalent to the cancer classifications from IARC (1999) (Group 2A: Probably Carcinogenic to Humans), NICNAS (2013) (Cat. 1B [H350] May cause cancer), and NTP (2016) (Reasonably Anticipated to be a Human Carcinogen).

2.4.7 Cancer Dose-Response Assessment

EPA conducted BMD modeling for cancer, which is discussed below. Cancer was considered separately for oral and inhalation routes of exposure. A mutagenic mode of action was found to be the most consistent with the available information on ethylene dibromide, so multistage linear non-threshold modeling was used for dose-response assessment. The dose-response assessment of relevant non-cancer endpoints, including selection of studies and chosen PODs, was discussed in Section 2.3.2.2. Due to lack of appropriate data, dermal PODs could not be identified in the evaluated references for cancer. Route-to-route extrapolation was used to convert the oral and inhalation cancer slope factors/unit risk values to dermal-equivalent values. Though epidemiological data were insufficient for dose-response assessment, animal toxicological data was sufficient to identify the following PODs:

- Cancer Inhalation (sufficient for BMD modeling);
- Cancer Oral (sufficient for BMD modeling); and
- Cancer Dermal (insufficient data, utilized default modeling for route-to-route extrapolation).

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

The selection of representative cancer studies and locations of tumors/tumor types for dose-response analysis is described below based on the following considerations:

- overall quality determination ratings;
- dose range and sufficiency of dose-response information;
- strength of the evidence supporting the associated tumor type;
- MOA conclusions;
- relevance (*e.g.*, what species was the effect in, was the study directly assessing the effect, is the endpoint the best marker for the toxicological outcome?);
- uncertainties not captured by overall quality determination ratings;
- endpoint sensitivity;
- uncertainty and sensitivity of BMR selection from BMD modeling; and
- relevance and uncertainty of dose metric for PBPK model (as applicable).

The below sections discuss how the selection criteria listed above were applied in the selection of PODs for inhalation and oral, as well as any adjustments made to adjust for exposure duration, age, etc. Evaluation of cancer endpoints was also conducted in accordance with EPA's 2005 "Guidelines for Carcinogen Risk Assessment" ([U.S. EPA, 2005a](#)). The applicability of studies for deriving dermal PODs is discussed in Section 2.4.7.4

2.4.7.1.1 Inhalation Route of Exposure

For the inhalation route of exposure, the NTP bioassay ([NTP, 1982](#)) was selected as the basis for the cancer POD based on its high overall determination rating, adequate dose response characterization, and relevance to the mutagenic mode of action. There were no other inhalation studies on ethylene dibromide with chronic dosing regimens that received an acceptable OQD. Table 2-11 lists all tumor types where the incidence was at least 10% in either the low- or high-exposure group for all species and sexes included in the critical study. The basis for dose-response modeling is bolded (male and female rat, nasal cavity tumors). The study provided sufficient evidence of carcinogenicity, and tumor data used for quantitative assessment including treatment related increases in multiple tumor types, most notably nasal cavity carcinomas, adenocarcinomas, alveolar/bronchiolar tumors. These tumor responses were observed across sexes (combined sex F344 rats), supporting relevance of the carcinogenic response following inhalation exposure. Overall, the inhalation cancer dose-response assessment is supported by robust tumor data and appropriate application of BMD modeling and linear extrapolation.

Table 2-11. Neoplasm Incidences in Rats and Mice Exposed to Ethylene Dibromide by Inhalation ([NTP, 1982](#))

Tumor Type	0 ppm (Control)	10 ppm (76.83 mg/m ³)	40 ppm (307.3 mg/m ³)
Male rats			
Subcutaneous tissue, fibroma	3/50	6/50	8/50
Nasal cavity^a	0/50	39/50	41/50
Multiple organs, monocytic leukemia	6/50	7/50	1/50
Spleen, hemangiosarcoma	0/50	1/50	15/50
Pituitary, adenoma, NOS (not otherwise specified)	0/45	7/48	2/47
Adrenal, Pheochromocytoma	4/49	5/49	0/48
Testis, interstitial-cell tumor	35/50	45/50	10/49

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Tumor Type	0 ppm (Control)	10 ppm (76.83 mg/m³)	40 ppm (307.3 mg/m³)
Brain, carcinoma, NOS, invasive (from nasal cavity)	0/50	0/50	10/49
Tunica vaginalis, mesothelioma, NOS	0/50	7/50	25/50
Multiple organs, mesothelioma, malignant	0/50	5/50	1/50
<i>Total animals with primary tumors</i>	45/50	50/50	49/50
<i>Total animals with benign tumors</i>	40/50	47/50	26/50
<i>Total animals with malignant tumors</i>	18/50	39/50	43/50
<i>Total animals with secondary tumors</i>	3/50	3/50	14/50
<i>Total animals with tumors uncertain-benign or malignant</i>	2/50	7/50	25/50
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/50	0/50	0/50
Female rats			
Nasal cavity ^a	1/50	34/50	43/50
Multiple organs, monocytic leukemia	6/50	5/50	1/50
Spleen, hemangiosarcoma	0/50	0/49	5/48
Pituitary, adenoma, NOS	1/50	18/49	4/45
Mammary gland, fibroadenoma	4/50	29/50	24/50
Brain, carcinoma, NOS, invasive (from nasal cavity)	0/50	0/50	11/48
<i>Total animals with primary tumors</i>	33/50	49/50	46/50
<i>Total animals with benign tumors</i>	27/50	41/50	31/50
<i>Total animals with malignant tumors</i>	9/50	31/50	43/50
<i>Total animals with secondary tumors</i>	2/50	1/50	12/50
<i>Total animals with tumors uncertain-benign or malignant</i>	2/50	0/50	3/50
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/50	0/50	0/50
Male mice ^b			
Lung, alveolar/bronchiolar adenoma	0/41	0/48	11/46
Lung, alveolar/bronchiolar carcinoma	0/41	3/48	19/46
<i>Total animals with primary tumors</i>	3/44	5/48	27/46
<i>Total animals with benign tumors</i>	0/44	0/48	20/46
<i>Total animals with malignant tumors</i>	3/44	5/48	20/46
<i>Total animals with secondary tumors</i>	0/44	0/48	0/46
<i>Total animals with tumors uncertain-benign or malignant</i>	0/44	0/48	0/46
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/44	0/48	0/46
Female mice			
Subcutaneous tissue, fibrosarcoma	0/50	4/50	11/50
Nasal cavity ^a	0/50	0/50	11/50
Lung/bronchus, adenoma, NOS	0/49	0/49	5/50
Lung, alveolar/bronchiolar adenoma	3/49	7/49	13/50
Lung, alveolar/bronchiolar carcinoma	1/49	5/49	37/50
Broad ligament, hemangiosarcoma	0/50	6/48	3/48
Liver, hepatocellular carcinoma	2/50	5/50	1/50
Mammary gland, adenocarcinoma, NOS	2/50	14/50	8/50

Tumor Type	0 ppm (Control)	10 ppm (76.83 mg/m ³)	40 ppm (307.3 mg/m ³)
<i>Total animals with primary tumors</i>	22/50	45/50	49/50
<i>Total animals with benign tumors</i>	12/50	14/50	22/50
<i>Total animals with malignant tumors</i>	13/50	42/50	48/50
<i>Total animals with secondary tumors</i>	1/50	12/50	10/50
<i>Total animals with tumors uncertain-benign or malignant</i>	0/50	0/50	0/50
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/50	0/50	0/50
^a Nasal cavity tumors include adenomatous polyp, adenoma, adenocarcinoma, carcinoma, and squamous cell carcinoma ^b The principal cause of early death in control and dosed male mice was ascending, suppurative urinary tract infection that resulted in necrotic, ulcerative lesions around the urethral opening, chronic or suppurative cystitis (often with urinary tract obstruction), and ascending suppurative pyelonephritis. Note: Only tumor types with incidence ≥10% in either the 10 or 40 ppm group were included in this table for brevity Bolded value = identified for cancer slope factor modeling using EPA's Benchmark Dose Software <i>Italicized value</i> = summary incidence across all sites			

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2.4.7.1.2 Oral Route of Exposure

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For the oral route of exposure, the NCI bioassay ([NCI, 1978](#)) was selected as the basis for the cancer POD based on its overall study quality and relevance for evaluation of cancer risk following oral exposure. There were no other oral studies on ethylene dibromide with chronic dosing regimens that received an acceptable OQD. Table 2-12 lists all tumor types where the incidence was at or above 10% in either the low- or high-dose group for all species and sexes included in the critical study. The basis for dose-response modeling is bolded (male rat, total animals with primary tumors). The study demonstrated treatment-related increases in tumor incidence, including squamous cell carcinoma of the forestomach. Other tumors that reached statistical significance were hepatocellular carcinomas or neoplastic nodules of the liver, and cortical adenomas and cortical carcinomas of the adrenal gland in female rats; and thyroid tumors and hemangiosarcomas in male rats ([NCI, 1978](#)). The study included time-weighted exposure considerations; however, limitations were noted in exposure timing and study design. Despite these limitations, the datasets were considered suitable for quantitative cancer assessment.

The oral cancer slope factor was derived based on the primary tumor response consistent with a mutagenic mode of action. Some limitations of the oral cancer study included significant early attrition at the highest dose, which could be compensated for statistically but was a limitation compared to the inhalation study. Similarly, the dose spacing for the oral study was non-ideal due to adjustments to dosing that took place mid-study (prompted by the high attrition rate) whereas the inhalation study was able to maintain its initial dose spacing for the entire length of the study. Because of the high attrition, the incidence of cancer in the high dose group is suppressed; the animals simply did not live long enough to develop tumors. To illustrate, 18 high-dose male rats died during or immediately after intubation in week 15. In Table 2-12, this can be seen for multiple tumor types (including total animals with primary tumors) where the incidence is higher in the low dose group than in the high dose group. To better understand the potential impacts of the higher reported incidence rates at the lower dose group, Poly K adjustment was considered, which is a statistical method available in EPA's Benchmark Dose Software. Poly K adjustment corrects for treatment-related differences in survival across dose groups. Inputs to Poly K include the adjustment power (defaults to 3), study duration in days, and the individual animal data with both tumor incidence and survival. The output is an adjusted number of animals per dose group *N* (taking on non-integer values) and adjusted incidence (integer values only), which can be plugged in to the Multistage Cancer Model.

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Alternatively, a bounding scenario was also considered where the control and low dose incidence was kept constant and the incidence in the high dose group was set to 100%. Incidence is bounded between 0% and 100% (unlike continuous measures such as body or organ weights) so a “worst-case” scenario is clearly definable. Given that the benchmark response of 10% extra risk lies between the control and low dose groups for this dataset, the influence of the high dose group on the slope factor is minimal. Running this bounding scenario allowed EPA to determine the maximum possible increase in the slope factor compared to the experimentally-reported values by positing an extreme case where every animal in the high dose group had survived and had one or more primary tumors. EPA decided to use the bounding scenario because it mathematically simpler and conceptually easier to interpret.

Table 2-12. Neoplasm Incidences in Rats and Mice Exposed to Ethylene Dibromide by Oral Gavage (NCL, 1978)

Tumor Type	Untreated Control	Vehicle Control	Low Dose ^a	High Dose ^a
Male rats				
Spleen, squamous cell carcinoma, metastatic	0/20	0/20	4/50	10/49
Spleen, hemangiosarcoma	0/20	0/20	10/50	3/49
Liver, squamous cell carcinoma, metastatic	0/20	0/20	18/50	14/50
Pancreas, squamous cell carcinoma, metastatic	0/20	0/20	10/49	9/46
Forestomach, squamous cell carcinoma	0/20	0/20	45/50	33/50
Thyroid, follicular-cell adenoma	0/19	0/20	4/50	7/49
Total animals with primary tumors	6/20	0/20	46/50	35/50
<i>Total animals with benign tumors</i>	2/20	0/20	6/50	8/50
<i>Total animals with malignant tumors</i>	6/20	0/20	45/50	34/50
<i>Total animals with secondary tumors</i>	0/20	0/20	25/50	19/50
<i>Total animals with tumors uncertain-benign or malignant</i>	0/20	0/20	2/50	1/50
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/20	0/20	0/50	0/50
Female rats				
Spleen, squamous cell carcinoma, metastatic	0/20	0/20	11/49	4/48
Liver, squamous cell carcinoma, metastatic	0/20	0/20	21/47	12/48
Liver, hepatocellular carcinoma	1/20	0/20	1/47	5/48
Pancreas, squamous cell carcinoma, metastatic	0/20	0/20	11/45	8/47
Forestomach, squamous cell carcinoma	0/20	0/20	40/50	29/50
<i>Total animals with primary tumors</i>	14/20	2/20	40/50	29/50
<i>Total animals with benign tumors</i>	12/20	2/20	3/50	6/50
<i>Total animals with malignant tumors</i>	6/20	1/20	40/50	29/50
<i>Total animals with secondary tumors</i>	1/20	0/20	29/50	18/50
<i>Total animals with tumors uncertain-benign or malignant</i>	0/20	0/20	0/50	1/50
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/20	0/20	0/50	0/50
Male mice				
Lung, alveolar/bronchiolar adenoma	0/18	0/20	4/45	10/47

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Tumor Type	Untreated Control	Vehicle Control	Low Dose^a	High Dose^a
Spleen, squamous cell carcinoma, metastatic	0/19	0/20	18/45	16/33
Bronchial lymph node, squamous cell carcinoma, metastatic	0/18	0/18	5/41	4/32
Mesenteric lymph node, squamous cell carcinoma, metastatic	0/18	0/18	12/41	7/32
Liver, squamous cell carcinoma, metastatic	0/19	0/20	18/45	20/48
Pancreas, squamous cell carcinoma, metastatic	0/19	0/19	23/44	24/36
Forestomach, squamous cell carcinoma	0/20	0/20	45/50	29/49
Small intestine, squamous cell carcinoma, metastatic	0/18	0/19	9/42	4/42
Duodenum, squamous cell carcinoma, metastatic	0/18	0/19	0/42	7/42
Large intestine, squamous cell carcinoma, metastatic	0/19	0/19	4/42	3/40
Kidney, squamous cell carcinoma, metastatic	0/19	0/20	10/45	5/47
Urinary bladder, squamous cell carcinoma, metastatic	0/17	0/19	3/40	6/45
Adrenal, squamous cell carcinoma, metastatic	0/19	0/20	13/43	16/46
Prostate, squamous cell carcinoma, metastatic	0/18	0/20	5/37	6/35
Testis, squamous cell carcinoma, metastatic	0/19	0/20	8/45	14/47
Epididymis, squamous cell carcinoma, metastatic	0/19	0/20	10/50	10/49
Abdominal muscle, squamous cell carcinoma, metastatic	0/19	0/20	7/50	2/49
<i>Total animals with primary tumors</i>	5/19	2/20	45/50	33/49
<i>Total animals with benign tumors</i>	0/19	0/20	4/50	13/49
<i>Total animals with malignant tumors</i>	5/19	1/20	45/50	30/49
<i>Total animals with secondary tumors</i>	0/19	0/20	29/50	26/49
<i>Total animals with tumors uncertain-benign or malignant</i>	0/19	1/20	0/50	0/49
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/19	0/20	0/50	0/49
Female mice				
Lung, alveolar/bronchiolar adenoma	0/20	0/20	10/43	6/46
Spleen, squamous cell carcinoma, metastatic	0/20	0/20	24/42	11/42
Bronchial lymph node, squamous cell carcinoma, metastatic	0/20	0/19	8/43	2/29
Mesenteric lymph node, squamous cell carcinoma, metastatic	0/20	0/19	18/43	8/29
Liver, squamous cell carcinoma, metastatic	0/20	0/20	26/44	12/47
Gallbladder, squamous cell carcinoma, metastatic	0/20	0/20	7/48	2/50
Pancreas, squamous cell carcinoma, metastatic	0/19	0/20	31/43	13/39
Forestomach, squamous cell carcinoma, metastatic	0/20	0/20	46/49	28/50
Duodenum, squamous cell carcinoma, metastatic	0/20	0/20	6/41	5/42
Kidney, squamous cell carcinoma, metastatic	0/20	0/20	7/43	1/46
Adrenal, squamous cell carcinoma, metastatic	0/19	0/19	12/41	4/45
Uterus, squamous cell carcinoma, metastatic	0/20	0/20	8/38	1/44

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Tumor Type	Untreated Control	Vehicle Control	Low Dose ^a	High Dose ^a
Ovary, squamous cell carcinoma, metastatic	0/20	0/20	10/37	2/41
Mesentery, squamous cell carcinoma, metastatic	0/20	0/20	8/48	1/50
<i>Total animals with primary tumors</i>	6/20	0/20	47/48	31/50
<i>Total animals with benign tumors</i>	1/20	0/20	12/48	8/50
<i>Total animals with malignant tumors</i>	6/20	0/20	47/48	29/50
<i>Total animals with secondary tumors</i>	1/20	0/20	34/48	16/50
<i>Total animals with tumors uncertain-benign or malignant</i>	0/20	0/20	1/48	0/50
<i>Total animals with tumors uncertain-primary or metastatic</i>	0/20	0/20	0/48	0/50
^a Due to dosing issues, the doses administered did not match the initial planned nominal doses; the actual doses, represented as time-weighted average human equivalent doses (time-weighted average [TWA] HEDs) were: Low dose: 11.02 mg/kg/day (male rat), 9.99 mg/kg/day (female rat), 9.3 mg/kg/day (mice, both sexes) High dose: 11.89 mg/kg/day (male rat), 10.53 mg/kg/day (female rat), 16.05 mg/kg/day (mice, both sexes) Note: Only tumor types with incidence $\geq 10\%$ in either the low- or high-dose group included in this table for brevity Bolded value = identified for cancer slope factor modeling using EPA's Benchmark Dose Software <i>Italicized value</i> = summary incidence across all sites				

2.4.7.2 Duration, Dosimetric, Unit, and Age-Dependent Adjustment Factor (ADAF) Adjustments, Route-to-Route Extrapolation

As described in Section 2.4.7, EPA considered studies for ethylene dibromide for quantitative dose response analysis. The sections below describe the steps used to derive the hazard values used to calculate risks for ethylene dibromide.

2.4.7.2.1 Duration, Dosimetric, Unit and ADAF Adjustments for Inhalation Hazard Values

Dosimetric Adjustments

Ethylene dibromide is a liquid at standard temperature and pressure. However, due to its volatility, vapor exposure is possible. When inhaled, ethylene dibromide is considered a category 3 gas. This is because effects from ethylene dibromide are seen at sites distant from the portal of entry and not merely in the nasal cavity, tracheobronchial region, or the pulmonary region. For example, effects on the liver are seen across sexes and species for all doses tested.

Duration Adjustments

The critical studies for both oral and inhalation cancer endpoints were chronic studies. Dosing was adjusted to 7 days per week, and to 24 hours per day (for inhalation exposure).

Unit Conversion

It is often necessary to convert between ppm and mg/m³ due to variation in concentration reporting in studies and the default units for different OPPT models. Therefore, EPA presents all inhalation hazard values in Table 2-15 in both units. Equation 2-6 presents the conversion of the HEC from mg/m³ to ppm.

Equation 2-6. IUR Unit Conversion: per ppm to per µg/m³

$$\text{IUR (per mg/m}^3\text{)} = \text{IUR (per ppm)} \times (24.45 \div \text{molecular weight}) \times (1 \text{ mg}/1,000 \text{ }\mu\text{g})$$

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.

For route-to-route extrapolation of cancer PODs, Inhalation Unit Risks (IURs) and Cancer Slope Factors (CSFs) can be interconverted using the same exposure factors to estimate the internal dose by simply inverting the arithmetic. CSFs are thus calculated from IURs using Equation 2-7 below.

Equation 2-7. Conversion of IUR to CSF

$$\text{CSF (per mg/kg)} = \text{IUR (per } \mu\text{g/m}^3) \times (\text{body weight [kg]} \div (1,000 \mu\text{g/mg} \times \text{hourly inhalation rate [m}^3/\text{h]} \times \text{exposure duration [hours])})$$

2.4.7.2.2 Duration, Dosimetric, and Unit and ADAF Adjustments for Oral Hazard Values

EPA reviewed the PBPK model for ethylene dibromide and used it as described elsewhere in this document.

For comparison purposes, EPA adjusted the BMDL for the CSF 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 2-8.

Equation 2-8. 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 updated the DAFs using a human body weight of 80 kg for this draft risk evaluation ([U.S. EPA, 2011a](#)). The Agency used the body weights of 0.025 and 0.25 kg for mice and rats, respectively, as presented in ([U.S. EPA, 2011b](#)). The resulting DAFs for mice and rats are 0.13 and 0.24, respectively.

Duration Adjustments

Oral exposures in the chronic oral gavage study were adjusted to mg/kg/day based on averaging the dose over the entire study period. The high-dose group (nominal starting dose 80 mg/kg/day) had a dosing holiday followed by a reduction in the top dose; a time-weighted average was calculated to serve as the dose metric.

2.4.7.2.3 Age-Dependent Adjustment Factor (ADAF) for all routes of exposure

The last step is to apply the ADAFs, which adjust the “adult-based” lifetime age-specific slope factors for children. The weighted sum of these three partial slope factors is the ADAF-adjusted lifetime slope factors for primary tumors. ADAFs are applied based on the determination of a mutagenic MOA (Section 2.4.6) and in accordance with ([U.S. EPA, 2005b](#)).

Table 2-13. Incorporation of ADAF to Obtain the Combined Slope Factors of Primary Tumors

Age	ADAF Adjustment	Adjusted Partial Life and General Population Slope Factors
0 to <2	10×	Slope factor $\times 10 \times (2 \div 78) = 0.25641 \times \text{SF}$
2 to <16	3×	Slope factor $\times 3 \times (14 \div 78) = 0.53846 \times \text{SF}$
$\geq 16^a$	1×	Slope factor $\times 1 \times (62 \div 78) = 0.79487 \times \text{SF}$
0–78	1.59	1.58974·SF (same equation for inhalation, oral, and dermal)
ADAF = age-dependent adjustment factor; SF = slope factor		
^a Adjusted IUR value is based on an assumption of 78 years lifetime (U.S. EPA, 2011a).		

After ADAF adjustment, the combined IUR is 0.68 per ppm (8.9×10^{-5} per $\mu\text{g}/\text{m}^3$), the combined oral slope factor is 0.24 per mg/kg/day, and the combined dermal cancer slope factor is 0.48 per mg/kg/day.

2.4.7.2.4 PBPK: Convert Dermal Cancer HED to Cancer Slope Factor (CSF) (Cancer Only)

The CSF, in units $(\text{mg}/\text{kg}/\text{d})^{-1}$, is calculated by dividing the benchmark response rate *BMR* by the cancer HED such that $CSF = \frac{BMR}{HED}$, with *BMR* = 0.1. The *CSF* represents the upper-bound slope of the low-dose cancer dose-response curve. The CSF is then used to estimate lifetime cancer probability from exposure by using the lifetime chronic retained dose (LCRD), such that $Cancer\ Risk = LCRD \times CSF$.

2.4.7.3 Oral and Inhalation Exposure BMD Modeling Results

Benchmark dose modeling for inhalation exposure for cancer was found to be acceptable according to the decision logic in EPA’s Benchmark Dose Technical Guidance ([U.S. EPA, 2012b](#)). The Benchmark Dose Software produced two viable models (Multistage 1 and Multistage 2) with identical fits; the simpler Multistage 1 model was selected. A plot of the selected model versus the data is shown in Figure_Apx D-7. More information on this modeling can be found in Appendix D.6.

Benchmark dose modeling for oral exposure for cancer was found to be acceptable according to the decision logic in EPA’s Benchmark Dose Technical Guidance ([U.S. EPA, 2012b](#)). The Benchmark Dose Software produced two viable models (Multistage 1 and Multistage 2) with identical fits; the simpler Multistage 1 model was selected. A plot of the selected model versus the data is shown in Figure_Apx D-8. More information on EPA’s multistage cancer modeling using the Benchmark Dose Software can be found in Appendix D.7.

Even under an extreme scenario (bounding condition) where the incidence of cancer at the high dose was set to 100% (50 out of 50 animals affected), the slope factor was 2.2 times higher than the value from the measured data. This puts an upper-bound on the slope factor for later analyses in the risk evaluation. The Benchmark Dose Software produced two viable models (Multistage 1 and Multistage 2) with nearly-identical fits; the Multistage 2 model was selected based on a slightly lower AIC, although the slope factor differed by 4.7% between the two fits. A plot of the selected model versus this bounding

scenario is shown in Figure_Apx D-10. The Benchmark Dose Software output showing the results of EPA's multistage cancer modeling can be found in Appendix D.8.

2.4.7.4 Dermal Route-to-Route Extrapolation Approach

Due to lack of appropriate data, dermal PODs could not be identified in the evaluated references for cancer endpoints. Route-to-route extrapolation was conducted to identify acceptable cancer slope factors based on oral and inhalation animal points of departure PODs. Derivation of dermal hazard values was performed by first calculating the benchmark dose using BMD modeling, to which the default approach (where an oral or inhalation toxicity value is scaled using chemical-specific and exposure-factor information) and a PBPK modeling approach were both applied for route-to-route extrapolation. The consistent evidence of observed toxicological effects resulting from both oral and inhalation routes of exposure and systemic toxicity provides confidence in performing route-to-route extrapolation of available oral and inhalation data using a PBPK model to derive dermal PODs for cancer.

As discussed in Section 2.4.3, tumor responses were observed in male and female F344 rats and male and female B6C3F1 mice exposed to oral and inhaled ethylene dibromide, indicating a consistent carcinogenic response across rodent model ([NTP, 1982](#)). Thus, the critical endpoint that was considered acceptable for route-to-route extrapolation from the oral cancer study was the incidence of all primary tumors. Note that tumors were found in multiple sites in rats, including the forestomach. Again, though humans do not have a forestomach, this endpoint was still considered appropriate for oral-to-dermal and animal-to-human extrapolation due to the existence of widespread tumors in the body. The critical endpoint chosen for modeling of the inhalation cancer study was respiratory tract tumors. This would normally be unacceptable for route-to-route extrapolation given that it is a portal-of-entry effect but these tumors were seen in oral and dermal cancer studies of ethylene dibromide, indicating that they are not route of administration-dependent (*i.e.*, these tumors developed from systemic exposure and are not sequestered to portal-of-entry effects).

A dose-response model was fit to the tumor data from inhalation and oral exposures (described in Section 2.4.7.2.1 and Section 2.4.7.2.2, respectively) to estimate the doses associated with a benchmark response (0.23 ppm and 2.24 mg/kg/d for inhalation and oral exposures, respectively). These benchmark doses were then used in the inhalation-to-dermal and oral-to-dermal route-to-route extrapolation approach for cancer and are reported in Table 2-14.

2.4.7.4.1 Default Approach and Assumptions

The "default approach" for route-to-route extrapolation can be broken down into three distinct components: (1) adjusting for interspecies differences in toxicokinetics by deriving a HED or HEC; (2) modeling the dose-response relationship from the experimental data in the critical study (benchmark dose modeling) using the HED/HEC values; and (3) adjusting for differences in absorption between the original route of exposure (oral or inhalation) and the extrapolated route of exposure (dermal).

Oral and inhalation PODs were developed independently from critical studies identified through EPA's systematic review process. When considering the suitability of route-to-route extrapolation, a number of considerations need to be accounted for. The Interdepartmental Group on Health Risks from Chemicals has published "Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals," where Section 4 of these guidelines lays out five criteria to consider when conducting route-to-route extrapolation ([IGHRC, 2006](#)).

1. Absorption is the same between routes, or the difference is known and can be quantified.

2. The critical target tissue is not at the portal of entry of the compound (*i.e.*, the concern is with systemic toxicity and not local effects).
3. There is no significant metabolism of the chemical by oral, gut or skin enzymes or in pulmonary macrophages, or transformation by other processes in the gut or lung.
4. First-pass effects are minimal.
5. The chemical is relatively soluble in body fluids.

Going through each criterion in turn:

1. For ethylene dibromide, the difference in absorption is known and can be quantified; specifically, absorption via oral or inhalation exposure is taken as 100% and absorption via dermal exposure is adjusted for by mathematically adjusting the applied dose to get an absorbed dose.
2. Consideration #2 is specific to the endpoint, duration, and route of exposure. See below for details.
3. There is metabolism in the liver, kidneys, lungs, testes, stomach, small intestines, and skeletal muscle. However, rate in extrahepatic tissues is a small fraction of the hepatic metabolism, so this is still considered reasonable. ($V_{\max}$ liver = 413.8 $\mu\text{mol/h/kg}$, $V_{\max}$ kidneys = 0.15 $\mu\text{mol/h/kg}$, $V_{\max}$ lungs = 0.04 $\mu\text{mol/h/kg}$).
4. First-pass effects are moderately important for oral-to-dermal extrapolation and negligible for inhalation-to-dermal extrapolation. The role of first pass metabolism is unclear; because ethylene dibromide (parent) and several metabolites are all mutagenic (see Section 2.4.5), a clear delineation of “active” vs. “inactive” chemical species cannot be made. Since metabolism is not simply “detoxifying” nor “bioactivating” but represents a shift in reactivity with unclear effects on potency, EPA decided to consider both oral and inhalation studies as the starting point for extrapolation to dermal. First-pass effects are moderately important for oral-to-dermal extrapolation and negligible for inhalation-to-dermal extrapolation. The role of first pass metabolism is unclear; because ethylene dibromide (parent) and several metabolites are all mutagenic, a clear delineation of “active” vs. “inactive” but the liver is also a principal site of toxicity, so EPA considered this reasonable.
5. Ethylene dibromide is sufficiently soluble in body fluids to allow for systemic exposure following oral, dermal, and/or inhalation administration.

Adjustment for absorption is performed last to account for differences in bioavailability by different routes of exposure. Bioavailability is defined as the fraction of a dose that is absorbed into the systemic circulation. For example, if a chemical has an oral bioavailability of 0.5, one possibility is that half of the dose is absorbed into the bloodstream while the other half passes through the digestive tract and is eliminated unabsorbed and unchanged in the feces. For ethylene dibromide, given its physical-chemical properties, absorption via oral or inhalation exposure is expected to be effective, so the assessment team assumed bioavailability of 1 (*i.e.*, 100% absorption). For dermal exposures, EPA had a choice of adjusting the point of departure (*i.e.*, hazard) values for less than complete absorption, or adjusting the dermal dose (*i.e.*, exposure) values to account for absorption, evaporation, and other processes that affect the level of absorption. The Agency decided to account for dermal absorption on the exposure side. Therefore, the absorbed dose used in the dermal risk calculator is less than the applied dose; the difference between the absorbed dose and applied dose constitutes the amount unavailable to the systemic circulation.

2.4.7.4.2 PBPK Approach and Assumptions

Dermal HEDs were calculated using the following steps, as described in Section 2.2.5.2.

Step 1: Identify Animal PODs Associated with Toxicity Studies

Animal PODs are also described in the introduction to Section 2.4.7.4. and are reported in Table 2-14. The critical endpoint chosen for modeling the inhalation cancer study was respiratory tract tumors (NTP, 1982), which was ultimately determined acceptable because oral and dermal studies also resulted in respiratory tract tumors, indicating that these tumors are due to systemic exposure. The benchmark dose associated with a benchmark response was calculated as 0.23 ppm (see Section 2.4.7.2.1). The critical endpoint that was considered acceptable for route-to-route extrapolation from the oral cancer study was the incidence of all primary tumors (NTP, 1982), resulting in a benchmark dose of 2.24 mg/kg/day (see Section 2.4.7.2.2).

Step 2: Estimate Internal Doses from Animal PODs

EPA considered the amount of ethylene dibromide metabolized by the GST pathway in the liver per liver volume (weight) per day ($\mu\text{M-d}$) as the most appropriate dose metric considering its mutagenic mode of action discussed in Section 2.4.5. Using the PBPK model parameterized for rats, forward dosimetry was used to calculate internal dose metrics for each rat POD_{BDM} (i.e., 2.24 mg/kg/day oral or 0.23 ppm continuous inhalation). The rat PODs and corresponding internal doses are reported in Table 2-14.

Table 2-14. Rodent Internal Doses for Inhalation and Oral Exposures for Amount Metabolized in Liver per L liver per Day ($\mu\text{M/d}$) for Each Rat POD from Cancer Studies (NTP, 1982)

PBPK-Derived Internal Dose: Amount Metabolized in Liver by GST per Liter Liver per Day ($\mu\text{M-d}$)	Rat POD_{BDM}	Route of Exposure	Exposure Scenario	Species	Endpoint	Source
28.3	2.24 mg/kg/d	Oral	Daily gavage in corn oil, 5 days/ week for 365 days	Male Osborne-Mendel Rat	Cancer (forestomach tumors) NTP (1982)	BMD modeling of oral cancer study from NTP (1982), described in Section 2.4.7.2.2.
13.1	0.23 ppm	Inhalation	Continuous	Combined Sex F344 Rat	Cancer (nasal cavity tumors) NTP (1982)	BMD modeling of inhalation cancer study from NTP (1982), described in Section 2.4.7.2.1.
BMD = benchmark dose; GST = glutathione S-transferase; PBPK = physiologically-based pharmacokinetic; POD = point of departure						

Step 3: Calculate Dermal HEDs to Reach Target Internal Dose Metrics

For each of the same exposure COUs as described in Section 2.2.5.2, dermal HEDs were calculated for each corresponding internal dose.

Step 4: Interpret HEDs Within Context – Convert Dermal Cancer HED to Cancer Slope Factor (CSF) or Inhalation Unit Risk (IUR)

The HED corresponding to the benchmark tumor response is considered the point of departure for cancer potency. The CSF, in units $(\text{mg/kg/d})^{-1}$, is calculated by dividing the benchmark response rate BMR by the cancer HED such that $\text{CSF} = \frac{\text{BMR}}{\text{HED}}$, with $\text{BMR} = 0.1$. The CSF represents the upper-bound slope of the low-dose cancer dose-response curve. The CSF is then used to estimate lifetime cancer probability from exposure by using the lifetime chronic retained dose (LCRD), such that $\text{Cancer Risk} = \text{LCRD} \times \text{CSF}$. A summary of these values is presented in Table 2-15. The full list of results for each specific scenario is presented in Table 2-22.

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2.4.7.5 Summary of Cancer Results

EPA has identified IURs and OSFs based on empirical cancer data resulting from inhalation and oral routes of exposure and also present CSFs that result from route-to-route extrapolation from IURs and OSFs (Table 2-16). The cancer slope factor for dermal exposures was calculated for both inhalation-to-dermal and oral-to-dermal route-to-route extrapolation, and both are presented in Table 2-16. For risk calculations, the inhalation-to-dermal value of $0.48 \text{ (mg/kg/day)}^{-1}$ for the general population aged 0-78 and the value of $0.30 \text{ (mg/kg/day)}^{-1}$ for workers and consumers aged 16 to 78 years were chosen as they match the ADME characteristics of the inhalation route better. Specifically, both dermal and inhalation exposures bypass first-pass metabolism, which can affect the potency of a chemical toxicant through metabolic transformation in the liver. Because exposures via both inhalation and dermal routes are distributed systemically immediately upon exposure and lack a first-pass effect, they were considered more similar and therefore preferable to oral-to-dermal extrapolation, considering all other factors to be equal. In addition, the overall quality determination for the inhalation cancer study was higher than for the oral study, increasing confidence in the final risk value, and the dose-response relationship was monotonic. The oral study showed significant early attrition at the highest dose, which could be compensated for statistically but was a limitation compared to the inhalation study. Similarly, the dose spacing for the oral study was non-ideal due to adjustments to dosing that took place mid-study (prompted by the high attrition rate) whereas the inhalation study was able to maintain its initial dose spacing for the entire length of the study. Finally, the PBPK model allowed EPA to adjust for differences in absorption, distribution, metabolism, and elimination in a route-specific manner for both inhalation and dermal, strengthening confidence in the final value and reducing uncertainty in the extrapolation. In the end, the conclusion was that extrapolation from inhalation-to-dermal for cancer risk from ethylene dibromide using the PBPK model described in Section 2.2.5 represented the best available science for filling the data gap for quantitative dermal cancer assessment.

Table 2-15. Summary of Cancer PODs for Oral, Inhalation and Dermal (via Route-to-Route Extrapolation)

Route	POD	Type	Sex/Strain/Species	Benchmark MOE	Confidence
Oral	$0.24 \text{ (mg/kg/day)}^{-1}$	OSF	Male Osborne-Mendel Rat	N/A	Robust
Inhalation	$8.9\text{E-}05 \text{ (}\mu\text{g/m}^3\text{)}^{-1}$ 0.68 (ppm)^{-1}	IUR	Combined Sex F344 Rat	N/A	Robust
Inhalation-to-dermal extrapolation	$0.48 \text{ (mg/kg/day)}^{-1}$	IUR	Combined Sex F344 Rat	N/A	Robust
Oral-to-dermal extrapolation	$0.24 \text{ (mg/kg/day)}^{-1}$	OSF	Male Osborne-Mendel Rat	N/A	Slight
IUR = inhalation unit risk; OSF = oral slope factor					

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Table 2-16. IUR, OSF, and CSFs Used for Risk Estimates Across Various Routes of Exposure

IUR/OSF/CSF	Applied Population	Value
Inhalation		
Inhalation unit risk	General population aged 0–78 years	$8.9\text{E-}05 (\mu\text{g}/\text{m}^3)^{-1}$; 0.68 (ppm) ⁻¹
Adult unit risk	Workers aged 16–78 years and consumers aged 16–78 years	$5.6\text{E-}05 (\mu\text{g}/\text{m}^3)^{-1}$; 0.43 (ppm) ⁻¹
Oral		
Oral slope factor	General population aged 0–78 years	$0.24 (\text{mg}/\text{kg}/\text{day})^{-1}$
Adult oral slope factor	Workers aged 16–78 years and consumers aged 16–78 years	$0.15 (\text{mg}/\text{kg}/\text{day})^{-1}$
Dermal		
Cancer slope factor (inhalation-to-dermal route-to-route extrapolation)	General population aged 0–78 years	$0.48 (\text{mg}/\text{kg}/\text{day})^{-1}$
Adult cancer slope factor (inhalation-to-dermal route-to-route extrapolation)	Workers aged 16–78 years and consumers aged 16–78 years	Default: $0.30 (\text{mg}/\text{kg}/\text{day})^{-1}$ PBPK: $0.21 (\text{mg}/\text{kg}/\text{day})^{-1}$
Cancer slope factor (oral-to-dermal route-to-route extrapolation)	General population aged 0–78 years	$0.24 (\text{mg}/\text{kg}/\text{day})^{-1}$
Adult cancer slope factor (oral-to-dermal route-to-route extrapolation)	Workers aged 16–78 years and consumers aged 16–78 years	Default: $0.15 (\text{mg}/\text{kg}/\text{day})^{-1}$ PBPK: $(\text{mg}/\text{kg}/\text{day})^{-1}$
CSF = cancer slope factor; IUR = inhalation unit risk; OSF = oral slope factor; PBPK = physiologically-based pharmacokinetic		

EPA has also considered findings from previous assessments and briefly outlined designations below. Additional details can also be found below in Table_Apx C-1, which summarizes previous assessment PODs, and the basis for non-cancer and cancer hazard conclusions. The U.S. EPA 2004 assessment *Toxicological review of 1,2-dibromoethane (CAS no. 106-93-4)* reported an oral cancer slope factor $2.0 (\text{mg}/\text{kg}/\text{day})^{-1}$ and inhalation unit risk of $6 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ ([U.S. EPA, 2004b](#)). Although the numerical values presented in this document differ from those reported in and other agencies, the proposed oral cancer slope factor and IUR as described above in Table 2-15 are $0.24 (\text{mg}/\text{kg}/\text{day})^{-1}$, and $8.9 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$, respectively; these remain with the same order of magnitude of carcinogenic potency.

2.5 Weight of Scientific Evidence Conclusions for Human Health Hazard

EPA considered evidence integration conclusions and dose-response considerations from Sections 0 through 2.6.3 and additional factors to determine overall hazard confidence levels based on the following considerations:

- 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 sub-sections summarize the weight of scientific evidence for human health hazard drawing upon information from previous sections and additional considerations as needed. Specifically, the strengths, limitations, assumptions, and key sources of uncertainty are considered for the non-cancer and cancer analysis as pertaining to POD selection.

2.5.1 Toxicity Endpoints Selected for Risk Characterization

2.5.1.1 Acute and Intermediate Non-Cancer

Evidence Integration Conclusions

Considering both acute, intermediate, and chronic exposure, EPA concluded that ethylene dibromide likely causes effects on liver, lung, and reproductive function in humans under relevant exposure circumstances based primarily on animal data. EPA also concluded that ethylene dibromide likely causes effects on mortality; the evidence for this conclusion may be found in Appendix B.1. The Agency has moderate-to-robust overall confidence in the evidence integration, study/endpoint selection, exposure scenario applicability, dose-response analysis, PESS sensitivity, and PBPK modeling supporting derivation of PODs for ethylene dibromide based on the endpoints described below.

Selection of the Most Critical Endpoint and Study

EPA identified liver, gastrointestinal, mortality, and reproductive/developmental effects as the most sensitive non-cancer outcomes supported by the strongest evidence. Available studies consistently show similar effects on related endpoints.

For acute and intermediate inhalation, EPA selected ([Short et al., 1978](#)) as the basis for the PODs because it evaluated a range of doses and a comprehensive set of sensitive reproductive and developmental endpoints. This reference follows exposure to ethylene dibromide in pregnant mice and rats, evaluating a variety of maternal and fetal effects. Mouse fetal developmental abnormalities and increased late resorptions were selected as the basis for the POD used for characterizing risk from exposure to ethylene dibromide due to the severity of outcomes. Because exposure took place over several days during gestation, this dosing regimen falls under the “intermediate” duration for toxicity studies. However, without highly specialized studies to probe the “window of susceptibility” of the developing fetus to the toxic effect, it cannot be ruled out that a single dose (*i.e.*, a single, acute exposure) would have been sufficient for the adverse effects seen in the study. Because of this uncertainty, the same value is used for both acute exposures for inhalation. The significant effects on reproductive endpoints reported in ([Short et al., 1978](#)) are supported by additional studies [Short et al. \(1979\)](#), [NTP \(1982\)](#), and [NCI \(1978\)](#), which reported significant reproductive effects at doses ranging from 10 to 89 ppm.

For the acute and intermediate oral PODs, EPA selected ([Ghanayem et al., 1986](#)), which allows for dose-response analysis. This reference follows exposure to ethylene dibromide in male rats, evaluating histopathological changes to organs. Forestomach epithelial cell proliferation and hyperkeratosis was selected as the basis for the POD used for characterizing risk from exposure to ethylene dibromide due to its sensitive LOAEL of 80 mg/kg/day and the severity of outcomes. This experiment involved exposing test animals to ethylene dibromide 5 times per week, for 10 total exposures. For oral studies, the available study for dose-response had multiple oral exposures. This dosing regimen falls under the “intermediate” duration for toxicity studies because there was more than one exposure to the same dosing groups. Because of the low number of exposures (10 exposures over 2 weeks) and because there were no high-quality single exposure studies for dose response, this study was used to derive an acute/intermediate POD for oral exposures. Importantly, the POD for intermediate effects should be protective for acute effects as well ([U.S. EPA, 2002a](#)). Existing reports of human acute exposures confirms that nausea, vomiting, and other signs of gastrointestinal distress are the most common findings following oral exposure to ethylene dibromide (see Section 2.3.2.4 and Table_Apx A-9).

Because the Ghanayem ([1986](#)) study dosed ten times, the effects observed in this study are inclusive of single dose effects (*e.g.*, any effects from the first dose will also be reported). Again, though effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case it was being examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. The only endpoint available for dose-response analysis for oral exposure that was of sufficient quality was cell proliferation and hyperkeratosis in the forestomach ([Ghanayem et al., 1986](#)). The HED from benchmark dose modeling was calculated to be 2.7 mg/kg/day. The forestomach is a rodent-specific structure lined with squamous epithelium and is not present in humans, rodents also possess a glandular stomach, which is more closely comparable to the human stomach due to its specialized mucosal epithelium involved in secretion of gastric enzymes and acid. Although effects observed in the rodent forestomach are not assumed to be directly relevant to humans, this may be reconsidered when supported by mode of action evidence. Proctor et al. ([2007](#)) provides three criteria that determine human health relevance of forestomach tumors observed in rodent studies. Those criteria are well-established genotoxicity, its ability to induce tumors at multiple sites across a range of doses, and the observation that these effects occur in the absence of forestomach irritation. Ethylene dibromide meets these criteria which suggests that forestomach effects are relevant to the cancer assessment because it is likely to cause cancer via oral exposure in humans, despite the anatomical difference. The changes seen in Ghanayem ([1986](#)) are indicative of non-cancer outcomes that precede and do not inevitably progress to tumorigenesis but are relevant to chronic and cancer outcomes from ethylene dibromide exposure.

For characterizing risk for acute and intermediate dermal exposures to ethylene dibromide, route-to-route extrapolation was applied to the acute and intermediate inhalation PODs. However, the above-described acute and intermediate inhalation PODs based on ([Short et al., 1978](#)) were not considered appropriate for PBPK route-to-route extrapolation because they were measured in a species for which EPA lacks a PBPK model. Instead, for route-to-route extrapolation, EPA selected ([Short et al., 1979](#)), a rat study that evaluated the effects of ethylene dibromide exposure on male and female reproductive endpoints including implantations and resorptions. Male or female rats were exposed then mated with non-exposed controls. A female LOAEL of 80 ppm was determined for uterine epithelium degeneration and effects on the estrous cycle. A male LOAEL of 89 ppm was determined for lowered fertility, and testicular atrophy. The study durations were different among sexes; female rats were exposed to 80 ppm for shorter durations than the male rats exposed to 89 ppm. This resulted in a lower internal dose from the 89 ppm exposures. Thus, the 89 ppm LOEL was chosen for route-to-route extrapolation because it would be protective across sexes.

Relevance to Exposure Scenarios

The inhalation POD is based on effects in a developmental study in mice and rats ([Short et al., 1978](#)) that EPA determined to be relevant for acute/intermediate exposures in humans. Although there were 10 total exposures in this study, fetal development can be impacted differently depending on gestational day of exposure. Ferreri et al. ([1983](#)) examined single-day ethylene dibromide exposure in human embryonic epithelial cells at 10^{-4} , 10^{-3} and 10^{-2} M, where exposure resulted in high mutagenic efficiency. A significant and dose-dependent increase in the number of mutants were seen at 10^{-4} M (19 $\mu\text{g/L}$; 19 ppb) and 10^{-3} M (190 $\mu\text{g/L}$; 190 ppb), while 10^{-2} M (1.9 mg/L, 1,900 ppb) killed all the cells ([Ferreri et al., 1983](#)). Mitra et al. ([1992a](#)) observed significant bioactivation and binding of ethylene dibromide to DNA in the presence of anionic human fetal liver GST isoenzyme. When GD 10 rat embryos were cultured with this isoenzyme and exposed to 0.75 mM ethylene dibromide for 2 hours, followed by further incubation in culture media 40 hours, significant decreases of crown rump length and yolk sac diameter, as well as significant adverse effects in the central nervous system, optic and olfactory systems, and the hind limb were observed.

Collectively, these data suggest that even brief exposure to ethylene dibromide during pregnancy has potential for fetal toxicity in humans and it therefore cannot be ruled out that the effects described in ([Short et al., 1978](#)) could not also be seen in a single exposure during a sensitive period of gestational development. Similarly, the oral POD selected is based on a short-term study, in which exposure takes place over 10 total days ([Ghanayem et al., 1986](#)). EPA considers this endpoint to be relevant for acute/intermediate exposures in humans because the route of exposure is oral, and the effects observed are at the oral portal of entry; although the effects would be expected in the oral cavity and/or esophagus of humans as opposed to the forestomach, which humans do not have. In this study, cellular changes in the forestomach were observed at the most sensitive exposure level. The toxicity associated with ethylene dibromide exposure is found in the same organ systems with acute, intermediate, and chronic exposure, where the effects with chronic exposure display increased severity.

Dose-Response Considerations

EPA analyzed all reasonably available references for potential use in dose response assessment. The selected oral study was sufficient for BMDL modeling. Although the selected inhalation study was the best-fit in the reasonably available data pool to be utilized for dose-response, the study was ultimately not sufficient for benchmark dose modeling, as high mortality levels in high-dose experimental animals confounded findings, preventing authors from accurately analyzing outcomes on the proposed exposure timeline. No principal study was selected for acute dermal exposure to ethylene dibromide due to lack of data availability. The acute and intermediate dermal PODs were calculated by the default and PBPK route-to-route extrapolation methods in a tiered manner.

Consideration of PESS

Extrapolation from the inhalation POD is expected to be protective of sex-specific effects across most lifestages. It is based on the best available science in a short-term reproductive study and is therefore expected to be protective of effects resulting from in-utero exposure. Although the POD is based on a female reproductive endpoint most relevant to adult females and fetal development, extrapolation from this POD is protective of other endpoints that may be affected by ethylene dibromide, including male reproductive outcomes, and respiratory and liver effects relevant to other groups and lifestages. As discussed in Section 2.6 other factors that may contribute to biological susceptibility were considered qualitatively but not quantitatively incorporated into the POD. A $10\times$ UF_H factor was applied to account for human toxicokinetic and toxicodynamic variability, which is expected to account for differences in dose-response and toxicokinetics due to factors such as limited coverage of infants and children's exposure as well as interindividual variability. For example, considerations such as existing disease

states and genetic polymorphisms in metabolizing enzymes or transporters can vary chemical clearance and distribution within subpopulations. For example, disease states (such as inflammatory bowel diseases) that result in variations in gastrointestinal tract compositions may affect absorption and overall distribution (especially for first-pass metabolism in the gut wall) of the test chemical. Hepatic diseases can change the liver volume and metabolic processes, potentially changing internal kinetics.

2.5.1.2 Chronic Non-Cancer

Evidence Integration Conclusions

Considering acute, intermediate, and chronic exposure, EPA concluded that ethylene dibromide likely causes effects on liver, lung, and reproductive function in humans under relevant exposure circumstances based primarily on animal data. EPA also concluded that ethylene dibromide likely causes effects on mortality; the evidence for this conclusion may be found in Appendix B.1. The Agency has moderate-to-robust overall confidence in the evidence integration, study/endpoint selection, exposure scenario applicability, PBPK modeling, and derivation of PODs for ethylene dibromide for the endpoints described below. The selection of references for PODs is consistent with prior risk evaluations for ethylene dibromide published by ([ATSDR, 2018](#)) and ([U.S. EPA, 2004b](#)).

Selection of the Most Critical Endpoint and Study

EPA identified liver, lung, adrenal, gastrointestinal, mortality, and reproductive/developmental effects as the sensitive non-cancer endpoints supported by the strongest evidence. Available studies consistently show similar effects on related endpoints.

For chronic inhalation, EPA selected ([NTP, 1982](#)) as the basis for POD determination because it evaluates sensitive dose levels and the endpoints reported reflect patterns seen in both inhalation and oral exposure studies at various durations. At 38 mg/kg/day, co-critical effects of liver peliosis, adrenal cortex degenerative lesions, and testicular atrophy were identified in rats. The oral chronic study utilized for POD determination for non-cancer endpoints, ([NTP, 1982](#)), describes similar hazards. At 10 ppm exposure in rats, a critical outcome of liver necrosis is identified. Additionally, adrenal cortex degradation and testicular degradation are significant, as well as retinal atrophy, nasal cavity inflammation, and splenic hematopoiesis. These adverse liver, adrenal, and testicular outcomes also were found in many non-cancer studies described in Section 2.3.

For characterizing non-cancer hazard from chronic dermal exposure to ethylene dibromide, route-to-route extrapolation was applied to the chronic inhalation POD and chronic oral POD described in the previous paragraph. Both references are appropriate for route-to-route extrapolation because they both study exposure in rats, and they both describe endpoints that are systemic rather than being localized to portal of entry.

Relevance to Exposure Scenarios

The inhalation and oral PODs are based on effects found in cancer studies by the National Cancer Institute (NCI) and the National Toxicology Program (NTP). Both institutions apply standardized protocols based on the best available science for appropriate testing of chemicals for carcinogenicity, while also reporting non-cancer effects. EPA considers the resulting non-cancer chronic effects described in both studies to be relevant for chronic exposures in humans.

Dose-Response Considerations

EPA analyzed all reasonably available references for dose response assessment. Ultimately, no chronic non-cancer references were identified as appropriate for dose-response modeling. Instead, chronic inhalation and chronic oral PODs were identified in references that described sensitive endpoints. No

critical study was selected for chronic dermal exposure to ethylene dibromide due to lack of data availability. A PBPK model was built for route-to-route extrapolation to determine a chronic dermal value. Furthermore, EPA completed default route-to-route calculations to identify a chronic dermal POD based on oral chronic data to compare to the resulting PBPK-derived value.

Consideration of PESS

There were insufficient data to quantitatively assess PESS. The chronic POD for hepatic outcomes is equal to or lower than the POD for subchronic and chronic reproductive and developmental outcomes in animal studies. Therefore, extrapolation from the hepatic POD is expected to be protective of PESS that are susceptible to reproductive and developmental outcomes, with the caveat that lower average exposure levels were observed to be associated with male reproductive toxicity in epidemiology studies as discussed in Section 2.3.1.1.

2.5.1.3 Cancer

Evidence Integration Conclusions

EPA concluded that ethylene dibromide likely causes carcinogenic effects on the gastrointestinal tract, cardiovascular system, lungs, hematopoietic system, skin, nasal cavity, pituitary, spleen, liver, kidney, pancreas, mammary gland, testes, lymphatic system, and subcutaneous tissue in humans under relevant exposure circumstances based primarily on animal data. EPA has robust overall confidence in the evidence integration, study/endpoint selection, and exposure scenario applicability for ethylene dibromide based on the respective endpoints described below. The selection of references for the Agency's PODs is consistent with prior risk evaluations for ethylene dibromide published by ([ATSDR, 2018](#)) and ([U.S. EPA, 2004b](#)).

Selection of the Most Critical Endpoint and Study

The references that EPA identified for chronic non-cancer POD calculation were also used for identification of potential cancer PODs. Studies of cancer endpoints demonstrate systemic toxicities of ethylene dibromide exposure, with tumors spread across many organ systems regardless of exposure type. The selected inhalation study, ([NTP, 1982](#)), is determined to be the best available science identified with a positive cancer identification at 10 ppm in rats. Although the POD is based on carcinomas and adenocarcinomas of the nasal cavity, the authors report tumors in a wide variety of organ systems.

The selected oral exposure study ([NCI, 1978](#)) is the best available science from EPA's literature review, with the lowest cancer-causing dose at 38 mg/kg/day, resulting in forestomach squamous-cell carcinomas and hemangiosarcomas in rats. Hepatocellular carcinomas were also observed at the higher experimental dose (*i.e.*, 39 mg/kg/day). Several references utilizing drinking water as a mode of exposure ([Van Duuren et al., 1986](#); [Van Duuren et al., 1985](#)) were ultimately not selected for POD determination due to uncertainty concerning the palatability of the mixture significantly and chronically decreasing the volume of water ingested by test animals, leading to chronic dehydration and chemical uncertainties as a result of reactivity between ethylene dibromide and water. The average dosing in Van Duuren ([1985](#)) (*i.e.*, 103 or 116 mg/kg/day) is approximately double that which was utilized by NCI ([1978](#)) and exposure was in mice rather than rats.

Despite these differences, similarly increased mortality and consistent tumorigenesis was observed in these studies, with Van Duuren ([1985](#)) reporting forestomach stomach, liver, and esophageal tumors. The presence of esophageal tumors is reflective of the drinking water dosing method, where NCI ([1978](#)) instead utilized gavage to pass the test material directly to the stomach. Van Duuren ([1986](#)) exposed mice to a much lower average dose (*i.e.*, 1.2 or 1.4 mg/kg/day) via drinking water and authors still

reported observing forestomach and esophageal tumors, though mortality is not clearly reported. NCI (1978) also exposed mice to ethylene dibromide via gavage, but these animals underwent a more complex dosing paradigm during which exposure levels were changed several times over the course of the experiment, making the experiment inappropriate for use in dose response calculations. In this experiment, mice were exposed to 62 or 107 mg/kg/day, so the high-dose group approximately matches the dosing in (Van Duuren et al., 1985). The NCI (1978) mice also developed forestomach tumors. Together, this consistent evidence of gastrointestinal tumorigenesis in mice and rats following ethylene dibromide exposure strengthens our confidence in the selected POD reference.

Relevance to Exposure Scenarios

The inhalation and oral PODs are based on effects in cancer studies by NCI and NTP. Both institutions apply standard protocols based on best available science for appropriate testing of chemicals for carcinogenicity. EPA considers the resulting cancer effects described in both studies to be relevant for chronic exposures in humans.

Dose-Response Considerations

EPA analyzed all reasonably identified references for potential use in dose response assessment. The NCI study (male rats) and NTP studies (male and female rats) were used as inputs to BMD modeling using a multi-stage cancer model to estimate the slope factor (oral) or inhalation unit risk (inhalation). No key study was selected for dermal exposure to ethylene dibromide due to lack of data availability. Instead, route-to-route extrapolation was performed from the oral and inhalation cancer studies.

The dose-response analysis resulted in CSFs that are in line with those derived as part of other assessments on ethylene dibromide and also a close analogue, 1,2-dichloroethane, which differ in that the two bromine atoms have been replaced with chlorine atoms. Ethylene dibromide and 1,2-dichloroethane share substantial similarities in chemical structure, genotoxicity, mode of action, and toxic effects. Both are alkylating agents. Ethylene dibromide is expected to be a more potent alkylator due to bromide being a better leaving group than chloride. This is borne out in the cancer slope factors for these two chemicals. According to EPA's analysis, ethylene dibromide is approximately 3.2 times more potent than 1,2-dichloroethane oral exposure, 15 times more potent via inhalation exposure, and 7.7 times more potent via dermal exposure. This roughly half-log to 1-log difference in potency is consistent with the kinetics of bimolecular nucleophilic substitution reactions (S_N2) of the brominated vs. chlorinated ethane (U.S. EPA, 2026j).

These numbers are similar to those derived by other U.S. regulatory agencies. OEHHA, part of the California state government, found that ethylene dibromide is approximately 3.4 times more potent than 1,2-dichloroethane (CalEPA, 2023). When comparing EPA to OEHHA's CSFs for inhalation, the values are within 4% of each other, with OEHHA predicting that ethylene dibromide is slightly less potent than EPA's estimate (CalEPA, 2023). With 1,2-dichloroethane, the estimates showed more of a spread, around 25% different. Overall, OEHHA and EPA's values agreed within a few percentage points for both chemicals with EPA's estimates predicting slightly greater potency than OEHHA. This is almost certainly due to the inclusion of an age-dependent adjustment factor (ADAF) in EPA's assessment, which was not included at the time of OEHHA's assessment. The closeness of the values is also not surprising given that the critical studies published in 1978 (for oral exposure) and 1982 (for inhalation exposure) were used by both agencies.

The U.S. EPA 2004 assessment *Toxicological Review of 1,2-Dibromoethane (CAS No. 106-93-4)* reported an oral cancer slope factor of $2.0 \text{ (mg/kg/day)}^{-1}$ and inhalation unit risk of $6 \times 10^{-4} \text{ (}\mu\text{g/m}^3\text{)}^{-1}$ (U.S. EPA, 2004b). Although the numerical values presented in this document differ from those reported

in and other agencies, the proposed oral cancer slope factor and IUR as described above in Table 2-16 are $0.24 \text{ (mg/kg/day)}^{-1}$ and $8.9 \times 10^{-5} \text{ (}\mu\text{g/m}^3\text{)}^{-1}$, respectively; these remain with the same order of magnitude of carcinogenic potency.

Taken together, this analysis enhances EPA's confidence in the cancer slope factor calculations for ethylene dibromide. The numbers are consistent with other assessments and show greater potency than 1,2-dichloroethane (which would be expected) but the values are not extremely disparate (less than $\approx 1\text{-log}$; *i.e.*, ≤ 10 times).

Consideration of PESS

Although there are several factors that may increase susceptibility to cancer in general, few studies assessed susceptibility specifically in combination with ethylene dibromide exposure. In one epidemiologic study, which did not find a statistically significant association between ethylene dibromide exposure alone and breast cancer, a classification tree analysis found an association for ethylene dibromide in combination with lower levels of methylene chloride and higher levels of propylene dichloride exposure in women ages 40 to 58 ([Niehoff et al., 2019](#)). Thus, there is some indication that middle-aged women and individuals with specific co-exposures may be PESS with increased susceptibility to breast cancer, but this finding comes from only one study, which did not find a statistically significant association between ethylene dibromide and breast cancer in single pollutant analyses ([Niehoff et al., 2019](#)). Another epidemiologic study also did not find a statistically significant association between high levels of ethylene dibromide exposure and breast cancer ([Hart et al., 2018](#)).

The combined ethylene dibromide inhalation IUR for tumor development, primarily adenoma/carcinoma of the nasal cavity, utilized the lower 95th percentile modeling estimate, assuming a low dose extrapolation based on mode of action evidence integration. CSF was determined for oral and dermal exposure. EPA incorporated age-based susceptibility to mutagenic carcinogens through the inclusion of an age-dependent adjustment factor for general population exposures. Due to insufficient data, the Agency was unable to quantitatively incorporate other considerations such as genetic polymorphisms, lifestyle activities (*e.g.*, smoking or nutrition), other co-exposures, or sociodemographic factors such as income.

PBPK Modeling Endpoints

As discussed in Section 2.2.5.2, the PBPK model output outputs are influenced by the COUs and OESs of ethylene dibromide. Formulation of ethylene dibromide is the main determinant in bioavailability. As cancer risk evaluation involves chronic exposure, despite no long-term pharmacokinetic validation, ethylene dibromide has rapid clearance, meaning a lower steady state is reached quickly and higher exposures are needed to reach the target internal dose of concern. This also addresses a concern that the model assumes time-invariant physiology and enzyme activity, which may introduce uncertainty when extrapolating from experimental durations to lifetime exposure scenarios.

2.5.2 Dermal Route-to-Route Extrapolation

EPA conducted route-to-route extrapolation in a tiered manner and estimated dermal HEDs, as described in Section 2.3.2.5 (for non-cancer endpoints) and Section 2.4.7.4 (for cancer endpoints). The default method provided an initial, screening-level tier. The PBPK model was then applied in a refinement tier as PBPK models explicitly represent physiology, enabling chemical-specific, biology-based extrapolation with inter/intraspecies and duration effects built in, reducing uncertainty versus defaults. Specifically, PBPK-based refinement predicted context-specific human equivalent dermal exposures tailored to specific exposure scenarios and COUs under TSCA.

2.5.2.1 Default Approach

Due to a lack of chemical-specific ethylene dibromide dermal absorption data, dermal HEDs were calculated through default route-to-route methods at the screening tier. The default approach to quantify ethylene dibromide absorption involves assuming a fixed bioavailability by route; absorption is assumed to be 100% via oral exposure, 100% via inhalation exposure, and 1.16% via dermal exposure. Bioavailability is assumed to be constant and is not dependent on solvent, concentration, or other factors. Interspecies extrapolation via default assumptions follows existing HED and HEC guidance. Calculating HEDs is done via allometric scaling, specifically by body weight to the $\frac{3}{4}$ -power ($BW^{3/4}$). Calculating HECs involved adjusting from the exposure parameters of the experimental study to continuous exposure (e.g., from 6 hours per day, 5 days per week to 24 hours per day, 7 days per week) and then applying an RGDR. For ethylene dibromide, the RGDR is 1, as it is a category 3 gas. Again, these adjustment factors depend on the experiment but are fixed proportionality constants that are not dependent on dose. Performing route-to-route extrapolation from oral-to-dermal simply involves multiplying by a fixed ratio of bioavailability for the two routes. Route-to-route extrapolation from inhalation-to-dermal requires the use of a breathing rate (m^3/day) and body weight assumptions, but these are fixed at central tendency values and again are a fixed proportionality constant applied to the dose. Because the default approach involves adjusting the doses in an animal study by fixed ratios, there is no scenario-dependence in the point of departure values. Thus, a single POD from an animal study translates to a single POD used for human health risk assessment that is applied across multiple scenarios, with the ratio of these PODs being a constant. This could result in mischaracterizing hazard values for scenario- and dose-specific exposures.

2.5.2.2 PBPK Approach

As a refined tier approach, the ethylene dibromide PBPK model (described in Section 2.2.5.1) predicted HEDs that were tailored to the conditions of use, making them context-sensitive. The model explicitly accounts for ethylene dibromide concentration in the media (formulation) and the media volume on exposed surface area of skin. To evaluate the applicability of the PBPK model for route-to-route extrapolation, EPA conducted uncertainty analysis for the systemic model described in Hissink et al. (2000) and the *in silico* dermal sub-model separately. Table 2-16 summarizes these analyses and they are further discussed and provided in *Draft PBPK Reporting Document for Ethylene Dibromide* (U.S. EPA, 2026g).

EPA conducted sensitivity analysis, which identified dermal permeability, body composition, and metabolism rates as highly influential in predicting the internal dose metric of interest (the amount of ethylene dibromide metabolized in the liver via GST per liter liver per day). EPA's uncertainty analysis demonstrates that variability in these factors could account for inter-individual differences in dermal absorption and systemic exposure. High confidence in parameterization of body composition (from *in vivo* data) and metabolism parameters (*in vitro* experiments) strengthen confidence in quantifying results for applicable dose metrics. The lack of ethylene dibromide specific *in vivo* or *in vitro* dermal exposure data poses a limitation, and simplifying assumptions about dermal skin exposure could mischaracterize dermal absorption. Yet, given the challenges in dermal pharmacokinetic studies—especially VOCs—EPA made efforts to reduce these uncertainties to the extent possible by selecting *in silico* models that are developed based on experimental data for chemicals with physicochemical properties similar to ethylene dibromide and consistent with IH SkinPerm, the *in silico* dermal prediction model used in the human exposure estimates (AIHA, 2024). Furthermore, HEDs are calculated as retained dose, meaning that they are more sensitive to the systemic model and less influenced by evaporation. While uncertainties are inherent to PBPK models as with other model-based approaches, EPA considers them reasonably characterized or scientifically justified and they do not preclude application of the model to conduct route-to-route extrapolation across species (rats and humans), routes (oral, inhalation, and

dermal) and exposure conditions within the defined domain of applicability. Based on these reasons, EPA has medium-to-high confidence in the PBPK-based route-to-route extrapolation for both dermal and systemic exposure.

Table 2-17. Map of Ethylene Dibromide PBPK Model Uncertainties and Confidence.

BPBK Model Component	Confidence	Uncertainties
Systemic ethylene dibromide body model Hissink et al. (2000) parameterized for rats and humans for oral and IV routes of exposure.	Based on widely-used and peer-reviewed VOC model structure Sweeney and Gargas (2016); Andersen et al. (1987); Ramsey and Andersen (1984) with oral, IV, and inhalation routes of exposure. IVIVE with targeted <i>in vitro</i> studies for parameters and evaluation. Rat <i>in vivo</i> data was used to validate model performance (blood PK, metabolism, and exhalation profiles). Although Hissink et al. (2000) did not provide explicit PBPK equations, the model details in the narration were sufficient for recreation in R.	Original code and equations were not provided by Hissink et al. (2000). Inhalation model evaluated by oral exhalation data and IV data. Limited extrahepatic GST expression information.
Dermal route of exposure as sub-model added to systemic ethylene dibromide model, consisting of: • A dermal skin compartment Meade et al. (2026), • Dermal permeability, calculated with the Potts and Guy (1992) model, which is based on physio-chemical properties Evaporation flux, estimated <i>in silico</i> from the following parameters: temperature, vapor pressure, molecule radius, height above exposed surface, molar fraction, Boltzman constant, air viscosity, gas constant, activity.	Simple skin compartment and solvent compartments. Uses <i>in vivo</i> skin blood flow, tissue volume Brown et al. (1997) and <i>in silico</i> skin-to-media partitioning Chen et al. (2015) as seen in the dermal <i>httk</i> model Meade et al. (2026). Core equations based on Fick's Law. Evaporation, permeation, and skin-to-media partitioning characterization is similar methods as for partitioning as in IH SkinPerm AIHA (2024). Skin permeability calculated with Potts and Guy (1992) model based on physio-chemical properties; ethylene dibromide is in the domain of applicability of the Potts and Guy training set ($n = 9, =1, 18 < MW < 750, -3 > \log P < 6, R^2 = 0.68$); uses a Simple equation (best regression practices) and is empirically validated (derived from <i>in vivo</i> human skin permeability data). Ethylene dibromide in the domain of applicability for (Deacon et al., 2024) validated model ($n = 23$ VOCs, $92 < MW < 241, -0.09 < \log P < 4.20, 0.002 < VP < 55, R^2 = 0.73$ in log scale) using IVPT human skin data from Cosmetics Europe ADME Task Force published data. Evaporation flux method improved dermal PBPK model performance for some VOCs above (those for PBPK models available). Evaporation flux derived from evaporation mass transfer(Kasting and Miller (2006)), which informs IH SkinPerm (AIHA (2024)).	Core equations based on Fick's Law; the skin compartment is simplified considering rapid uptake of ethylene dibromide. Limited information on exposure details pertaining to ethylene dibromide vehicle type, volume, and exposure duration. Evaporation method does not account for pH or ionization., ignores formulation of vehicle, assumes passive diffusion, and assumptions change evaporation flux. Temperature heat drives evaporation, but body heat is not accounted for in the model. Ethylene dibromide is not spherical, so the radius is estimated. The Deacon (2024) evaporation flux method does not assume vehicle solvent (Deacon et al. (2024) has not gone beyond peer review).
GST = glutathione S-transferase; IVIVE = <i>in vitro</i> to <i>in vivo</i> extrapolation; IV = intravenous; PBPK = physiologically-based pharmacokinetic; VOC = volatile organic compounds		

2.5.2.2.1 PBPK Model Uncertainty Analysis

Modeling Approach

EPA's route-to route extrapolation for oral-to-dermal and inhalation-to-dermal extrapolation were supported by a NAM-based PBPK modeling and a parallelogram approach ([Mallick et al., 2020](#); [U.S. EPA, 2019](#); [Yoon et al., 2015](#)). Given this NAMs-based framework, EPA conducted structured analyses of model uncertainty and confidence for key components.

Systemic PBPK Model

For the application of route-to-route extrapolation, model confidence depends on uncertainties arising from both systemic and exposure components of the PBPK model. The ethylene dibromide PBPK model described in Hissink et al. ([2000](#)) was developed to describe pharmacokinetics of ethylene dibromide after inhalation, oral, and intravenous dosing, including pulmonary exchange, first pass metabolism, and competing metabolic pathways for ethylene dibromide. The systemic PBPK model structure is based on the widely-accepted PBPK model for VOCs which has been applied to other relevant volatile organic compounds (VOCs) ([Sweeney and Gargas, 2016](#); [Andersen et al., 1987](#); [Ramsey and Andersen, 1984](#)).

EPA identified some uncertainties and errors in the Hissink et al. ([2000](#)) publication. Hissink et al. ([2000](#)) did not provide their code and their written model description was inadequate for a faithful reproduction of their model. EPA had to attempt to recreate the model in R (version 4.4.0) by making various assumptions about the model equations that may introduce uncertainty. The Hissink et al. ([2000](#)) publication also included mislabeled figures and data. EPA addressed these uncertainties in the *Draft PBPK Reporting Document for Ethylene Dibromide* ([U.S. EPA, 2026g](#)).

The original model by Hissink et al. ([2000](#)) was applied to inhalation simulations, but inhalation data were not explicitly used in the model development. However, model was able to reasonably capture exhalation time profile after oral or IV dosing of ethylene dibromide, which is sensitive to blood-to-air partitioning and dependent on timing of gas-exchange vs. hepatic metabolism. Under the high-dose conditions used in rodent toxicity studies, GST-mediated metabolism may have started to deviate from linear kinetics. The impact of this uncertainty would be potential overestimation of GST-mediated metabolism and the internal dose metric in rats for reverse dosimetry. This uncertainty would propagate to human dermal POD estimation resulting in a higher human dose.

Dermal PBPK Model

In Silico Model: Due to a lack of *in vitro* or *in vivo* data to inform dermal kinetics, an *in silico* model was used to predict evaporation from skin and permeation into the skin. The absorption of ethylene dibromide was characterized with physical-chemical properties via the *in silico* dermal model. The *in silico* dermal model was not validated with experimental data since neither *in vitro* nor *in vivo* data that evaluated evaporation or dermal permeation of ethylene dibromide were found. However, ethylene dibromide falls within the domain of applicability for the Potts and Guy Model, which was developed using *in vitro* skin data from almost 100 compounds ([Potts and Guy, 1992](#)). The *in silico* evaporation model was evaluated using *in vitro* permeation test study (IVPT) results conducted with human skin ([Deacon et al., 2024](#)); this model was not directly evaluated for ethylene dibromide, but it was trained and evaluated for chemicals with similar physical-chemical properties as ethylene dibromide. Despite a lack of ethylene dibromide-specific validation data, the support of these predictions have been accepted regulatorily; for example, exposure estimates already make use of *in silico* models to predict dermal bioavailability, via IH SkinPerm ([AIHA, 2024](#)).

Uncertainties may arise from the use of these *in silico* models and the parameters that govern evaporation and skin permeation absorption. EPA identified several limitations. For the dermal model

specifically, several assumptions were made that were used for predictions of the applied dose. Characterization of evaporation and absorption depended on assumptions about temperatures and approximations of molecule size. Also, the dermal model assumes an absence of explicit skin metabolism. These assumptions primarily affect delivered dose via dermal exposure rather than internal toxicokinetic structure of the model. This uncertainty was mitigated by estimating the retained HED, which is driven more by systemic model assumptions and parameters.

For VOCs such as ethylene dibromide, uncertainty in dermal exposure estimation is associated with the fraction of the applied dose that evaporates before skin uptake can occur. To address this, both the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)) and current hazard assessment use a retained dose measure rather than total applied dose. In this context, retained dose represents the fraction of material remaining on or within the skin after evaporation loss and is therefore available for dermal and systemic uptake. For practical purposes, this measure is treated as the biologically relevant dose driving systemic exposure. However, retained dose may not always be identical to the amount ultimately absorbed into systemic circulation. A portion of retained material may remain within skin layers, variability in skin conditions may prevent total absorption, or other factors may hinder it from becoming systemically available. Accordingly, some uncertainty exists regarding the exact relationship between retained and full absorbed dose. Importantly, this uncertainty does not create an inconsistency between the exposure (*Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#))) and current hazard assessments because both are based on the same retained dose framework and therefore remain directly comparable.

Dermal Assumptions: Because the original Hissink et al. ([2000](#)) Model was developed and evaluated with oral and inhalation data, dermal application introduces uncertainty related to fractional absorption into skin, rate of absorption relative to evaporation and clearance, and length of exposure time. Skin metabolism is not included in the model as a source of extrahepatic metabolism; however, the major GST enzyme expressed in skin is *pi* form, which shows low activity to ethylene dibromide and is not one of the major GSTs contributing to ethylene dibromide conjugation. This indicates that skin metabolism via GST would be negligible and have little-to-no measurable effect on the ADME of ethylene dibromide and omitting skin metabolism in the PBPK model would not have a measurable impact on model predictions. Predicting dermal exposures introduces boundary-condition uncertainty as well. For VOCs, dermal exposure introduces competition among evaporation, dermal absorption, and systemic clearance for overall bioavailability in the body. Assumptions are made about the surface film thickness, airflow and temperature, which affect delivered dose. The HEDs must also be evaluated in context with the applied volume of liquid exposure. For example, for the high-end occupational Import and Repackaging OES (Manufacture – Import 60 wt %), the acute and intermediate inhalation-to-dermal extrapolations yielded retained HEDs of 3,200 total mg ethylene dibromide (40 mg/kg/day) mixed with 40% solvent (*i.e.*, octanol) with an applied volume of 32 mL. The chronic inhalation-to-dermal extrapolation for the same scenario resulted in a retained HED of 272 total mg of ethylene dibromide (3.4 mg/kg/day) mixed with 40% solvent in an applied volume of 2.7 mL. The extent to which these applied volumes are applicable to each COU may inform exposure assumption uncertainty.

Sensitivity Analysis

Sensitivity analysis was conducted to measure the proportional (unitless) change in the dose metric (amount metabolized in the liver by GST) produced by proportional changes in the parameter value. A complete analysis can be found in the *Draft PBPK Reporting Document for Ethylene Dibromide* ([U.S. EPA, 2026g](#)). For both the acute and chronic human dermal exposure model for both low (1%) and high (100%) ethylene dibromide formulations, the parameters most influential to the dose metric included body weight, liver and muscle volume, the first order GST-mediated metabolic rate constant in the liver,

the maximum metabolic rate for CYP pathway, skin permeability, and ethylene dibromide evaporation flux. For the lowest molar fraction chemical concentrations (*i.e.*, 1% ethylene dibromide), exposed surface area of skin, the enzyme's binding affinity, and solvent density were considerably more influential for the chronic endpoints. Body weight, tissue volumes, liver metabolism parameters, respiration rate, and blood-to-air partitioning were influential for the rat model. Variability in these parameters could account for inter-individual differences in dermal absorption and systemic exposure.

High confidence in parameterization of body composition (from *in vivo* data) and metabolism parameters (*in vitro* experiments) strengthen confidence in quantifying results for applicable dose metrics. Since physiological parameters are known with a high degree of confidence ([Brown et al., 1997](#)), the route-to-route extrapolation results that rely solely on these influential parameters have correspondingly high levels of confidence. However, model uncertainty can increase for dose metric for which dermal evaporation and permeation are most influential if the parameters used in the evaporation and permeation QSARs are not well characterized. Due to a lack of *in vivo* or *in vitro* dermal exposure data, dermal parameters were not validated against experimental data and could mischaracterize dermal absorption.

Model pathways that are responsible for the scenario-dependent variability in output also contribute to uncertainty. The factors primarily affecting dermal model uncertainty are the factors that primarily affect delivered dose, which include evaporation, absorption, and the simplified skin structure; whereas pulmonary exchange and competing oxidative and GST metabolic pathways are the prime factors determining systemic model uncertainty.

Exposure Scenarios

Assumptions regarding the exposure-specific parameters such as exposed surface area, volume of vehicle, solvent in vehicle, COU, permeability, and evaporation dynamics are explicitly incorporated into the PBPK-estimation of internal dose. As a result, the retained dose used in the risk estimate reflects both the chemical-specific absorption processes and exposure-specific conditions. This integration supports exposure-relevant comparison between estimated internal dose and toxicity values derived from animal studies, consistent with the internal dose paradigm underlying route-to-route extrapolation. The estimated human-equivalent dermal PODs from route-to-route extrapolation should be tied to defined exposure scenarios and characteristics. Because dermal bioavailability is driven by surface concentration, mass-only metrics may be inadequate. Both default and PBPK approaches address interspecies extrapolation, but PBPK methods explicitly model bioavailability (via absorption and evaporation) and scenario-specific factors. PBPK modeling increases confidence because it can capture time- and concentration-dependent changes in dermal flux and resulting bioavailability.

The PBPK model applied the dermal exposure scenarios described in Section 4.1.1.2 of the *Draft Risk Evaluation for Ethylene Dibromide* ([U.S. EPA, 2026h](#)) (and in Section 2.2.5.2 of the current document) to simulate exposure details (frequency, duration, and exposed skin surface area) as well as product formulation. The predicted HEDs represent the volume and mass (mg) of the dose necessary to reach the target internal dose metrics of hazard because mass, alone, does not fully represent the human equivalent exposure for a given scenario; that is, HEDs are COU- and scenario-specific. See Table 2-21 for a complete table of HEDs for 1 hand skin exposure scenarios (535 cm²) and 1 palm skin exposure scenarios (267.5 cm²). Deviations in specific exposure conditions in the model simulations can lead to uncertainty. The simulated exposure scenarios and assumptions are matched with those used in the human exposure assessment.

The model provides a scientific basis to differentiate risks across scenarios and demonstrated that OESs with lower ethylene dibromide concentrations reduce dermal bioavailability sufficiently such that exposures are not expected to reach levels of concern. Such was the case for consumer exposure scenarios, where the formulation concentration is expected to be 0.085 to 0.1%. PBPK-derived HEDs for the consumer exposure are reported as “N/A (unable to reach target internal dose)” in Table 2-21, which means that for the consumer exposure duration, frequency, and 0.085 to 0.1% formulation, no dermal dose or dermal volume could be calculated that would be large enough to reach the target internal dose metric of hazard. This means that the internal dose associated with these exposure conditions was asymptotically lower than the target internal dose metric and that a predicted external dose was not achievable.

Exposure Durations

Model uncertainty is not uniform across exposure scenarios. For acute exposure simulations, the largest uncertainties can arise from blood-to-air partitioning assumptions and timing of pulmonary exchange and hepatic and extrahepatic metabolic clearances. However, the partition coefficients are experimentally measured parameters, and all metabolic parameters are derived using the *in vitro* measured, the validity of which was evaluated based on *in vivo* PK data by Hissink et al. (2000). Model parameters describing respiration and cardiac output are data-rich parameters as well. Because confidence is high for these parameters, high confidence translates to the rest of the model. For acute and high-dose exposures, oxidative metabolism can approach capacity and GST-mediated pathways may dominate clearance.

Despite lack of long-term PK data, ethylene dibromide’s rapid clearance ensures that steady state is reached quickly (within 4 weeks) and can thus be modeled as such. This also addresses the concerns regarding the model assumptions of time-invariant physiology and enzyme activity, which may introduce uncertainty when extrapolating from experimental durations to lifetime exposure scenarios. Chronic exposure simulations may be less sensitive to short-term kinetic uncertainty, but more sensitive to assumptions about metabolic routing and clearance efficiency (e.g., fractional metabolism through GST vs. oxidative pathways over time). Long-term *in vivo* data for ethylene dibromide were not available; as such, the PBPK model was not validated with chronic exposure conditions. However, given the rapid clearance of ethylene dibromide as shown by almost complete clearance within 24 hours following oral or IV exposure in rats (Hissink et al., 2000), uncertainty regarding lack of model evaluation with long term PK data may not be a concern for ethylene dibromide. The model assumes time-invariant physiology and enzyme activity, which introduces uncertainty when extrapolating from experimental durations to lifetime exposure scenarios.

Inter-Individual Variability

Uncertainties may arise from interindividual variability and polymorphisms in GST activity and limited data to describe enzyme saturation thresholds. Model predicted internal doses based on parent compounds or reactive intermediate formation may be sensitive to the ratio between maximum metabolic activity and enzyme affinity for saturating enzymes. The ethylene dibromide used in this assessment was parameterized for an average human adult and did not incorporate variability that may be found among people with altered metabolism or physiological states.

2.5.2.2.2 Comparison of Dermal Route-to-Route Extrapolated HEDs

In this assessment, PBPK-based weight of scientific evidence has been discussed based on the predicted exposure doses expressed in mass units. This compares to the default approach, which reports HEDs in mass units, but using only mass-based dose metrics for risk evaluation may lose the context of potency

and volume of ethylene dibromide for a given condition of exposure, and thus not fully capture potential of risk, or lack thereof, under the relevant COU.

The default and PBPK-based methods differ in how scientific evidence is used to address uncertainty. In default approaches, external exposure levels (*e.g.*, administered dose) are the basis for assessing risk, whereas PBPK modeling relies on internal dose metrics (*e.g.*, concentration of chemical in target tissues or amount metabolized in tissues), which are directly linked to toxic effects. PBPK models incorporate interspecies and intra-species differences and exposure duration considerations directly into the model, reducing the overall uncertainty as these factors apply to default extrapolations. As such, uncertainty in PBPK extrapolations from animal to human is limited to model error. The weight of scientific evidence conclusion is therefore strong when the model is well-validated and biologically credible, internal dose metrics are relevant to toxicity, and parameters are well-characterized.

The PBPK-based dermal route-to-route extrapolation approach enables estimation of both the applied dermal dose and the resulting retained dose under defined exposure conditions. Specifically, PBPK-simulated dermal absorption is based on chemical-specific physiochemical properties and scenario-specific exposure parameters. This permits explicit characterization of the relation between applied and internal dose, such that the retained dose associated with a given exposure scenario can be directly estimated and compared to internal dose metrics derived from the oral and inhalation animal toxicity studies. The mechanistic PBPK approach captures dynamic changes in systemic exposure driven by changes in dermal permeation. It also incorporates exposure-scenario specific assumptions into the model, which integrates exposure dynamics into the risk evaluation. See Table 2-18 for a comparison table of approaches.

Table 2-18. Comparison of Default and PBPK Dermal Route-to-Route Approaches

Attribute	Default Dermal Route-to-Route Approach	PBPK Dermal Route-to-Route Approach
POD basis	Derived BMDL from chronic oral and chronic inhalation study and POD from intermediate inhalation study	BMDL (chronic oral and inhalation) and POD (intermediate inhalation) to derive internal dose metric (amount metabolized in the liver via GST pathway)
Dermal absorption	Applied as fixed fraction	Estimated dynamically by model, is dose- and time-dependent
Exposure conditions (surface area exposed, duration, COU)	Not explicitly considered	Incorporated into model
Volatilization	Not explicitly considered	Incorporated into model
Applied dose estimation	Not generated	Simulated using exposure inputs
Retained systemic dose	Estimated via default fraction	Simulated using exposure inputs
Dose metric compared to POD	Retained dose	Retained dose
BMDL = benchmark dose lower 95% confidence limit; COU = condition of use; GST = Glutathione <i>S</i> -transferase; POD = point of departure		

2.6 Consideration of PESS and Aggregate Exposure

2.6.1 Hazard Considerations for Aggregate Exposure

Section 2605(b)(4)(F)(ii) of TSCA requires EPA, as a part of the risk evaluation, to describe whether aggregate or sentinel exposures under the conditions of use were considered and the basis for their consideration. EPA has defined aggregate exposure as “the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways” (40 CFR § 702.33).

For use in the risk evaluation and assessing risks from other exposure routes, EPA conducted route-to-route extrapolation of the toxicity values from the inhalation studies for use in the dermal exposure route and scenarios. Most of the available ethylene dibromide toxicity studies deemed suitable for route-to-route extrapolation were inhalation studies in animal models.

There is no reasonably available hazard data that allows for aggregated non-cancer risk calculation for acute or intermediate oral and inhalation exposure. The selected oral POD is based on a portal of entry effect, and authors did not measure any systemic effects in this study ([Ghanayem et al., 1986](#)). Furthermore, the endpoints observed across all identified intermediate oral and inhalation studies are distinct, with no identifiable POD for a shared outcome across exposure types. With no shared outcome, an acute and/or intermediate aggregate risk for these exposure types cannot be calculated. However, non-cancer dermal and inhalation acute and intermediate exposures can be aggregated, as the dermal POD is based on route-to-route extrapolation from inhalation, and are therefore based on the same effect from the same critical study.

Risk can be aggregated across oral, inhalation, and dermal chronic exposure routes for non-cancer effects. The selected POD references for chronic inhalation ([NTP, 1982](#)) and oral exposure ([NCI, 1978](#)) are based on related liver endpoints, and the dermal POD is based on route-to-route extrapolation from inhalation and are therefore based on the same effect from the same critical study. EPA therefore concludes that for consideration of aggregate exposures, it is reasonable to assume that exposures and risks across oral, dermal, and inhalation routes may be additive for the selected PODs in Sections 2.3.2.3, 2.3.2.4, and 2.4.7.1 if, for the given receptor, the various routes of exposure are complete/present.

Aggregation cancer data for ethylene dibromide was reasonable, supported by its genotoxic MOA involving metabolic activation to intermediates interacting with DNA. This MOA of tumor development is systemic regardless of the route. Tumors were observed across several organs in animal studies, including forestomach, liver, nasal cavity, tunica vaginalis, and other tissues, following oral and inhalation exposure, with dermal risk based on route-to-route extrapolation ([NTP, 1982](#); [NCI, 1978](#)). While effects on the forestomach are generally considered to be specific to rodents and of questionable human relevance, in this case it was being examined specifically for early key events in a chain of events that could lead to DNA damage and cancer outcomes. Proctor et al. ([2007](#)) provides three criteria that determine human health relevance of forestomach tumors observed in rodent studies. Those criteria are well-established genotoxicity, its ability to induce tumors at multiple sites across a range of doses, and the observation that these effects occur in the absence of forestomach irritation. Ethylene dibromide meets these criteria which suggests forestomach effects are relevant to the cancer assessment because it is likely to cause cancer via oral exposure in humans, despite the anatomical difference.

Given the tumor responses across oral, dermal, and inhalation cancer bioassays and the mutagenic MOA, cancer risks were considered appropriate for aggregation. Combining cancer risk from exposures

from multiple routes of exposure that co-occur for a given COU or a single exposure scenario provides a more robust and integrative estimate of carcinogenic potential.

2.6.2 PESS Based on Greater Susceptibility

In this section, EPA addresses subpopulations expected to be more susceptible to ethylene dibromide exposure than other populations. Table 2-19 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 ethylene dibromide. As shown in Table 2-19, potential PESS specific to ethylene dibromide include males and females of reproductive age and their offspring, workers exposed to ethylene dibromide, and individuals with other co-exposures.

EPA examined sources of biological susceptibility for each of the factors in Table 2-19. 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.

For cancer, the dose-response model applied to animal tumor data employed low-dose linear extrapolation, and this assumes *any* ethylene dibromide exposure is associated with some non-zero risk of getting cancer. EPA made this assumption given the known mutagenic mode of action for ethylene dibromide and according to guidance from the Agency's EPA's *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)). An age-dependent adjustment factor was incorporated into the cancer slope factor and inhalation unit risk for general population risk estimates. Separate cancer slope factors and inhalation unit risk values without this factor were used for risk estimates for occupational and consumer exposures, since these exposures affect individuals aged 16 and older. Even though the cancer dose-response modeling assumes any exposure is associated with a certain risk, EPA presents risk estimates in comparison with benchmark risk levels (1 in 1,000,000 [1×10^{-6}] to 1 in 10,000 [1×10^{-4}]).

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Table 2-19. Ethylene Dibromide PESS Evidence Crosswalk for Biological Susceptibility Considerations

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to Ethylene Dibromide		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to Ethylene Dibromide		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Reference(s)	Description of Interaction	Key Reference(s)	
Life stage	Pre-mating/ mating	In animal studies, exposure to ethylene dibromide in females resulted in estrus cycle abnormalities. Exposing males resulted in fewer successful implantations when mated to non-exposed females.	Short et al. (1979)	No indirect evidence identified	N/A	This susceptibility was addressed qualitatively in Section 2.3.1.1.
	Embryos/ fetuses/infants	In an epidemiological study, maternal exposures to ethylene dibromide were significantly associated with low birth weight in offspring. In animal studies, exposure to ethylene dibromide during pregnancy resulted in fetal growth restriction and skeletal malformations	Gong and Zhan (2022) ; Short et al. (1978)	No indirect evidence identified	N/A	In an epidemiological study, this susceptibility was addressed qualitatively in this section and in Section 2.3.1.1 Gong and Zhan (2022) . Short (1978) was utilized quantitatively in Section 2.3.2.2 as the POD for acute and intermediate inhalation hazard. Effects included fetal skeletal malformation and late resorptions. UF = 30 was applied when calculating a human equivalent POD.
	Pregnancy/ lactating status	Female animals exposed to ethylene dibromide experienced diestrus, late resorptions, and maternal weight loss. Ovarian cysts were also observed.	Short et al. (1979) ; Short et al. (1978) .	No indirect evidence identified	N/A	Short (1978) was utilized quantitatively in Section 2.3.2.2 as the POD for acute and intermediate inhalation hazard. Effects included fetal skeletal malformation and late resorptions. UF = 100 was applied when calculating a human equivalent POD. Short (1979) was addressed qualitatively in Section 2.3.1.1.

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to Ethylene Dibromide		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to Ethylene Dibromide		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Reference(s)	Description of Interaction	Key Reference(s)	
Life stage	Males of reproductive age	Epidemiological studies found statistically significant associations between exposure to ethylene dibromide and semen and sperm parameters including sperm count per ejaculate, the percentage of viable and motile sperm, and the proportion of sperm with specific morphological abnormalities. These findings indicate that males of reproductive age may be a susceptible subpopulation. This is supported by animal studies in which exposing males to ethylene dibromide resulted in fewer successful implantations when mated with unexposed females. Animal studies also show atrophy of the testes, epididymis, prostate, and seminal vesicles. Testicular tumors were also observed.	Ratcliffe et al. (1987) ; Schrader et al. (1987) ; NTP (1982) ; Takahashi et al. (1981) ; Short et al. (1979) ; Wong et al. (1979) ; NCI (1978)	No indirect evidence identified	N/A	This susceptibility was addressed qualitatively in Section 2.3.1.1. Many workers are males of reproductive age and thus may have increased exposure.
	Children	No direct evidence identified	N/A	No indirect evidence identified	N/A	UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2. ADAF of 1.59 was applied when calculating general population cancer risks to address greater susceptibility of children.
	Elderly	No direct evidence identified	N/A	No indirect evidence identified	N/A	UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2.

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Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to Ethylene Dibromide		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to Ethylene Dibromide		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Reference(s)	Description of Interaction	Key Reference(s)	
Pre-existing disease or disorder	Health outcome/target organs	No direct evidence identified	N/A	Any pre-existing condition affecting a target organ will increase susceptibility to ethylene dibromide-toxicity in that organ.	N/A	UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2.
	Toxicokinetics	No direct evidence identified	N/A	Higher metabolism of reactive metabolites would increase susceptibility	N/A	p UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2, which includes a factor 3 for toxicokinetic differences within the human population
Lifestyle activities	Smoking	No direct evidence identified	N/A	Heavy smoking and other tobacco usage may increase susceptibility for reproductive outcomes and cancer.	CDC (2023a, 2023b)	N/A
	Alcohol consumption	No direct evidence identified	N/A	Alcohol consumption increases risk for several types of cancer, although it is not associated with leukemia or bladder cancer	CDC (2023b)	N/A
	Physical activity	No direct evidence identified	N/A	Insufficient activity may increase susceptibility to multiple health outcomes. Overly strenuous activity may also increase susceptibility.	CDC (2023a, 2023b, 2022)	N/A

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to Ethylene Dibromide		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to Ethylene Dibromide		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Reference(s)	Description of Interaction	Key Reference(s)	
Sociodemographics	Sex	Evidence indicates that ethylene dibromide may be associated with male and female reproductive toxicity outcomes.	Ratcliffe et al. (1987) ; Schrader et al. (1987) ; Takahashi et al. (1981) ; Wong et al. (1979)	No indirect evidence identified	N/A	This susceptibility was addressed qualitatively in Section 2.3.1.1.
Nutrition	Diet	No direct evidence identified	N/A	Obesity can increase susceptibility to cancer, although this is not established for leukemia or bladder cancer	CDC (2023a)	UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2.
	Malnutrition	No direct evidence identified	N/A	Micronutrient malnutrition can lead to multiple conditions that include birth defects, maternal and infant deaths, preterm birth, low birth weight, poor fetal growth, childhood blindness, undeveloped cognitive ability.	CDC (2023c)	UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2.
Genetics/epigenetics	Health outcome/target organs	An <i>in vitro</i> assessment of cytosol derived from human erythrocytes found evidence of polymorphisms in the glutathione conjugation activity of human erythrocytes towards ethylene dibromide. Additionally, an <i>in vitro</i> study of human nasal mucosa cells found differences between cells from different individuals in the concentration of ethylene	Hölzer et al. (2008) ; Ploemen et al. (1995)	Deficient DNA repair would increase susceptibility to cancer.	N/A	UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2, which includes a factor 3 for toxicodynamic differences within the human population

Susceptibility Factor	Examples of Specific Factors	Direct Evidence this Factor Modifies Susceptibility to Ethylene Dibromide		Indirect Evidence of Interaction with Target Organs or Biological Pathways Relevant to Ethylene Dibromide		Susceptibility Addressed in Risk Evaluation?
		Description of Interaction	Key Reference(s)	Description of Interaction	Key Reference(s)	
Genetics/epigenetics		dibromide associated with DNA damage.				
	Toxicokinetics	An <i>in vitro</i> assessment of cytosol derived from human erythrocytes found evidence of polymorphisms in the glutathione conjugation activity of human erythrocytes towards ethylene dibromide.	(Ploemen et al., 1995)	Genetic variation across populations may explain differences in relative mutation and genotoxicity rates seen across Texas, Chinese, and Czech cohorts		UF _H = 10 for human variability was applied to non-cancer PODs in Section 2.3.2.2, which includes a factor 3 for toxicokinetic differences within the human population
Other chemical and nonchemical stressors	Built environment	No direct evidence identified	N/A	Poor-quality housing is associated with a variety of negative health outcomes.	ODPHP (2023a)	N/A
	Social environment	No direct evidence identified	N/A	Social isolation and other social determinants (<i>e.g.</i> , decreased social capital, stress) can lead to negative health outcomes.	ODPHP (2023b)	N/A
	Chemical co-exposures	A classification tree analysis identified combinations of ethylene dibromide, age, BMI, and other chemicals related to overall breast cancer, with an association for ethylene dibromide in combination with methylene chloride and propylene dichloride in women ages 40–58.	(Niehoff et al., 2019)	No indirect evidence identified	N/A	There was insufficient data to address this quantitatively in the risk evaluation. Therefore, co-exposures were only addressed qualitatively in Section 2.5.1.3.
POD = point of departure; UF = uncertainty factor; ADAF = age-dependent adjustment factor						

2.6.3 Summary of Human Health Hazard Dose-Response Analysis

Upon weighing the scientific evidence, EPA identified the following data to inform the dose-response analysis for non-cancer and cancer human health hazard outcomes presented below. EPA did not identify sufficient human health hazard data resulting from dermal exposure that could be used for dose-response, therefore as outlined in Sections 2.3.2.5 and 2.4.7, EPA conducted route-to-route extrapolation to estimate dermal HEDs using the default and PBPK approaches in a tiered manner for non-cancer and cancer human health outcomes.

As described above in Section 2.3.2.4, acute or intermediate oral PODs could not be identified for potential route-to-route extrapolation for determining dermal acute or intermediate PODs because the adverse effects were observed at the portal of entry, thereby making this endpoint invalid for route-to-route extrapolation.

For oral and inhalation toxicity values for non-cancer effects (PODs) and cancer (slope factors or IURs), the confidence in the final values were slight to robust. Table 2-20 provides the basis for the oral and inhalation PODs and benchmark MOEs. For the studies that served as the basis for toxicity values, the main distinguishing feature between an OQD of Moderate and an OQD of High was specifically Domain 3 “Exposure Characterization” especially Metric 8 “Consistency of exposure administration.” In the NCI study (1978) there was early attrition in the high dose group and this group had to go on a dosing holiday and then were restarted at a lower dose. Despite this irregular dosing, EPA chose to use this study as the basis for the oral non-cancer chronic POD and the oral cancer slope factor. The actual toxicity values were all considered to have Robust confidence with the exception of the acute and intermediate PODs for all routes (oral, dermal, and inhalation).

The intermediate PODs were considered moderate confidence, because a no-adverse effect level could not be identified from any of the available intermediate studies. Strengths include well-reported studies underlying the PODs. Limitations include the relative lack of information on the shape of the dose-response relationship in the low-dose region. Uncertainties include database deficiencies related to newer endpoints like thyroid hormone homeostasis given the age of the ethylene dibromide database and the fact that these endpoints were not standard during the time period during which most of the toxicity studies were performed on this chemical. Thyroid hormone levels in particular would have been useful given the increase in thyroid-follicular cell adenomas in male and female rats via both gavage and inhalation that occurred, in some cases without any observation of non-cancerous histopathological changes in this tissue (NCI, 1978).

The acute PODs were considered slight confidence, because they were set equal to the intermediate PODs but were more uncertain given the extrapolation from one duration to another in the absence of experimental data that could be used for dose-response analysis of acute effects. Strengths include concordance with available epidemiological evidence for acute gastrointestinal disturbance following oral exposure and a strong mode of action link to developmental toxicity for alkylating agents. Limitations include the lack of single dose studies that could be used for direct derivation of a POD rather than applying intermediate PODs to the acute duration. Uncertainties include the relative insensitivity of rodent models for nausea and vomiting (since they physically lack the ability to vomit) and the lack of experimental data on histopathological changes in the liver. Rowe, et al. (1952) showed that a single exposure to ethylene dibromide in rats was sufficient to cause centrilobular fatty degeneration and necrosis in the liver observable 16 to 24 hours post-exposure, but this study was considered unusable for POD derivation as the exposure concentrations were not reported).

The chronic non-cancer PODs and the cancer slope factors and inhalation unit risk values were all considered robust confidence and all were able to be modeled adequately using EPA's Benchmark Dose Software. This modeling increased confidence in the final toxicity value because the software explicitly addresses uncertainty in the dose-response relationship when calculating the lower 95% confidence limit on the benchmark dose. Strengths include well-reported studies underlying the PODs. Limitations include the relative lack of information on the shape of the dose-response relationship in the low-dose region, the limited number of dose groups (only two dose groups plus controls), and early attrition in the oral chronic study. Uncertainties include the potential for saturation of biological processes (direction of effect is uncertain as both the parent chemical and several metabolites are all bioactive), the early termination of the study (less than 104 weeks of treatment), and the interpretation of portal-of-entry effects and their relevance to humans. More detailed discussions of the toxicity values may be found above: non-cancer PODs (Section 2.3.2.7) and cancer slope factors/IURs (Section 2.4.7.5). Evidence integration conclusions, selection of the most critical endpoint and study, relevance to exposure scenarios, dose-response considerations, and considerations of PESS are found in Section 2.5.1.1 for acute and intermediate non-cancer PODs, Section 2.5.1.2 for chronic non-cancer PODs, and Section 2.5.1.3 for cancer slope factors/IURs. Section 2.5.1.1 for acute and intermediate non-cancer PODs, Section 2.5.1.2 for chronic non-cancer PODs, and Section 2.5.1.3 for cancer slope factors/IURs.

As previously mentioned, EPA characterized human health hazards from dermal exposure to ethylene dibromide with a tiered route-to-route extrapolation approach, applying both default screening methods and then refinements through PBPK-based methods, to derive dermal HEDs for non-cancer and cancer endpoints. The default approach was used at the screening level tier to translate animal toxicity values from oral and inhalation toxicity studies to HEDs using allometric scaling. Table 2-20 provides the derivation of dermal PODs and benchmark MOEs that resulted from route-to-route extrapolation from inhalation or oral PODs using the default approach used for non-cancer and cancer analysis (more details available above in Sections 2.3.2.5 and 2.4.7.4, respectively).

At the refinement tier, a PBPK model was used to derive dermal HEDs. The PBPK-based route-to-route extrapolation used a mechanistic model to simulate the kinetics for each rat POD or BMDL provided by the default screening approach. The model then used reverse dosimetry to determine the retained dermal dose and vehicle volume that produces the internal dose metric of hazard, under defined exposure conditions. Specifically, the model simulated dermal uptake as a function of chemical-specific physiochemical properties and scenario-specific exposure parameters to explicitly characterize the relation between external and internal dose, such that the external retained dose associated with a given exposure scenario can be directly estimated and compared to internal dose metrics derived from the oral and inhalation animal toxicity studies. The hazard values from route-to-route extrapolation summarized for both cancer and non-cancer endpoints were previously described in the document (the default-derived HEDs/HECs and PBPK-derived dermal non-cancer HEDs are summarized in Table 2-6 in Section 2.3.2.7; the cancer hazard values are summarized in Table 2-15 of Section 2.4.7.5). However, the following tables presented below and described herein (Table 2-21 reports non-cancer dermal HEDs and Table 2-22 reports cancer HEDs, CSFs, and IURs) provide more context to the PBPK-derived dermal HEDs, which were calculated for specific exposure COUs and exposure scenarios described in the *Draft Risk Evaluation for Ethylene Dibromide* ([U.S. EPA, 2026h](#)).

Table 2-21 contains PBPK modeled dermal HEDs reported from high-end (HE) and central tendency (CT) formulation exposures per OESs and COUs; details about the model application are available above in Section 2.2.5.2 and in the *Draft PBPK Reporting Document for Ethylene Dibromide* ([U.S. EPA, 2026g](#)). Each COU is associated with HE or CT formulation concentrations. Typically, COUs are also associated with scenarios as to the bodily extremity and its corresponding surface area that is

expected to be exposed. The high-end exposure assumption is that 1,070 cm² of skin (or 2 hands) or 535 cm² (1 hand) are exposed. The central tendency exposure assumes that 535 cm² (2 hands exposed) or 267.5 cm² (1 hand exposed); low end exposures assume 267.5 cm² is exposed (1 hand or 1 palm). Although final non-cancer HEDs are reported in *Draft Risk Evaluation for Ethylene Dibromide* ([U.S. EPA, 2026h](#)) for high-end COU formulations and high end surface area combinations (and, similarly, for central tendency COU formulations and central tendency surface areas of skin), note that non-cancer HEDs are reported in Table 2-21 for all combinations of COU concentrations and exposed surface area of skin (1,070, 535, or 267.5 cm²) (e.g., high-end COU formulation were simulated for central tendency [535–267.5 cm²] and low-end [267.5 cm²] skin surface areas in addition to the high-end surface area [1,070 cm²]). This was done so that multiple exposure assumptions could be simulated to better understand the impact of uncertain exposure assumptions, even if not all of these assumptions pertained explicitly to that respective COU.

An example of how to read Table 2-21 is as follows: the first row that shows the COU formulation (Manufacture – Import (45–60 wt %)) indicates that the HE formulation is 60 % wt and the CT formulation is 45% wt ethylene dibromide, which is shown in the columns titled “Mass (%)”. The surface area of skin simulated is in the “Exposed skin surface area” column, which is 1,070 cm² for both the 45% solution (CT) and the 60% solution (HE). The HEDs for this first row correspond to either 45% solution over 1,070 cm² of skin or 60 % over 1,070 cm² of skin.

Table 2-22 reports the PBPK-derived cancer HEDs. Note that the cancer CSF or IUR values in Table 2-22 also report high-end COU formulations and high end surface area combinations (and, similarly, for central tendency COU formulations and central tendency surface areas of skin); this is because the values did not differ from one another, as seen in Table 2-22. Additional information regarding the OESs and COUs are available in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)). Benchmark MOEs are not applicable for cancer thresholds.

Table 2-20. Human Health Hazard Values for Oral, Dermal and Inhalation Exposure

Duration	Route	POD or Cancer Slope Factor/IUR	Type	Sex/Strain/Species	Benchmark MOE	Confidence
Non-cancer: acute and intermediate	Oral	2.7 mg/kg/day	HED/BMDL	Male F344 Rat	30	Slight (acute duration) Moderate (intermediate duration)
Non-cancer: chronic	Oral	3.3 mg/kg/day	HED/BMDL	Male Osborne-Mendel Rat	30	Robust
Cancer: chronic	Oral	0.24 (mg/kg/day) ⁻¹	OSF	Male Osborne-Mendel Rat	N/A	Robust
Non-cancer: acute and intermediate	Inhalation	150 mg/m ³ 20 ppm	HEC/LOAEC	Combined Sex CD Rats & CD-1 Mice	100	Slight (acute duration) Moderate (intermediate duration)
Non-cancer: chronic	Inhalation	11 mg/m ³ 1.5 ppm	HEC/BMDL	Male F344 Rat	30	Robust
Cancer: chronic	Inhalation	8.9E-05 (μg/m ³) ⁻¹ 0.68 (ppm) ⁻¹	IUR	Combined Sex F344 Rat	N/A	Robust

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Duration	Route	POD or Cancer Slope Factor/IUR	Type	Sex/Strain/Species	Benchmark MOE	Confidence
Non-cancer: acute/intermediate	Inhalation-to-dermal extrapolation	28 mg/kg/day (HED)	LOAEC 89 ppm	Combined Sex CD Rats & CD-1 Mice	100	Slight (acute duration) Moderate (intermediate duration)
Non-cancer: chronic	Inhalation-to-dermal extrapolation	2.2 mg/kg/day (HED)	BMCL 9 ppm	Male F344 Rat	30	Robust
	Oral-to-dermal extrapolation	3.3 mg/kg/day (HEC)	BMDL 11 mg/kg/d	Male Osborne-Mendel Rat	30	Robust
Cancer: chronic	Inhalation-to-dermal extrapolation	0.48 (mg/kg/day) ⁻¹	IUR	Combined Sex F344 Rat	N/A	Robust
	Oral-to-dermal extrapolation	0.24 (mg/kg/day) ⁻¹	OSF	Male Osborne-Mendel Rat	N/A	Robust
BMDL = benchmark dose lower 95% confidence limit; HEC = human equivalent concentration; HED = human equivalent dose; IUR = inhalation unit risk; LOAEC = lowest-observed-adverse-effect concentration; MOE = margin of exposure; OSF = oral slope factor; POD = point of departure						

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4664 **Table 2-21. PBPK Route-to-Route Extrapolation of Non-Cancer Human Health Hazard PODs for Dermal Exposure for High-End**
 4665 **(HE) and Central Tendency (CT) Concentrations Across Different COUs and Skin Exposure Assumptions (1,070 cm², 535 cm², or**
 4666 **267 cm² Exposed Skin^a)**

Route-to-Route Route of Exposure and POD _{rat} Duration	COU	OES or Consumer Scenario	Dermal HEDs for HE Concentrations				Dermal HEDs for CT Concentrations			
			Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)	Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)
Non-cancer, Chronic, oral-to- dermal BMDL 11 mg/kg/d Male Osborne- Mendel Rat	Manufacture – Import (45–60 wt %)	Import and Repackaging	60	1,070	5.0E–03	5.6	45	1,070	7.3E–03	5.7
	Processing – Repackaging (50–100 wt %)	Import and Repackaging	100	1,070	1.0E–03	5.5	50	1,070	6.2E–03	5.6
	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	60	1,070	5.0E–03	5.6	30	1,070	1.3E–02	5.8
	Processing – As a reactant; Industrial use – Other use (55–100 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	100	1,070	1.0E–03	5.5	55	1,070	5.3E–03	5.6
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	1,070	N/A (unable to reach target internal dose)		0.085	1,070	N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	1,070	1.0E–03	5.5	50	1,070	6.2E–03	5.6
	Disposal (50–100 wt %)	Waste Handling, Treatment, and Disposal	100	1,070	1.0E–03	5.5	50	1,070	6.2E–03	5.6
	Manufacture – Import (45–60 wt %)	Import and Repackaging	60	535	5.0E–03	5.7	45	535	7.5E–03	5.8
	Processing – Repackaging (50–100 wt %)	Import and Repackaging	100	535	1.0E–03	5.5	50	535	6.4E–03	5.8
	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	60	535	5.0E–03	5.7	30	535	1.4E–02	6.0
	Processing – As a reactant; Industrial use – Other use (55–100 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	100	535	1.0E–03	5.5	55	535	5.4E–03	5.7

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Route-to-Route Route of Exposure and POD _{rat} Duration	COU	OES or Consumer Scenario	Dermal HEDs for HE Concentrations				Dermal HEDs for CT Concentrations			
			Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)	Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)
Non-cancer, Chronic, oral-to- dermal BMDL 11 mg/kg/d Male Osborne- Mendel Rat	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	535	N/A (unable to reach target internal dose)		0.085	535	N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	535	1.0E–03	5.5	50	535	6.4E–03	5.8
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	267.5	1.0E–03	5.5	50	267.5	6.6E–03	6.0
	Disposal (50–100 wt %)	Waste Handling, Treatment, and Disposal	100	535	1.0E–03	5.5	50	535	6.4E–03	5.8
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	267.5	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	
	Consumer use – Fuels and related products (Avgas) (2 hands, 0.085–0.1 wt %)	Consumer	0.1	1,070	N/A (unable to reach target internal dose)		0.085	535	N/A (unable to reach target internal dose)	
	Consumer use – Fuels and related products (Avgas) (1 hands, 0.085–0.1 wt %)	Consumer	0.1	535	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	
Non-cancer chronic inhalation-to- dermal, BMCL, 9 ppm, Male F344 Rat	Manufacture – Import (45–60 wt %)	Import and Repackaging	60	1,070	2.7E–03	3.4	45	1,070	4.4E–02	3.4
	Processing – Repackaging (50–100 wt %)	Import and Repackaging	100	1,070	8.3E–04	3.3	50	1,070	3.7E–02	3.4
	Processing – Incorporation into formulation, mixture, or reaction product – (30–60 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	60	1,070	2.7E–03	3.4	30	1,070	7.8E–02	3.5
	Processing – As a reactant; Industrial use – Other use (55–100 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	100	1,070	8.3E–04	3.3	55	1,070	3.2E–02	3.4

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Route-to-Route Route of Exposure and POD _{rat} Duration	COU	OES or Consumer Scenario	Dermal HEDs for HE Concentrations				Dermal HEDs for CT Concentrations			
			Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)	Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)
Non-cancer chronic inhalation-to- dermal, BMCL, 9 ppm, Male F344 Rat	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	1,070	N/A (unable to reach target internal dose)		0.085	1,070	N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	1,070	8.3E–04	3.3	50	1,070	3.7E–02	3.4
	Disposal (50–100 wt %)	Waste Handling, Treatment, and Disposal	100	1,070	8.3E–04	3.3	50	1,070	3.7E–02	3.4
	Manufacture – Import (45–60 wt %)	Import and Repackaging	60	535	3.2E–03	3.4	45	535	4.5E–03	3.5
	Processing – Repackaging (50–100 wt %)	Import and Repackaging	100	535	8.3E–04	3.3	50	535	3.8E–03	3.5
	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	60	535	3.2E–03	3.4	30	535	7.9E–03	3.6
	Processing – As a reactant; Industrial use – Other use (55–100 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	100	535	8.3E–04	3.3	55	535	3.3E–03	3.4
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	535	N/A (unable to reach target internal dose)		0.085	535	N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	535	8.3E–04	3.3	50	535	3.8E–03	3.5
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	267.5	1.0E–02	3.4	50	267.5	3.9E–03	3.5
	Disposal (50–100 wt %)	Waste Handling, Treatment, and Disposal	100	535	8.3E–04	3.3	50	535	3.8E–03	3.5

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Route-to-Route Route of Exposure and POD _{rat} Duration	COU	OES or Consumer Scenario	Dermal HEDs for HE Concentrations				Dermal HEDs for CT Concentrations			
			Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)	Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)
Non-cancer chronic inhalation-to- dermal, BMCL, 9 ppm, Male F344 Rat	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	267.5	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	
	Consumer use – Fuels and related products (Avgas) (2 hands, 0.085–0.1 wt %)	Consumer	0.1	1,070	N/A (unable to reach target internal dose)		0.085	535	N/A (unable to reach target internal dose)	
	Consumer use – Fuels and related products (Avgas) (1 hands, 0.085–0.1 wt %)	Consumer	0.1	535	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	
Acute and intermediate inhalation-to- dermal, LOAEC, 89 ppm, combined Sex CD Rats & CD-1 Mice	Manufacture – Import (45–60 wt %)	Import and Repackaging	60	1,070	3.2E–02	40	45	1,070	5.4E–02	42
	Processing – Repackaging (50–100 wt %)	Import and Repackaging	100	1,070	9.4E–03	38	50	1,070	4.5E–02	41
	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	60	1,070	3.2E–02	40	30	1,070	0.11	44
	Processing – As a reactant; Industrial use – Other use (55–100 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	100	1,070	9.4E–03	38	55	1,070	3.8	40
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	1,070	N/A (unable to reach target internal dose)		0.085	1,070	N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	1,070	9.4E–03	38	50	1,070	4.5E–02	41
	Disposal (50–100 wt %)	Waste Handling, Treatment, and Disposal	100	1,070	9.4E–03	38	50	1,070	4.5E–02	41
	Manufacture – Import (45–60 wt %)	Import and Repackaging	60	535	3.5E–02	42	45	535	6.1E–02	44
	Processing – Repackaging (50–100 wt %)	Import and Repackaging	100	535	9.6E–03	38	50	535	4.9E–02	43

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Route-to-Route Route of Exposure and POD _{rat} Duration	COU	OES or Consumer Scenario	Dermal HEDs for HE Concentrations				Dermal HEDs for CT Concentrations			
			Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)	Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)
Acute and intermediate inhalation-to- dermal, LOAEC, 89 ppm, combined Sex CD Rats & CD-1 Mice	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	60	535	3.5E–02	42	30	535	0.23	45
	Processing – As a reactant; Industrial use – Other use (55–100 wt %)	Incorporation into Formulation, Mixture, and Reaction Product	100	535	9.6E–03	38	55	535	4.1E–02	43
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %)	Fuels and Related Products (avgas)	0.1	535	N/A (unable to reach target internal dose)		0.085	535	N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	535	9.6E–03	38	50	535	4.9E–02	43
	Commercial use – Other uses – Laboratory chemical (50–100 wt %)	Laboratory Use	100	267.5	1.0E–02	39	50	267.5	0.11	45
	Disposal (50–100 wt %)	Waste Handling, Treatment, and Disposal	100	535	9.6E–03	38	50	535	4.9E–02	43
	Industrial use – Fuel agent in petroleum refineries – Bulk Terminals (avgas) (0.09–0.1 wt %)	Fuels and related products (Avgas)	0.1	267.5	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	
	Consumer use – Fuels and related products (Avgas) (2 hands, 0.085– 0.1 wt %)	Consumer	0.1	1,070	N/A (unable to reach target internal dose)		0.085	535	N/A (unable to reach target internal dose)	
	Consumer use – Fuels and related products (Avgas) (1 hands, 0.085– 0.1 wt %)	Consumer	0.1	535	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	
COU = condition of use; CT = central tendency; HE = high-end; HED = human equivalent dose; OES = occupational exposure scenario; POD _{rat} = rat point of departure; wt % = weight percent “Dermal HEDs for HE Concentrations” describes HE mass % formulation for applicable COU for each exposed surface area of skin, and predicted volume of media and predicted HED. “Dermal HEDs for CT Concentrations” describes CT mass % formulation for applicable COU, for each exposed surface area of skin, and predicted volume of media and predicted HED.										

Route-to-Route Route of Exposure and POD _{rat} Duration	COU	OES or Consumer Scenario	Dermal HEDs for HE Concentrations				Dermal HEDs for CT Concentrations			
			Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)	Mass (%)	Exposed Skin Surface Area (cm ²)	Volume (L)	Retained HED (mg/kg/d)
“N/A (cannot reach internal dose)” means that under the given exposure scenario, no HED and volume of media large enough could be calculated to reach maximum internal dose threshold. The retained dose, or part of the applied dose that permeates into the skin and is not evaporated or washed, represents the biologically relevant dose driving systemic exposure.										
^a HE and CT concentrations were simulated for all skin area assumptions: 2-hands (HE: 1,070 cm ² ; CT: 535 cm ²) and 1-hand (HE: 535 cm ² ; CT: 267.5 cm ²)										
Reported HED (mg/kg/d) is retained dermal HED over specified surface area of skin (cm ²) and in specified volume of liquid (L). COU can include 1 or 2 hands. Rows that indicate “1 hand or 1 palm” or “2-hand” indicate COUs distinct by surface area of skin. The simulated skin surface area can be found under the “Exposed Skin Surface Area (cm ²)” column.										

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Table 2-22. PBPK Route-to-Route Extrapolation of Cancer Human Health Hazard PODs for Dermal Exposure

Route-to-Route Route of Exposure and POD _{rat}	COU	OES	Dermal CSF or IUR for HE COUs				Dermal CSF or IUR for CT COUs			
			Mass %	Exposed Skin Surface Area cm ²	Volume L	CSF or IUR (mg/kg/d) ⁻¹	Mass %	Exposed Skin Surface Area cm ²	Volume L	CSF or IUR (mg/kg/d) ⁻¹
PBPK Oral-to-dermal route-to-route extrapolation 2.24 mg/kg/day	Manufacture – Import (45–60 wt %) (2-hands)	Import and Repackaging	60	1,070	8.0E–04	0.1	45	535	1.3E–03	0.1
	Processing – Repackaging (50–100 wt %) (2-hands)	Import and Repackaging	100	1,070	2.5E–04	0.1	50	535	1.1E–03	0.1
	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %) (2-hands)	Incorporation into Formulation, Mixture, and Reaction Product	60	1,070	8.0E–04	0.1	30	535	3.3E–03	0.1
	Processing – As a reactant; Industrial use – Other use (55–100 wt %) (2-hands)	Incorporation into Formulation, Mixture, and Reaction Product	100	1,070	2.5E–04	0.1	55	535	9.3E–04	0.1
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %) (2 hands)	Fuels and Related Products (avgas)	0.1	1,070	N/A (unable to reach target internal dose)		0.085		N/A (unable to reach target internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %) (2-hand) (2-hands)	Laboratory Use	100	1,070	2.5E–04	0.1	50	535	1.1E–03	0.1
	Disposal (50–100 wt %) (2-hands)	Waste Handling, Treatment, and Disposal	100	1,070	2.5E–04	0.1	50	535	1.1E–03	0.1
	Commercial use – Other uses – Laboratory chemical (50–100 wt %) (1- palm/ 1 hand)	Laboratory Use	100	535	2.5E–04	0.1	50	267.5	1.1E–03	0.1
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %) (1 hand)	Fuels and Related Products (avgas)	0.1	535	N/A (unable to reach target internal dose)		0.085	267.5	N/A (unable to reach target internal dose)	

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Route-to-Route Route of Exposure and POD _{rat}	COU	OES	Dermal CSF or IUR for HE COUs				Dermal CSF or IUR for CT COUs			
			Mass %	Exposed Skin Surface Area cm ²	Volume L	CSF or IUR (mg/kg/d) ⁻¹	Mass %	Exposed Skin Surface Area cm ²	Volume L	CSF or IUR (mg/kg/d) ⁻¹
PBPK Inhalation-to-dermal route-to-route extrapolation 0.231 ppm	Manufacture – Import (45–60 wt %) (2-hands)	Import and Repackaging	60	1,070	3.9E–04	0.21	45	535	6.2E–04	0.21
	Processing – Repackaging (50–100 wt %) (2-hands)	Import and Repackaging	100	1,070	1.2E–04	0.21	50	535	5.2E–04	0.21
	Processing – Incorporation into formulation, mixture, or reaction product (30–60 wt %) (2-hands)	Incorporation into Formulation, Mixture, and Reaction Product	60	1,070	3.9E–04	0.21	30	535	1.1E–03	0.21
	Processing – As a reactant; Industrial use – Other use (55–100 wt %) (2-hands)	Incorporation into Formulation, Mixture, and Reaction Product	100	1,070	1.2E–04	0.21	55	535	4.5E–4	0.21
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %) (2 hands)	Fuels and Related Products (avgas)	0.1	1,070	N/A (cannot reach internal dose)		0.085	535	N/A (cannot reach internal dose)	
	Commercial use – Other uses – Laboratory chemical (50–100 wt %) (2 hands)	Laboratory Use	100	1,070	1.2E–04	0.21	50	535	5.2E–04	0.21
	Disposal (50–100 wt %) (2 hands)	Waste Handling, Treatment, and Disposal	100	1,070	1.2E–04	0.21	50	535	5.2E–04	0.21
	Commercial use – Other uses – Laboratory chemical (50–100 wt %) (1- palm/ 1 hand)	Laboratory Use	100	535	5.2E–04	0.21	50	267.5	5.2E–04	0.21
	Industrial use – Fuel agent in petroleum refineries; Commercial use – Fuels and related products (0.09–0.1 wt %) (1-hand)	Fuels and Related Products (avgas)	0.1	535	N/A (cannot reach internal dose)		0.085	267.5	N/A (cannot reach internal dose)	

Route-to-Route Route of Exposure and POD _{rat}	COU	OES	Dermal CSF or IUR for HE COUs				Dermal CSF or IUR for CT COUs			
			Mass %	Exposed Skin Surface Area cm ²	Volume L	CSF or IUR (mg/kg/d) ⁻¹	Mass %	Exposed Skin Surface Area cm ²	Volume L	CSF or IUR (mg/kg/d) ⁻¹
PBPK Inhalation-to-dermal route-to-route extrapolation 0.231 ppm	Consumer use – Fuels and related products (Avgas) (2 hands, 0.085–0.1 wt %)	Consumer	0.1	1,070	N/A (cannot reach internal dose)		0.85	535	N/A (cannot reach internal dose)	
	Consumer use – Fuels and related products (Avgas) (2 hands, 0.085–0.1 wt %)	Consumer	0.1	535	N/A (cannot reach internal dose)		0.85	267.5	N/A (cannot reach internal dose)	
COU = condition of use; CSF = cancer slope factor; CT = central tendency; HE = high-end; HED = human equivalent dose; IUR = inhalation risk; OES = occupational exposure scenario; POD_{rat} = rat point of departure; wt % = weight percent “N/A (cannot reach internal dose)” means that under the given exposure scenario, no HED and volume of media large enough could be calculated to reach maximum internal dose threshold. The retained dose, or part of the applied dose that permeates into the skin and is not evaporated or washed, represents the biologically relevant dose driving systemic exposure. CSF (mg/kg/d)⁻¹ = BMR/HED; BMR = 0.1. All HE and CT HEDs from inhalation-to-dermal route-to-route extrapolation = 0.47–0.48 mg/kg/d and All HE and CT HEDs for oral route-to-route extrapolation = 1 mg/kg/d. HED (mg/kg/d) is retained dermal human equivalent dose over specified surface area of skin (cm²) and in specified volume of liquid (L). HE dermal exposures were simulated for HE COU formulation and HE skin surface area (1,070 cm² for 2 hands or 535 cm² for 1 hand); CT dermal exposures were CT simulated for COU formulation and CT skin surface area (535 cm² for 2 hands or 267.5 cm² for 1 hand)).										

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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 to make conclusions about relevant adverse health effects from ethylene dibromide exposure. Following evidence integration, EPA performed hazard threshold analysis to derive hazard values for use in risk characterization. The Agency then evaluated the weight of scientific evidence for each aspect of the assessment and determined overall confidence ratings for each critical hazard outcome. The generalized process for conducting environmental hazard assessments under TSCA is presented below in Figure 3-1.

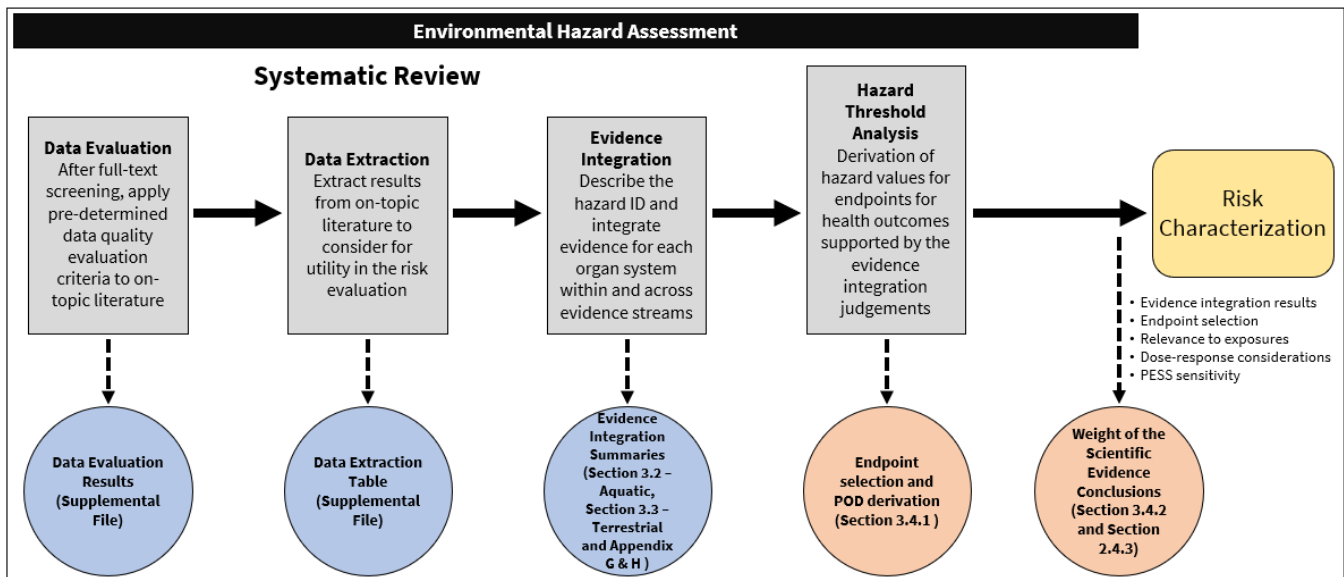


Figure 3-1. Approach for Environmental Hazard Identification, Evidence Integration, and Hazard Threshold Analysis for Ethylene Dibromide

3.1.1 Systematic Review

The searching and screening steps of the systematic review process for ethylene dibromide followed the the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)) covering all reasonably available literature published through April 2025. Full details and screening results for all the identified studies are described in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)).

For the consideration of all reasonably available information to characterize environmental hazard, EPA first screened titles and abstracts and then full texts of potentially relevant data sources, if available, using PECO screening criteria. All studies that met the screening criteria for environmental hazard were then evaluated for data quality using pre-established quality criteria and metrics, and relevant data were extracted. The data quality rating for each individual study is reported as an overall quality determination (OQD).

The results of data quality evaluation and extraction of data for the characterization of environmental hazard are presented in the following supplemental files:

- *Draft Data Quality Evaluation Information for Environmental Hazard for Ethylene Dibromide* ([U.S. EPA, 2026d](#))

- *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026c](#))

As described in Section 7 of the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)) and Section 6 of the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)), evidence integration is the last step of systematic review, encompassing the consideration of the quality and relevance of the data while taking into account the strengths and limitations of the data to appropriately evaluate evidence presented in this draft TSD.

EPA used the approach described below and in the identified documents to evaluate, extract, and integrate evidence for ethylene dibromide environmental hazard and hazard threshold analysis. This section provides an overview of the approach, which is based on the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)), with any updates in the implementation of the systematic review processes presented in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)) and the *Framework for Human Health Risk Assessment to Inform Decision Making* ([U.S. EPA, 2014a](#)). Since the publication of the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)) and since ethylene dibromide studies were originally evaluated and extracted, EPA has continued to improve and refined the systematic review process including how studies for environmental assessment are prioritized for data evaluation and extraction, steps that are independent from data integration and applicability of data. Data evaluation and extraction are independent steps from data integration and applicability for the use of specific endpoints for quantitative analysis (*e.g.*, hazard threshold analysis) used for a specific chemical risk evaluation. The goal of data quality evaluation is to objectively review considerations regarding experimental design and the resulting measured and observed effects, and is not the only consideration when determining which endpoints are candidates for quantitative analysis, as other chemical-specific considerations for a given risk evaluation should also weigh into the relevancy of the available endpoints for a specific exposure route and/or duration.

For the draft environmental hazard assessment, EPA systematically reviewed data sources identified in the initial literature search conducted in September 2019 and the updated peer-review literature search conducted in April 2025. Following the initial and updated literature searches, EPA first screened titles and abstracts and then full texts for relevancy using PECO screening criteria. Studies that met the full-text screening criteria were then evaluated and extracted. The data quality rating for each study is reported as an OQD.

EPA relied primarily on studies with apical (phenotypic) endpoints to identify possible candidates for hazard threshold analysis. Sub-organ level effects (referred to as mechanistic effects) generally did not formally undergo data quality evaluation or extraction. However, some mechanistic effects did undergo data quality and extraction for the characterization of environmental hazard and are presented in Sections 0 and 0, as relevant for aquatic and terrestrial hazard, respectively.

Following data quality evaluation, EPA extracted the toxicological information from each evaluated study into a supplemental file. The results of data quality evaluation and extraction of key study information for ecologically relevant animal phenotypic toxicity studies are presented in the following supplemental files:

- *Draft Data Quality Evaluation Information for Environmental Hazard for Ethylene Dibromide* ([U.S. EPA, 2026d](#))
- *Draft Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Ethylene Dibromide* ([U.S. EPA, 2026c](#))

EPA gave greater weight to studies that received medium or high overall quality determination ratings for hazard identification, evidence integration, and hazard threshold analysis. Information from studies of low or uninformative quality was considered for hazard identification and evidence integration to support the weight of scientific evidence as appropriate and were not used quantitatively for hazard threshold analysis.

After evaluating individual studies for data quality, EPA summarized hazard information by hazard outcome and considered the strengths and limitations of individual evidence streams (*i.e.*, animal toxicity studies with apical endpoints, and supplemental mechanistic information). The Agency integrated data from these evidence streams to arrive at an overall evidence integration conclusion for each health outcome category (*e.g.*, reproductive toxicity).

Finally, EPA assigned confidence ratings for each environmental hazard outcome chosen for acute and chronic exposure scenarios. These ratings considered evidence integration conclusions as well as additional factors such as relevance of the health outcome (and associated health effect[s]) to the exposure scenario (acute or chronic) and biological factors that increase susceptibility to ethylene dibromide. This overall weight of scientific evidence analysis is presented in Section 3.4.1.

3.1.2 Environmental Hazard Problem Formulation and Focus of Analysis

EPA completed the review of environmental hazard data/information sources during risk evaluation using the data quality review evaluation metrics and the rating criteria described in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)) and *Draft Risk Evaluation for Ethylene Dibromide – Systematic Review Protocol* ([U.S. EPA, 2026i](#)) and assigned an overall quality determination rating of high, medium, low, or uninformative for dose response. EPA systematically evaluated all data for this hazard characterization but relied upon high- and medium-quality studies for quantitative hazard characterization. However, references receiving an overall quality determination of low or uninformative were included in tables and descriptions to provide complete summaries of the reasonably available information. Reasons for low or uninformative ratings included inability to maintain ethylene dibromide test concentrations, lack of reporting of test concentrations, and/or uncertainty regarding the use of appropriate control groups.

EPA considered all reasonably available and potentially relevant studies to characterize the environmental hazards of ethylene dibromide to ecological receptor groups, including aquatic vertebrates, aquatic invertebrates, algae, plants, fungi, terrestrial vertebrates, and terrestrial invertebrates. For quantitative hazard characterization, the Agency prioritized apical endpoints of mortality, development, growth, and reproduction to inform acute and chronic exposure durations because they directly lead to adverse population-level effects. Mechanistic (*e.g.*, gene expression, protein expression/interactions, genotoxicity) and behavioral (*e.g.*, distance moved, feeding, swimming) endpoints were used to inform potential mechanisms that lead to acute and chronic environmental hazard effects but were not included in calculations for hazard thresholds (*i.e.*, only used qualitatively). No wild terrestrial mammalian studies containing endpoints that were quantifiable for establishing hazard thresholds were reasonably available; therefore, toxicological studies utilizing human health model organisms (*e.g.*, rodents) were used as surrogate data and considered for establishing hazard thresholds for terrestrial species. EPA considers exposure durations comprising less than 10% of an organism's lifespan as acute, while mammalian data may be categorized differently for human health applications. Hazard thresholds were not derived for aquatic or terrestrial organisms via oral exposure to ethylene dibromide because ethylene dibromide is not expected to bioaccumulate, as described in Section 8.4 in *The Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)).

3.1.2.1 Aquatic Species Hazard

For aquatic species exposed to ethylene dibromide, EPA derived concentrations of concern (COCs) to represent hazard thresholds. EPA uses probabilistic approaches (*e.g.*, species sensitivity distribution, or SSD) when acute toxicity data from at least eight species are available ([Raimondo et al., 2010](#)) and uses deterministic approaches when data from at least eight species are not available. For ethylene dibromide, two separate SSDs were derived for acute aquatic exposure hazards (*i.e.*, 1 for vertebrate species and another for invertebrate species), as described in Sections 3.2.1.1 and 3.2.2.1. Since data were available for four vertebrate species and four invertebrate species, the data were supplemented with predictions from the Web-based Interspecies Correlation Estimation ([Web-ICE](#), v4.0; accessed June 2026) toxicity value estimation tool. Deterministic approaches were used to assess chronic hazard in aquatic organisms. Appendix E contains additional details regarding the hazard effects that were used for SSD input parameters, as well as the resulting modeled outputs for estimating hazard thresholds for aquatic (acute vertebrate and invertebrate) species.

3.1.2.1.1 Acute Aquatic Species

An SSD is a model of the variation in sensitivity of species to a particular chemical stressor and is generated by fitting a statistical distribution to the proportion of species affected as a function of concentration or dose. This hazardous concentration (HC) is represented as an HC_p, where p is the % of species below the threshold of protection. EPA used an HC05 (a hazardous concentration threshold for 5% of species) to estimate a concentration that is protective of 95% of species. The HC05 was then used to derive the COC as the lower bound of the 95th percentile confidence interval (CI) of the HC05 to account for uncertainty across species and/or extrapolation from laboratory-controlled studies to the natural environment. EPA has more confidence in the probabilistic approach compared to the deterministic approach when enough data are available because an HC05 is representative of a larger proportion of species in the environment. Because empirical hazard values from reasonably available information for ethylene dibromide were only available for eight species, EPA used the Web-ICE (v4.0) toxicity predictions tool ([Raimondo et al., 2010](#)) to predict hazard data used to supplement the empirical data for the SSD analysis.

3.1.2.1.2 Chronic Aquatic Species

The chronic vertebrate and invertebrate COC values were derived using a deterministic approach after reviewing the lowest toxicity across a set of species for survival, reproduction, and growth endpoints. EPA calculated geometric means of the NOEC and LOEC values resulting in a chronic value (ChV) ([U.S. EPA, 2002b](#)). EPA then applied an assessment factor of 10 where appropriate to account for species-to-species differences and extrapolating from laboratory studies to the field ([Zeeman, 1995](#); [Zeeman and Gilford, 1993](#)). For aquatic vertebrate species, the only chronic study with a high overall quality determination rating that contained survival, reproduction, or growth data was on the Japanese medaka (fish), which is a species that was less sensitive in the acute data, and resulted in a COC that was higher than the acute COC. No chronic data were identified for aquatic invertebrate species. Therefore, EPA used the LC50 from the most sensitive acute species, applied an acute-to-chronic ratio (ACR) of 10 and an AF of 10 to arrive at the chronic vertebrate and invertebrate COCs, as described in Sections 3.2.3.2 and 3.2.4.1. This approach is more protective for vertebrate species than using the lone chronic study on a less sensitive species—especially when the Japanese medaka are typically shown to be more sensitive under chronic exposures than under acute exposures.

3.1.2.2 Terrestrial Species Hazard

For terrestrial species, EPA estimated hazard thresholds for birds, mammals, and terrestrial invertebrates using fitness-related endpoints (*e.g.*, mortality, development, growth, and reproduction) that are likely to result in population-level adverse effects due to the environmental release of ethylene dibromide. As a

matter of standard practice, assessment factors are generally not applied by EPA when deriving hazard thresholds for terrestrial organisms that may introduce uncertainty in whether the hazard threshold is sufficiently protective. Chapman ([1998](#)) reviewed assessment factor extrapolations in terrestrial environments and concluded that there is no clear or consistent relationship between laboratory- and field-based hazard effects on mammals and plants to be more or less conservative than the hazard concentration itself.

Ethylene dibromide poses potential hazard to terrestrial organisms through air exposure routes. Therefore, inhalation is an exposure pathway of potential concern for terrestrial organisms due to the potential for ethylene dibromide to release to air as well as its other chemical properties (*i.e.*, volatility). Additional details regarding the release profile and environmental exposure are available in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* TSD ([U.S. EPA, 2026b](#)). Due to the low bioaccumulation potential of ethylene dibromide, oral exposure is not considered by EPA to be a predominant route for environmental exposure (see also Section 4.6 in that draft TSD).

3.1.2.2.1 Terrestrial Vertebrates

Mammals

EPA considered mammalian studies that were used to characterize both environmental and human health hazard to derive environmental hazard thresholds resulting from environmental releases. In lieu of available wild mammalian studies, the Agency primarily reviewed laboratory rodent studies to characterize mammalian toxicity resulting from ethylene dibromide from dietary, inhalation, and injection routes of exposure ([U.S. EPA, 2024a, 2012c](#)). Hazard thresholds were determined based on relevant population-level effects (*e.g.*, mortality, reproduction) resulting from air releases and exposure via inhalation for both acute and chronic exposures.

Using inhalation data reported in Rowe et al. ([1952](#)) (listed as an EPA estimated value alongside author reported endpoints in Table 3-7), an acute LC50 hazard value was estimated based on Haber's Law ([Haber, 1924](#)). A 4-hour LC50 for inhalation exposure was estimated by dose-response curve analysis conducted using the drc (Dose-Response Curves²) package (version 3.0.1) ([Ritz et al., 2015](#)) in R ([R Core Team, 2025](#)). Additional information regarding the assumptions and methods used by EPA to calculate an LC50 based on toxicity data resulting from inhalation exposure are available below in Appendix G.

Birds

The lack of available empirical data for inhalation routes of exposure in avian taxa inhibits the calculation of an acute hazard value, thus EPA used the [Screening Tool for Inhalation Risk \(STIR\)](#) (accessed June 2026) to estimate an acute hazard effect concentration for avian species exposed to ethylene dibromide via air exposure ([U.S. EPA, 2010](#)). STIR uses empirical mammalian-oral, mammalian-inhalation, and avian-oral toxicity values to estimate an avian-inhalation toxicity value, corrected using an adjustment factor to account for differences in lung tissue thickness and surface areas between birds and mammals. Uncertainties include differences in vascularization of mammalian and avian lungs, which may affect diffusion rates of xenobiotics as well as differences in enzymatic activities in lung tissues. Birds have significantly higher lung surface area-to-body mass ratios and different lung physiology compared to mammals; however, STIR does not explicitly model avian lung surface area or species-specific respiratory anatomy. Instead, it incorporates avian respiratory physiology indirectly through higher default inhalation rates (IR) and assuming 100% absorption. Although STIR accounts for differences across lung membranes by applying an assessment/adjustment

² For additional details on the dose-response analysis, see the [drc CRAN package manual](#) (accessed June 18, 2026).

factor, it does not mechanistically account for avian-specific increases in gas exchange efficiency or larger surface area. For additional details, please see STIR v1.0 *User's Guide for Pesticide Inhalation Risk* ([U.S. EPA, 2010](#)) and Appendix H.

Chronic inhalation hazard could not be characterized or quantified due to lack of available empirical data. Although one study was identified which contained chronic empirical data for dietary exposure of chickens to ethylene dibromide, the duration of exposure was approximate and there was uncertainty regarding the amount of ethylene dibromide in the fumigated mash that was fed to the birds ([Alumot et al., 1968](#)). Additionally, although animal weight and ingestion rate were recorded for the first 10 weeks of the study, the data were not reported. Therefore, the uncertainties in the data introduced uncertainty into the hazard interpretation such that chronic inhalation hazard could not be estimated.

3.1.2.2.2 Terrestrial Invertebrates

For terrestrial invertebrate taxa exposed to ethylene dibromide, EPA derived an acute hazard threshold using a probabilistic approach (e.g., SSD) ([Raimondo et al., 2010](#)). As the minimum requirement of eight species were available for terrestrial invertebrate species, an SSD was derived using SSD Toolbox v1.1 for acute data representing ethylene dibromide exposure durations less than 10% of an organism's lifespan. Because the terrestrial database available in Web-ICE v4.0 only exists for birds and mammals, predicted hazard values for terrestrial invertebrate species are not available to supplement terrestrial invertebrate empirical data ([Raimondo et al., 2010](#)). Appendix E contains additional details regarding the hazard effects that were utilized for SSD input parameters, as well as the resulting modeled outputs for estimating acute hazard thresholds for terrestrial invertebrate species. The hazard threshold was rounded to the appropriate number of significant figures based on empirical data.

3.1.2.3 Weight of Scientific Evidence

EPA uses several considerations when weighing scientific evidence to determine confidence in the environmental hazard data. These considerations include the quality of the database, consistency, strength and precision, biological gradient/dose response, and relevance. This approach is described in Appendix F and the Draft Systematic Review Protocol ([U.S. EPA, 2021](#)).

3.2 Aquatic Species Hazard

EPA reviewed 13 studies for ethylene dibromide toxicity to aquatic organisms. Some studies included multiple endpoints, species, and test durations. Five of these studies received an overall quality determination rating of low or uninformative. The data from these low or uninformative studies were not used to derive hazard thresholds because insufficient information was provided on test concentrations or test concentrations were not maintained during the exposure period. Eight studies received an overall quality determination rating of high or medium quality. These studies were used to derive hazard thresholds and are detailed in the subsections below, and the overall quality determination ratings can be found after the citation in the tables. Additionally, as discussed above in Section 3.1.2.1, acute vertebrates and invertebrates were separated during SSD analysis due to poor fit of the models when the species were combined in the analysis. EPA had sufficient acute fish and invertebrate data to estimate hazard data for 81 species using EPA's Web-ICE (v4.0) tool ([Raimondo et al., 2010](#)), including predictions for 33 vertebrate species and 48 invertebrate species. No toxicity studies using spiked sediment for benthic exposures were identified for ethylene dibromide. Thus, all hazard data to benthic invertebrates were represented by water exposures.

3.2.1 Acute Aquatic Vertebrates

EPA reviewed three studies of either high or medium quality, two uninformative studies, and one supplemental study for ethylene dibromide acute toxicity in aquatic vertebrates—both freshwater and

marine species. Again, acute studies are designated for study exposure durations that are less than 10% of an organism's lifespan. Table 3-1 encompasses observations of mortality in aquatic vertebrate species, which includes LC50s (concentration at which 50% of the exposed organisms do not survive) and TL_{ms} (median tolerance limit describes the concentration at which 50% of the exposed organisms survive). While TL_m is an inverse of LC50, it is included in the table as reported by the study authors. For the Japanese medaka (*Oryzias latipes*), fathead minnow (*Pimephales promelas*), sheepshead minnow (*Cyprinodon variegatus*), and common snook (*Centropomus undecimalis*), the 48- and 96-hour LC50s ranged from 4.3 to 32.1 mg/L (Holcombe et al., 1995; Kinloch, 1983). These studies were conducted on larval or juvenile fish, which are generally more sensitive than older fish, and represent both freshwater and marine species.

An additional preliminary range-finding test was conducted using Japanese medaka where no mortalities were reported up to the highest treatment group (*i.e.*, 20.5 mg/L ethylene dibromide) (Hawkins et al., 1998). While no mortalities were observed, the authors reported lethargy, erratic swimming and loss of equilibrium in fish exposed to 20.5 mg/L of ethylene dibromide. The study by Davis and Hardcastle (1959) was determined to be uninformative primarily because insufficient information was reported about test concentrations and whether a control group was used in the study. The study by LAB Research Ltd (2010b) was determined to be uninformative because test concentrations were not maintained during the exposure, with concentrations in several treatment groups reported as below quantification limits at the end of the study.

In Fernandez et al. (1989), newt (*Pleurodeles waltl*) larvae were exposed to ethylene dibromide at nominal concentrations of 1.0, 2.5, and 5.0 mg/L for 12 days. After 12 days of exposure, blood was collected and the number of erythrocytes with micronuclei was determined. Micronuclei in the erythrocytes is an indication of the amount of chromosomal damage present in the red blood cells. All three concentrations evaluated in this study indicated ethylene dibromide is genotoxic to newt larvae; however, the results from this reference are underestimates of true toxicity because test concentrations were not analytically verified.

Table 3-1. Acute Aquatic Vertebrate Toxicity of Ethylene Dibromide

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Fathead minnow (<i>Pimephales promelas</i>) ^a	96-hour LC50	4.3 mg/L (4.01–4.62) ^{b c}	Mortality (juvenile)	Kszos et al. (2003) (High)
Sheepshead minnow (<i>Cyprinodon variegatus</i>) ^a	48-hour LC50	4.8 mg/L ^b	Mortality (juvenile)	Landau and Tucker (1984) (Medium)
Common snook (<i>Centropomus undecimalis</i>)	48-hour LC50	6.2 mg/L ^b	Mortality (juvenile)	
Japanese medaka (<i>Oryzias latipes</i>) ^a	96-hour LC50	32.1 mg/L ^b	Mortality (juvenile)	Holcombe et al. (1995) (High)
Bluegill sunfish (<i>Lepomis macrochirus</i>)	48-hour TL _m ^d	18 mg/L	Mortality (juvenile)	Davis and Hardcastle (1959) (Uninformative)
Largemouth bass (<i>Micropterus salmoides</i>)	48-hour TL _m ^d	15 mg/L	Mortality (juvenile)	
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-hour LC50	1.13 mg/L (0.88—1.40) ^c	Mortality (juvenile)	LAB Research (2010b) (Uninformative)

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
LC50 = concentration that is lethal to 50% of test organisms ^a Species used in Web-ICE as a surrogate to predict toxicity in other species. Not all species are available in the tool to use as a surrogate. ^b Bolded hazard values were used in the species sensitivity distribution (SSD). ^c 95% confidence interval around the LC50 as reported by the study authors. ^c Median tolerance limit (TL_m) is the concentration at which 50% of the test animals are able to survive.				

3.2.1.1 Acute Aquatic Vertebrate COC

The acute aquatic vertebrate COC for ethylene dibromide was derived from an SSD that contained 48- and 96-hour LC50s for four vertebrate species identified in systematic review, supplemented by an additional 33 vertebrate species predicted from the Web-ICE toxicity value estimation tool using vertebrate and invertebrate surrogates (see Appendix E.1). SSDs were derived using EPA's SSD Toolbox (v1.1) (Etterson, 2020b). All studies included in the SSD received an overall quality determination rating of high or medium. After reviewing the possible statistical distributions for the SSD, the Metropolis Hastings was chosen with a Gumbel distribution. This choice was based on an examination of p-values for goodness of fit (Table_Apx E-4), visual examination of Q-Q (quantile-quantile) plots (Figure_Apx E-1), and evaluation of the line of best fit near the low-end of the SSD (Figure 2-3). Q-Q plots look at how closely the empirical data align with the theoretical distribution of the model (*i.e.*, the predicted data). Empirical data that closely aligns with the model prediction fall on the curve of the model and will appear close to the 1:1 line in the Q-Q plot; whereas empirical data that are further from the curve of the model will appear further from the 1:1 line in the Q-Q plot. Because the data points within the Gumbel distribution Q-Q plot fell closer along the 1:1 line than the other distributions and the two lowest data points fell right on the 1:1 line, this distribution appeared to be the best fit, which is also indicated by the lowest Bayesian Information Criterion (BICc) value (Table_Apx E-4).

The HC05 for the above distribution is 0.81 mg/L. After taking the lower 95th percentile of this HC05, the acute aquatic COC for vertebrates is 0.55 or 550 µg/L (Figure 3-2). Alternatively, EPA considered using an assessment factor of 5 applied to the HC05 of 0.81 mg/L (as opposed to using the lower 95th percentile of the HC05), resulting in a COC for vertebrates of 0.16 mg/L or 160 µg/L. Because the 95% confidence interval around the HC05 was relatively tight (0.55–1.1 mg/L) and the HC05 is higher than one species (*Salvelinus namaycush*), EPA determined that using the lower limit of the 95th percentile was more appropriate than applying an assessment factor to account for uncertainties in the available data. Using the 95th percentile CI of the HC05 increases the confidence in protecting 95% of the species because it accounts for uncertainty resulting from variability across species or extrapolation from laboratory-controlled studies to the natural environment. EPA chose to use the lower limit of the 95% confidence interval using ethylene dibromide toxicity data as a basis for accounting for uncertainties as opposed to using a chemical-agnostic assessment factor.

Since the SSD analysis indicated vertebrates and invertebrates could not be combined in one distribution, EPA performed an additional SSD analysis with the vertebrate empirical data and using only vertebrate surrogates in Web-ICE. The resulting COC was 0.50 mg/L or 500 µg/L, thus limiting the surrogates in Web-ICE had little influence on the acute vertebrate COC, as compared to the COC of 550 µg/L derived from the SSD that used modeled vertebrate data from both vertebrate and invertebrate surrogates.

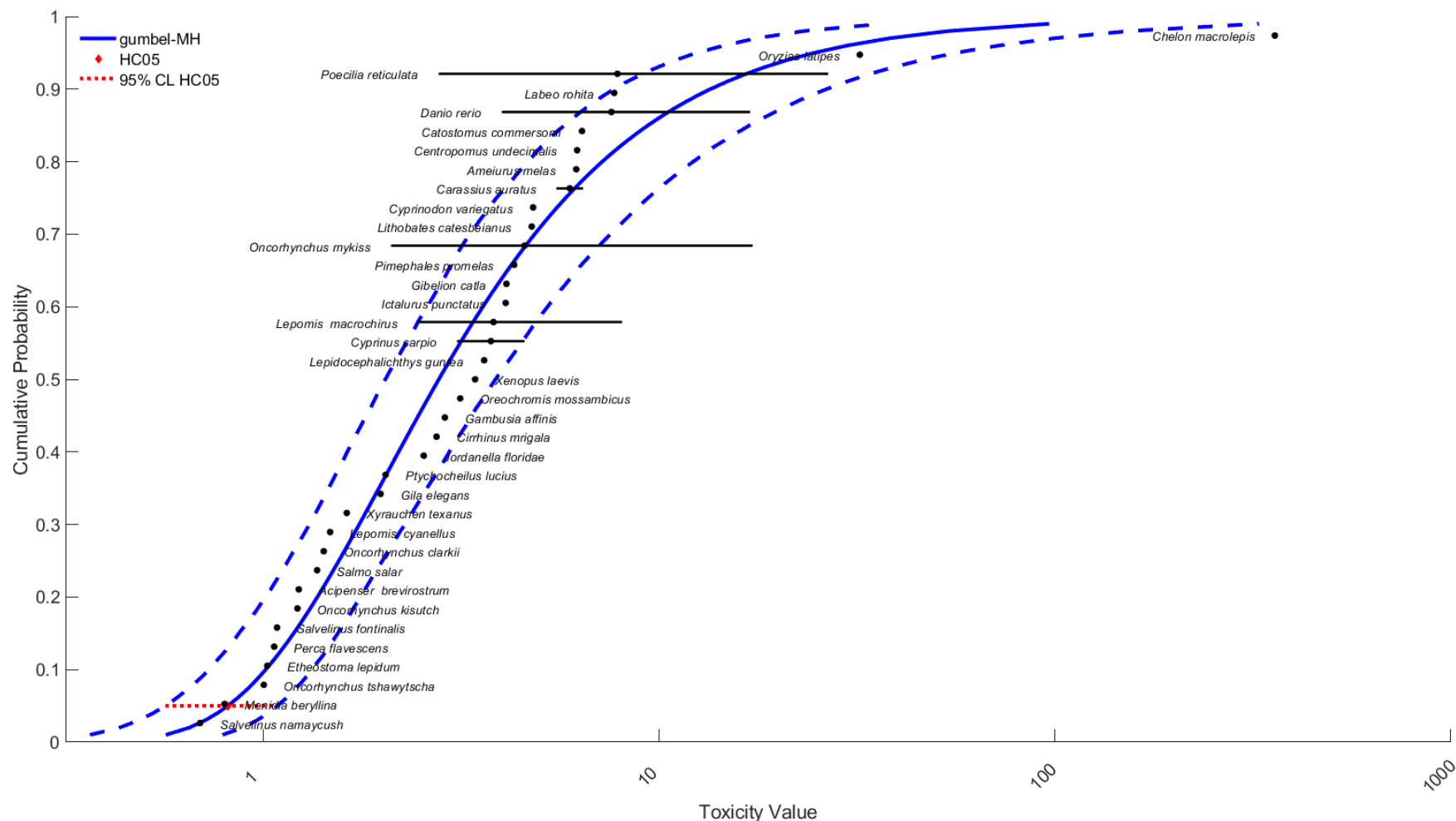


Figure 3-2. Species Sensitivity Distribution (SSD) of Acute Hazard Effects of Ethylene Dibromide on Aquatic Vertebrates

The x-axis displays empirical and estimated Web-ICE toxicity values (*i.e.*, LC50 or EC50 concentration in mg/L). The y-axis displays cumulative probability representing the cumulative proportion of aquatic vertebrate species affected by ethylene dibromide exposure. The horizontal black lines indicate the range of toxicity values for each species, with the black dot on that line indicating the geometric mean of the toxicity values. The dotted blue lines indicate the 95% confidence interval; the dotted red line indicates the 5% hazard concentration (HC05 = 0.81 mg/L).

3.2.1.2 Weight of Scientific Evidence for Acute Aquatic Vertebrate COC

The weight of scientific evidence suggests that ethylene dibromide poses acute hazard to vertebrate organisms at 550 µg/L. EPA has robust confidence in this hazard threshold. Table Apx F-1 summarizes the confidence for each environmental hazard threshold for exposure to ethylene dibromide. The Agency considered all acute vertebrate studies characterized in this draft assessment/TSD; however, the hazard threshold was derived using ecologically relevant endpoints that were of sufficient quality with overall quality determination ratings of high or medium as rated by the systematic review data quality evaluation. For a more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence levels, see Appendix F. The quality of the database of studies included three high or medium quality studies that consistently resulted in LC50s on four vertebrate species between 4.2 mg/L (Kszos et al., 2003) and 32.1 mg/L ethylene dibromide (Holcombe et al., 1995) and were supplemented with 47 predicted values for 33 vertebrate species calculated through Web-ICE. The three empirical studies were conducted with reasonable dose-response designs and results, which enabled precise LC50 calculations (Table 3-1).

EPA used a probabilistic technique (*i.e.*, SSD) to derive an acute COC, based on the estimated HC05 of 0.81 mg/L, that is protective of 95% of the taxa in the aquatic vertebrate community by incorporating hazard values across species and habitats. Note that lake trout (*Salvelinus namaycush*) fell below the HC05, indicating it is more sensitive than 95% of species to ethylene dibromide. EPA has robust confidence in the SSD with empirical data from 4 species and predicted data from 33 species that inhabit both freshwater and marine environments. These data include common test species (*e.g.*, *P. promelas*) and less common species (*e.g.*, *C. undecimalis*), thereby enhancing EPA's confidence that the COC is protective of a range of species. Limitations of an SSD include its reliance on model species that may not exist or interact in the same ecological community and are weighted equally. Also, 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). Another assumption that may limit the scope of SSD inference is whether the number of species used is adequate. The minimum number of species needed to fit a distribution is eight (Etterson, 2020b). Because EPA only had empirical data for four vertebrate species, Web-ICE was used to add surrogate LC50 data from additional species to the SSD distributions. However, adding modeled data also adds additional variation and epistemic uncertainty. Notwithstanding the limitations of SSD analyses, this method is widely used and accepted in risk assessments (Raimondo et al., 2010). The Gumbel distribution carried the majority of the BICc weight (92%); therefore, EPA used the hazard concentration from the model with the best statistical fit. EPA has robust confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the acute aquatic vertebrate COC for ethylene dibromide at 550 µg/L.

3.2.2 Acute Aquatic Invertebrates

EPA reviewed four studies of either high or medium quality and one uninformative study regarding the acute exposure of ethylene dibromide to freshwater and marine aquatic invertebrates (Table 3-2). LC50s of acute exposures of ethylene dibromide to aquatic invertebrates ranged from 3.61 to 83 mg/L for the water flea (*Ceriodaphnia dubia*), water flea (*Daphnia magna*), hydra (*Hydra oligactis*), and purple-spined sea urchin (*Arbacia punctulata*). Adams et al. (1988) received a low overall quality determination rating because much of the study design was reported in limited detail, control data was missing from tables, and few organisms were tested with unknown replication. LAB Research Ltd. (2010a) established an EC50 for immobilization (a surrogate for mortality in some species) that was higher than the LC50 reported in Kszos (2003). However, the LAB Research Ltd. (2010a) study was determined to be uninformative primarily because test concentrations were not maintained during the study, with

concentrations in many treatment groups reported as below quantification limits at the end of the study, and therefore the results cannot be compared.

In addition to mortality, Kennedy (1994) examined the effects of ethylene dibromide on embryos and plutei (*i.e.*, mature sea urchin larvae) development in the purple-spined sea urchin. In three experiments, the eggs and embryos or the sperm and embryos were exposed at nominal concentrations of 1, 10, 25, 50, 100, 250, 500, and 1,000 mg/L ethylene dibromide. One experiment started the exposure with eggs 30 minutes prior to insemination, a second experiment started the exposure with eggs at insemination, and a third experiment exposed sperm for 30 minutes prior to insemination of the eggs. In all three experiments, the exposure lasted 72-hours post-insemination. In the first experiment, the LC50 was 81 mg/L for pluteus mortality, the EC50 was 37 mg/L for formation of the pluteus stage, while the NOEC/LOEC for membrane elevation (the earliest detectable indication of sperm penetration into an egg when the membrane is lifted from the surface of the egg) and embryo cleavage efficiency (the percentage of eggs cleaving) were 500/1,000 mg/L, and were 10/25 mg/L for pluteus formation (embryo has developed into a pluteus). In the second experiment, the LC50 was 83 mg/L for pluteus mortality, and the EC50 was 37 mg/L for pluteus formation. The NOEC/LOEC for membrane elevation and embryo cleavage efficiency were 500/1,000 mg/L and were 10/25 mg/L for pluteus formation. In the third experiment, LC50s were not calculated. The NOEC/LOEC for membrane elevation, embryo cleavage efficiency, and pluteus formation were 500/1,000 mg/L.

Although Kennedy (1994) reported the EC50s for formation of the pluteus stage as LC50s, the plutei were examined for deformities, which is a measure for developmental effects, not mortality. While the reported LC50s for pluteus mortality were not a true test of mortality because the plutei were observed as transparent and disintegrating, this measurement can be interpreted as a surrogate for mortality since the plutei were breaking down. The results from this reference are underestimates of true toxicity because test concentrations were not analytically verified, and insufficient details were provided to determine if there was significant loss of ethylene dibromide from the test system. The experiments show that egg exposure to ethylene dibromide affects development more than sperm exposure to ethylene dibromide; however, there are statistically significant population-level effects (*i.e.*, pluteus formation) observed by Kennedy (1994) down to a concentration between 10 and 25 mg/L.

An additional reference observed hydra for 72 hours following a 24-, 48- or 72-hour exposure to 5 mg/L ethylene dibromide to examine the wound healing process and morphogenesis (Adams and Kennedy, 1992). After the 72-hour observation period following the 24-hour exposure to ethylene dibromide (96-hour study duration), regeneration of secondary tentacles decreased, while waist formation was increased. At the conclusion of the observation period following the 48-hour exposure (120-hour study duration), secondary foot formation and secondary tentacle regeneration were decreased, while waist formation was increased. Following the 72-hour exposure and 72-hour observation period (*i.e.*, 144-hour study duration), secondary foot formation and secondary tentacle regeneration were decreased while waist formation and separation at the graft border were increased. These results indicate that ethylene dibromide negatively affects wound healing in hydra following an acute exposure at 5 mg/L.

5094 **Table 3-2. Acute Aquatic Invertebrate Toxicity of Ethylene Dibromide**

Test Organism	Endpoint	Hazard Value	Effect(s)	Citation (Overall Quality Determination)
Water flea (<i>Ceriodaphnia dubia</i>) ^a	48-hour LC50	3.61 mg/L (3.26–3.99) ^{b c}	Mortality (neonate)	Kszos et al. (2003) (High)
Water flea (<i>Daphnia magna</i>) ^a	48-hour LC50	6.5 mg/L (no confidence limits) ^{b c}	Mortality (neonate)	
Hydra (<i>Hydra oligactis</i>)	72-hour LC50	50 mg/L ^b	Mortality (adult)	Herring (1988) (Medium)
Purple-spined sea urchin (<i>Arbacia punctulata</i>)	72-hour EC50 ^d	37 mg/L	Pluteus formation	Kennedy (1994) (High)
	72-hour LC50 ^d	83 mg/L ^b	Pluteus mortality	
	72-hour NOEC/LOEC ^d	500/1,000 mg/L	Membrane elevation, cleavage efficiency	
	72-hour NOEC/LOEC ^d	10/25 mg/L	Pluteus formation	
	72.5-hour EC50 ^d	37 mg/L	Pluteus formation	
	72.5-hour LC50	81 mg/L ^b	Pluteus mortality	
	72.5-hour NOEC/LOEC ^e	500/1,000 mg/L	Membrane elevation, cleavage efficiency	
	72.5-hour NOEC/LOEC ^e	10/25 mg/L	Pluteus formation	
	72.5-hour NOEC/LOEC ^f	500/1,000 mg/L	Membrane elevation, cleavage efficiency, pluteus formation	
Hydra (<i>Hydra oligactis</i>)	96-hour LOEC	5 mg/L	Secondary tentacle formation, Waist formation	Adams and Kennedy (1992) (Medium)
	96-hour NOEC	5 mg/L	Secondary budding region formation, secondary foot formation, separation at graft boarder, secondary head region formation, spike formation	
	120-hour LOEC	5 mg/L	Secondary foot formation, secondary tentacle formation, waist formation	
	120-hour NOEC	5 mg/L	Secondary budding region formation, separation at graft boarder, secondary head region formation, spike formation	
	144-hour LOEC	5 mg/L	Secondary foot formation, secondary tentacle formation, waist formation, separation at graft boarder	
	144-hour NOEC	5 mg/L	Secondary budding region formation, secondary head region formation, spike formation	
Atlantic pygmy octopus (<i>Octopus joubini</i>)	72-hour LC50	≈25 mg/L	Mortality (juvenile)	Adams et al. (1988) (Low)
Mexican four-eyed octopus (<i>Octopus maya</i>)	72-hour LC50	≈25 mg/L	Mortality (juvenile)	

Test Organism	Endpoint	Hazard Value	Effect(s)	Citation (Overall Quality Determination)
California two-spot octopus (<i>Octopus bimaculoides</i>)	72-hour LOEC ^g	25 mg/L	Chromatophore expansion and loss of locomotor response	
California two-spot octopus (<i>Octopus bimaculoides</i>)	72-hour LC50	<25 mg/L	Mortality (juvenile)	
Water flea (<i>Daphnia magna</i>)	48-hour EC50	11.61 mg/L (9.49–14.21) ^c	Immobilization (neonate)	LAB Research (2010a) (Uninformative)

EC50 = effective concentration that induces a biological response to 50% of test organisms; LC50 = Concentration that is lethal to 50% of test organisms; LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration

^a Species used in Web-ICE as a surrogate to predict toxicity in other species. Not all species are available in the tool to use as a surrogate.

^b **Bolded** hazard values used in the species sensitivity distribution (SSD)

^c 95% confidence interval around the LC50 as reported by the study authors

^d Exposure of eggs started at time of insemination

^e Exposure of eggs started 30 minutes prior to insemination

^f Exposure of sperm started 30 minutes prior to insemination

^g Exposure was 1 hour of a 72-hour study

3.2.2.1 Acute Aquatic Invertebrate COC

The acute aquatic invertebrate COC for ethylene dibromide was derived from an SSD that contained 48- to 72.5-hour LC50s for four invertebrate species identified in systematic review, bolstered by an additional 48 invertebrate species predicted LC50 values from the Web-ICE toxicity value estimation tool using vertebrate and invertebrate surrogates (see Appendix E.1). SSDs were derived using EPA's SSD Toolbox (v1.1) ([Etterson, 2020b](#)). All studies included in the SSD received an overall quality determination rating of high or medium. After reviewing the possible statistical distributions for the SSD, the Metropolis Hastings was chosen with a Logistic distribution based on an evaluation of p-values for goodness of fit (Table_Apx E-5), visual examination of Q-Q plots (Figure_Apx E-2), and evaluation of the line of best fit near the low-end of the SSD (Figure_Apx E-2). Because the data points within the Logistic distribution Q-Q plot fell closer along the 1:1 line than the other distributions—especially on the lower end of the plot—this distribution appeared to be the best fit, which is also indicated by the BICc value (Figure 3-3). The HC05 for this distribution is 0.40 mg/L. After taking the lower 95th percentile of this HC05, the acute aquatic COC for invertebrates is 0.19 mg/L or 190 µg/L (Table_Apx E-5).

Alternatively, EPA considered using an assessment factor of 5 applied to the HC05 of 0.40 mg/L (as opposed to using the lower 95th percentile of the HC05), resulting in a COC for invertebrates of 0.080 mg/L or 80 µg/L. Because the 95% confidence interval around the HC05 was relatively tight (0.19–0.75 mg/L) and the HC05 is higher than one species (*Americamysis bigelowi*), EPA determined using the lower limit of the 95th percentile was more appropriate than applying an assessment factor to account for uncertainties in the available data. Using the 95th percentile confidence interval of the HC05 increases the confidence in protecting 95% of the species because it accounts for uncertainty resulting from variability across species and/or extrapolation from laboratory-controlled studies to the natural environment. EPA chose to use the lower limit of the 95% confidence interval using ethylene dibromide toxicity data as a basis for accounting for uncertainties as opposed to using a chemical-agnostic assessment factor.

5123 EPA performed an additional analysis with the invertebrate empirical data and using only invertebrate
5124 surrogates in Web-ICE because the SSD analysis indicated vertebrates and invertebrates could not be
5125 combined in one distribution. The Agency was unable to get a good fit with any model. The acute COCs
5126 indicate aquatic invertebrates are more sensitive under acute conditions than vertebrate species, which is
5127 expected since ethylene dibromide is a fumigant.

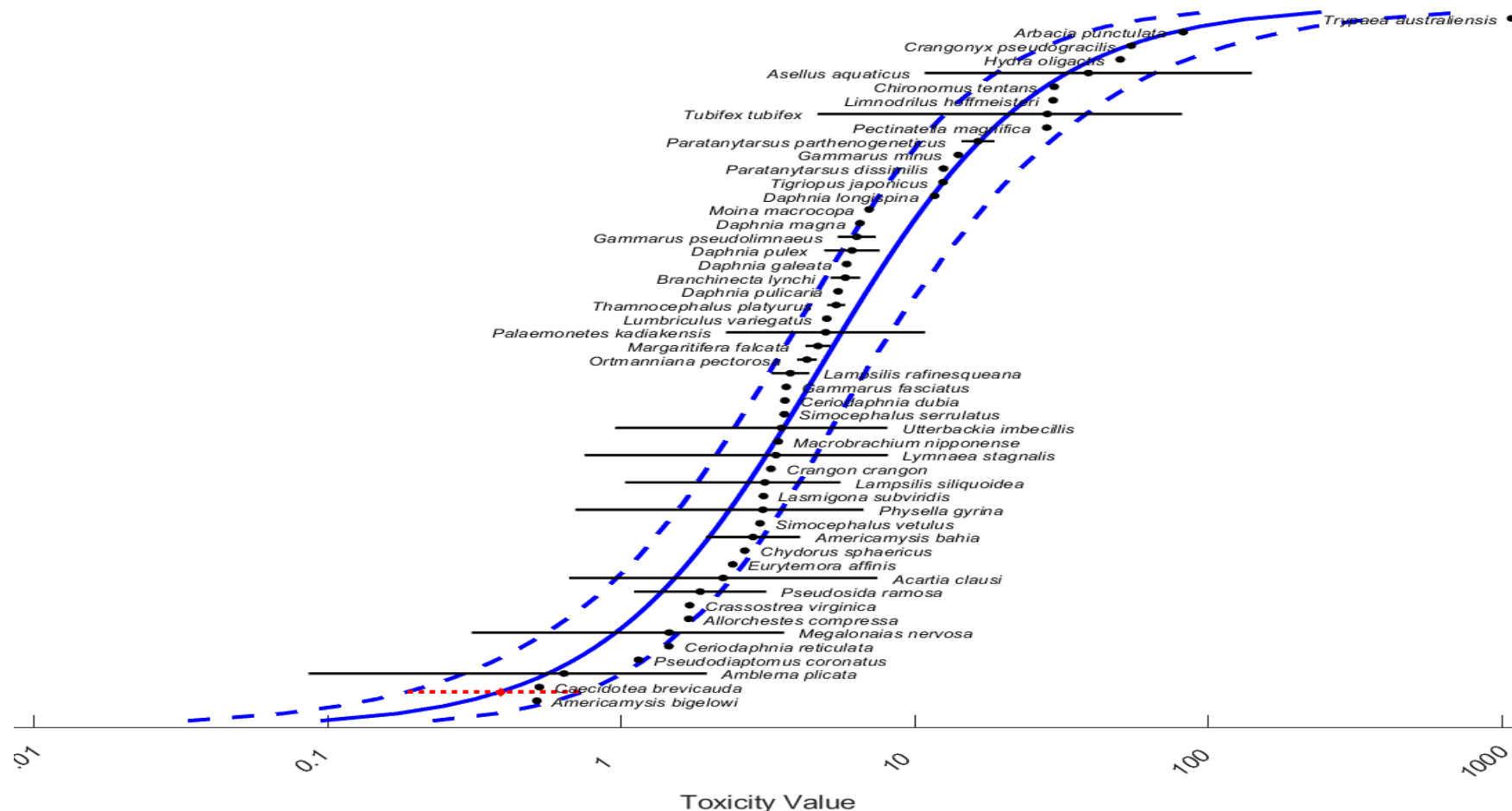


Figure 3-3. Species Sensitivity Distribution (SSD) of Acute Hazard Effects of Ethylene Dibromide on Aquatic Invertebrates
The x-axis displays empirical and estimated (Web-ICE) toxicity values (*i.e.*, LC50 or EC50 concentration in mg/L). The y-axis displays cumulative probability representing the cumulative proportion of aquatic invertebrate species affected by ethylene dibromide exposure. The horizontal black lines indicate the range of toxicity values for each species, with the black dot on that line indicating the geometric mean of the toxicity values. The dotted blue lines indicate the 95% confidence interval; the dotted red line indicates the 5% hazard concentration (HC05 = 0.40 mg/L).

3.2.2.2 Weight of Scientific Evidence for Acute Aquatic Invertebrate COC

The weight of scientific evidence suggests that ethylene dibromide poses acute hazard to invertebrate animals at 190 µg/L. EPA has robust confidence in this hazard threshold. Table_Apx F-1 summarizes the confidence for each environmental hazard threshold for exposure to ethylene dibromide. The Agency considered all acute invertebrate studies characterized in this draft assessment/TSD; however, the hazard threshold was derived using ecologically-relevant endpoints that were of sufficient quality with overall quality determination ratings of high or medium as rated by the systematic review data quality evaluation. For a more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence levels, see Appendix F. The quality of the database of studies included three high- or medium-quality studies that consistently resulted in LC50s between 3.61 mg/L ([Kszos et al., 2003](#)) and 83 mg/L ethylene dibromide ([Kennedy, 1994](#)). These three studies were all conducted with reasonable dose-response designs and well-reported results, which enabled precise LC50 calculations (Table 3-2). These hazard effects were supplemented with 77 predicted values for 48 invertebrate species calculated through Web-ICE and represents both freshwater and marine species.

EPA used a probabilistic technique (SSD) to derive an acute COC that is protective of 95% of the taxa in the aquatic invertebrate community by incorporating hazard values across species and habitats. The Agency has robust confidence in the SSD with empirical data from 4 species and predicted data from 47 species that inhabit both freshwater and marine environments. These data also include common test species (e.g., *D. magna*) and less common species (e.g., *H. oligactis*), thereby enhancing EPA's confidence that the COC is protective of a range of species. Limitations of an SSD include its reliance on model species that may not exist or interact in the same ecological community and are weighted equally. Web-ICE predicted the toxicity of ethylene dibromide for *Cloeon dipterum* to be several orders of magnitude lower than any other invertebrate species, which heavily influenced the invertebrate COC since the shape of the data distribution that is fitted to the effects data is dependent on the three or four lowest values ([Newman et al., 2000](#)). Although this species appears to be an outlier, Web-ICE models relative toxicity based on existing toxicity data. In the case of *C. dipterum*, the toxicity value was based on a vertebrate surrogate. However, many invertebrate species were added to the SSD based on vertebrate surrogates and were not outliers.

Vertebrate species were also added to the invertebrate SSD based on invertebrate surrogates. The *C. dipterum* toxicity value met the quality criteria (see Appendix E.1), and the SSD model was a good fit for the data. Therefore, EPA decided to leave the outlier in the model and report the conservative COC. Another assumption that may limit the scope of SSD inference is whether the number of species used is adequate. The minimum number needed to fit a distribution is eight ([Etterson, 2020b](#)). Because EPA only had empirical data for four invertebrate species, Web-ICE was used to add surrogate LC50 data from additional species to the SSD distributions. However, adding modeled data also adds additional variation and epistemic uncertainty. Notwithstanding the limitations of SSD analyses, this method is widely used and accepted in risk assessments ([Raimondo et al., 2010](#)). The Logistic distribution carried most of the BICc weight (100%); therefore, EPA used the hazard concentration from the model with the best statistical fit. The Agency has robust confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the acute aquatic invertebrate COC for ethylene dibromide at 190 µg/L.

3.2.3 Chronic Aquatic Vertebrates

Chronic fish hazard data for ethylene dibromide of either high or medium quality (Table 3-3) were identified in two studies for one freshwater species—Japanese medaka (([Holcombe et al., 1995](#)) and ([Hawkins et al., 1998](#))). Another reference was identified while preparing this draft assessment but did

not undergo systematic review: Battalora et al. (1990) was unable to establish a dose-response relationship with ethylene dibromide exposure and lymphoma in Japanese medaka, thus EPA did not conduct systematic review.

In a 28-day study on larval Japanese medaka, which utilized measured ethylene dibromide concentrations of 1.50, 2.52, 5.81, 9.62, and 20.3 mg/L, Holcombe et al. (1995) reported a NOEC and LOEC based on mortality of 9.62 and 20.3 mg/L, respectively. A chronic value (ChV) of 7.48 mg/L was also derived for growth (*i.e.*, wet weight) from the reported NOEC and LOEC of 5.81 and 9.62 mg/L, respectively. Since an acute exposure was also conducted by the authors (96-hour LC50 was 32.1 mg/L; see Table 3-1), an ACR was calculated at 4.3.

Hawkins et al. (1998) also conducted several experiments that evaluated the effects of ethylene dibromide exposure on Japanese medaka. The mortality, reproduction, and carcinogenicity data received a low overall quality determination rating because the chemical exposure was inconsistent in the three treatment groups. Specifically, the 18.58 mg/L mean measured treatment group was exposed to ethylene dibromide for 24 hours every 7 days while the other treatment groups were continuously exposed. The nominal concentrations in the 6.20 mg/L mean measured treatment group were lowered by 25% on day 44 of the study and again by an additional 25% on day 46 due to excessive mortality. Ethylene dibromide exposure in the 6.20 mg/L treatment group ceased on day 73, while the other treatment groups were exposed through day 97. Notably, one of the control groups was contaminated with ethylene dibromide (*i.e.*, mean, measured concentrations were 0.034 mg/L during the exposure), thus making reported endpoints and study conclusions difficult to interpret and possibly inappropriate. Additionally, the proportion of hatched embryos in the control groups was very low.

Another experiment conducted by Hawkins et al. (1998) found that Japanese medaka exposed to 1 mg/L of ethylene dibromide for 14 and 38 days had a statistically significant increase in GST activity when compared to control fish. This suggests that the livers in the exposed Japanese medaka are attempting to neutralize ethylene dibromide toxicity through metabolism.

Although the MOA is discussed at length above in Section 2.4.6 for mammals, EPA was unable to identify many studies that evaluated MOA in other vertebrates, specifically for aquatic taxa. Guobaitis et al. (1986) was unable to determine if ethylene dibromide was mutagenic or carcinogenic in the oyster toadfish (*Opsanus tau*) or the American eel (*Anguilla rostrata*). However, given the conservative nature of the metabolic pathways associated with ethylene dibromide exposure and how critical CYP2E1 and GST pathways are for xenobiotic metabolism in fish and other vertebrates, it is likely that aquatic taxa are also able to similarly metabolize ethylene dibromide (see Section 2.4.6).

5218 **Table 3-3. Chronic Aquatic Vertebrate Toxicity of Ethylene Dibromide**

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Japanese medaka (<i>Oryzias latipes</i>)	28-day NOEC/LOEC	9.62/20.3 mg/L	Mortality (larvae)	Holcombe et al. (1995) (High)
	28-day NOEC/LOEC/ChV	5.81/9.62/7.48 mg/L	Growth (wet weight; larvae)	
Japanese medaka (<i>Oryzias latipes</i>)	14-day LOEC	1 mg/L	GST activity	Hawkins et al. (1998)
	38-day LOEC	1 mg/L	GST activity	(Medium)
	≈97-day NOEC/LOEC ^a	0.13/6.20 mg/L	Hepatocellular neoplasms, cholangiocellular neoplasms	Hawkins et al. (1998) (Low)
	≈97-day NOEC/LOEC ^a	6.20/18.58 mg/L	Gall bladder neoplasms	
ChV = chronic value; LOEC = lowest-observable-effect concentration; NOEC = no-observed-effect concentration ^a Exposure duration varied between treatment groups: the control groups and 0.13 and 18.58 mg/L treatment groups were exposed for 97 days whereas the 6.20 mg/L treatment group was exposed for 73 days.				

3.2.3.1 Dietary Chronic Aquatic Vertebrates

5219 EPA reviewed one high-quality study for toxicity of dietary exposure to aquatic vertebrates (Table 3-4).
5220 Hendricks ([1995](#)) found increased neoplasms in both the liver and the stomach of rainbow trout that
5221 consumed a diet of 2,000 mg/kg dry weight ethylene dibromide when compared to the control group.
5222 The liver weights were slightly higher in the exposed fish relative to the control fish but did not affect
5223 the overall weight of the fish. A higher incidence of neoplasms was also observed in male trout (41%)
5224 versus females (21%) at 78 weeks.
5225

5226 **Table 3-4. Aquatic Vertebrate Toxicity of Ethylene Dibromide via Dietary Exposure**

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	18-month NOEC	2,000 mg/kg dry weight diet	Growth (body weight; juvenile)	Hendricks et al. (1995) (High)
	18-month LOEC	2,000 mg/kg dry weight diet	Growth (liver weight; juvenile)	
LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration				

3.2.3.2 Chronic Aquatic Vertebrate COC

5228 EPA reviewed three high- or medium-quality studies for chronic toxicity in aquatic vertebrates (Table
5229 3-3 and Table 3-4). The only species with chronic exposure to ethylene dibromide in water was the
5230 Japanese medaka. While a ChV for growth was determined to be 7.48 mg/L ([Holcombe et al., 1995](#)),
5231 this species does not represent the sensitivity observed in other vertebrate species as demonstrated by the
5232 empirical acute data. Additionally, using this ChV would result in a chronic vertebrate COC of
5233 0.748 mg/L or 748 µg/L (using an assessment factor of 10), which results in a COC less sensitive than
5234 the acute vertebrate COC of 0.55 mg/L (or 550 µg/L). Based on the medaka data alone, fish are more
5235 sensitive to chronic exposure than acute exposure. If chronic data were available for other species, such
5236 as the fathead minnow or sheepshead minnow, the chronic COC would likely be at least an order of
5237 magnitude lower than 0.748 mg/L as calculated from the medaka data; thus using the medaka data to
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calculate the chronic vertebrate COC would not be protective of other vertebrate species that are known to be more sensitive under acute exposures. Therefore, EPA used an ACR (10 for neutral organic chemical exposure to fish ([U.S. EPA, 2013](#))) to estimate chronic exposure toxicity to the most acutely sensitive vertebrate species (*i.e.*, fathead minnow LC50 was 4.3 mg/L) and applied an assessment factor of 10 (therefore the chronic vertebrate COC = 4.3 mg/L ÷ (ACR of 10 ÷ assessment factor of 10) = 0.043 mg/L or 43 µg/L). Although an ACR of 4.3 was established by Holcombe et al. ([1995](#)) for the Japanese medaka, this ACR does not necessarily represent the ratio for all vertebrate species, EPA used the standard ACR of 10 for neutral organic chemicals, which is the classification that includes ethylene dibromide. EPA acknowledges that the actual chronic vertebrate COC might be somewhere between 43 and 748 µg/L but selected the most sensitive COC to screen for potential risk. Using an ACR accounts for the uncertainty of extrapolating acute fathead minnow mortality data to various endpoints (*e.g.*, reproduction or growth) measured under chronic exposure durations. Applying an assessment factor accounts for uncertainty that fathead minnows are the most sensitive species under chronic exposure or that laboratory fish respond similarly when exposed to ethylene dibromide in the environment. Although there are many uncertainties due to the general lack of data for characterizing chronic vertebrate hazard resulting from ethylene dibromide exposure, the use of an ACR and assessment factor was a conservative screening hazard approach used to determine whether there may be potential environmental risk.

3.2.3.3 Weight of Scientific Evidence for Chronic Ethylene Dibromide Exposures to Aquatic Vertebrates

The weight of scientific evidence suggests that ethylene dibromide poses chronic hazard to aquatic vertebrate species at 43 µg/L. EPA has slight confidence in the hazard threshold, and Table_Apx F-1 summarizes the confidence for each environmental hazard threshold for exposure to ethylene dibromide. The Agency considered all chronic vertebrate studies characterized in this draft assessment/TSD; however, the hazard threshold was derived using an ecologically-relevant endpoint (*i.e.*, mortality) that was of sufficient quality with an overall quality determination rating of high or medium as rated by the systematic review data quality evaluation. For a more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence levels, see Appendix F.

EPA has slight confidence in the hazard threshold for five reasons. First, the reasonably available database of studies used for this determination includes one high-quality study to determine growth or reproduction effects using standard methods. Since this study was conducted with the most tolerant species within the empirical acute data available and almost the most tolerant species when predicted data from Web-ICE was included, there was only slight confidence in using this study to base the COC upon. Additionally, the chronic COC using these data was higher than the calculated acute vertebrate COC. However, using the acute data from the most sensitive species available within the empirical data and applying an ACR and an assessment factor, helped increased the confidence that the COC reflected a more sensitive species despite the data gap. Second, this study was conducted on a single species (*i.e.*, the Japanese medaka) (Table 3-3). Third, it found survival and growth effects within the same order of magnitude of ethylene dibromide concentrations. Fourth, this study was conducted with a reasonable dose-response design and results, which enabled precise estimations of effect concentrations. Finally, EPA decided to calculate the chronic vertebrate COC using the acute COC and applying an ACR and an assessment factor. This allowed EPA to utilize empirical acute data from a more sensitive vertebrate species. EPA considered a number of alternative methods to calculate the chronic COC (*e.g.*, taking the acute vertebrate COC, multiplying by an acute assessment factor, applying an ACR, and applying a chronic assessment factor [$550 \text{ µg/L} \times 5 \div 10 \div 10 = 28 \text{ µg/L}$] and applying an assessment factor of 100 to the only chronic study [$7.48 \text{ mg/L} \div 100 = 0.0748 \text{ mg/L} = 74.8 \text{ µg/L}$] and arrived at a similar chronic vertebrate COC). Thus, EPA has slight confidence in the quality, consistency, strength and precision,

and relevance of the studies used in determining the chronic aquatic vertebrate COC for ethylene dibromide to be 43 µg/L.

3.2.4 Chronic Aquatic Invertebrates

No studies were identified during systematic review that examined the chronic toxicity of ethylene dibromide to aquatic invertebrates.

3.2.4.1 Chronic Aquatic Invertebrate COC

Because no studies were identified for chronic toxicity in aquatic invertebrates, EPA used an ACR (10 for neutral organic chemical exposure to daphnids ([U.S. EPA, 2013](#))) to estimate chronic exposure toxicity to the most acutely sensitive invertebrate species (*i.e.*, *C. dubia* LC50 was 3.61 mg/L) and applied an assessment factor of 10 (*i.e.*, chronic invertebrate COC = 3.61 mg/L ÷ [ACR of 10 ÷ assessment factor of 10] = 0.0361 mg/L or 36.1 µg/L). Using an ACR accounts for the uncertainty of extrapolating acute *C. dubia* mortality data to various endpoints (*e.g.*, reproduction or growth) measured under chronic exposure durations. Applying an assessment factor accounts for uncertainty that *C. dubia* are the most sensitive species under chronic exposure or that laboratory organisms respond similarly when exposed to ethylene dibromide in the environment. Although there are many uncertainties due to the general lack of data for characterizing chronic invertebrate hazard resulting from ethylene dibromide exposure, the use of an ACR and assessment factor was a conservative screening hazard approach used to determine whether there may be potential environmental risk.

3.2.4.2 Weight of Scientific Evidence for Chronic Ethylene Dibromide Exposures to Aquatic Invertebrates

The weight of scientific evidence suggests that ethylene dibromide poses a chronic hazard to invertebrate species at 36.1 µg/L. EPA has slight confidence in the hazard threshold, and Table_Apx F-1 summarizes the confidence for each environmental hazard threshold for exposure to ethylene dibromide. The Agency considered all chronic invertebrate studies characterized in this technical support document; however, the hazard threshold was derived using an ecologically relevant endpoint (*i.e.*, mortality) that was of sufficient quality with an overall quality determination rating of high or medium as rated by the systematic review data quality evaluation. For a more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence levels, see Appendix F

EPA has slight confidence in the hazard threshold for five reasons. First, the reasonably available database of studies used for this determination did not include any chronic data on invertebrates. Second, the consistency between chronic studies could not be evaluated. Third, the biological significance of chronic effects could not be determined in invertebrates. Fourth, a dose-response could not be evaluated across or within studies to determine precise estimations of effect concentrations. Finally, no data were available to determine chronic effects to invertebrates. Therefore, EPA decided to calculate the chronic aquatic invertebrate COC using the acute aquatic invertebrate COC and applying an ACR and an assessment factor to fill the data gap. This allowed EPA to utilize empirical acute data from the most sensitive invertebrate species. EPA considered a number of alternative methods to calculate the chronic COC (*e.g.*, taking the acute invertebrate COC, multiplying by an acute assessment factor, applying an ACR, and applying a chronic assessment factor) and arrived at a similar chronic invertebrate COC (190 µg/L × 5 ÷ 10 ÷ 10 = 9.5 µg/L). Thus, EPA has slight confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the chronic aquatic invertebrate COC for ethylene dibromide to be 36.1 µg/L.

3.2.5 Aquatic Plants

EPA reviewed one uninformative study and one mechanistic study for ethylene dibromide toxicity in aquatic plants (Table 3-5). LAB Research Ltd. (2010c) was determined to be uninformative primarily because test concentrations were not maintained during the exposure, with concentrations in all treatment groups reported as below detection at the end of the study. Erickson and Hawkins (1980) evaluated radiolabeled ¹⁴C uptake in estuarine phytoplankton and found no significant effects at nominal ethylene dibromide concentrations of 0.5, 1.0 and 2.0 mg/L, indicating ethylene dibromide concentrations up to 2.0 mg/L do not affect photosynthesis in estuarine phytoplankton.

Table 3-5. Aquatic Plant Toxicity of Ethylene Dibromide

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Unicellular green alga (<i>Pseudokirchneriella subcapitata</i>)	72-hour EC50	<4.48 mg/L	Growth rate	LAB Research (2010c) (Uninformative)
	72-hour NOEC/LOEC	1.79/2.48 mg/L	Growth rate	
	72-hour EC50	<4.48 mg/L	Yield	
	72-hour NOEC/LOEC	1.79/2.48 mg/L	Yield	
	72-hour EC50	<4.48 mg/L	Biomass	
	72-hour NOEC/LOEC	1.33/1.79 mg/L	Biomass	
EC50 = effective concentration that induces a biological response to 50% of test organisms; LOEC = lowest-observed-effect concentration; NOEC = no-observed-effect concentration				

3.3 Terrestrial Species Hazard

EPA identified 87 terrestrial toxicity studies as potentially relevant for quantitative assessment. EPA assigned an overall quality determination rating of high, medium, or low to 54 acceptable studies, and 33 studies were determined to be uninformative. Of the acceptable studies reviewed by EPA, relevant terrestrial toxicity data were identified across taxa (vertebrates, invertebrates, plants, and fungi) from 11 terrestrial toxicity studies as the most relevant for quantitative assessment and deriving various hazard thresholds. Appendix I contains additional information about low and uninformative studies that were not used to derive hazard thresholds.

Terrestrial toxicity studies may have complex experimental designs to accommodate a wider variety of environmental conditions and taxa, as compared to aquatic toxicological studies. Certain experimental design decisions that result in an inability to discern exposure to ethylene dibromide and/or direct effects resulting from ethylene dibromide exposure may not be relevant for consideration. Specifically, as a reflection of ethylene dibromide's previous use as a pesticide (*i.e.*, fumigant), a subset of the identified studies focused on how crop species were generally positively affected as a result of ethylene dibromide exposure through the direct toxicological effects on parasitic nematodes that fed on the root systems of various crops. Many of these studies did not report direct effects on the nematodes, nor had proper controls that would allow for distinction of reported effects on the observed species. Additionally, due to this historical use, many identified studies reported results in terms of units and conditions specific to field applications as a fumigant (*e.g.*, soil injections), and/or dosing of ethylene dibromide was conducted in a manner (*e.g.*, 1-time applications) which make it difficult to determine the actual concentrations/doses of ethylene dibromide to which organisms were exposed. For instance, studies where ethylene dibromide was administered as part of a mixture (*e.g.*, with other pesticides, or part of a pesticidal product) were omitted from further discussion because this type of release is not a relevant or realistic environmental exposure to ethylene dibromide from releases in scope of this draft risk

assessment/TSD. Finally, when possible, EPA converted units to allow for comparative analysis to be done across studies; however, the Agency included studies in the discussion below in which unit conversions were not possible (e.g., doses/concentrations reported as an application rate that are specific to a product and type of crop application need).

3.3.1 Terrestrial Vertebrates

EPA identified 11 vertebrate studies (5 avian and 6 mammalian) which contained relevant endpoints for environmental assessment. Some studies included multiple endpoints, species, and test durations. In six studies, effects from ethylene dibromide exposure were observed (e.g., cellular, reproductive, biochemical, growth, and physiological) but were not determined to be statistically significant as compared to control groups ([Courtens et al., 1980](#); [Eljack and Hrudka, 1979](#); [Broda et al., 1976](#); [Amir and Volcani, 1965](#)). EPA assigned an overall quality determination rating of medium to one of the studies, while all others received an overall quality determination rating of low. In addition to the studies that underwent data quality evaluation and extraction processes specific to studies containing environmental hazard data (*Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#))), EPA also reviewed data from laboratory rodent studies to identify potentially relevant data for the characterization of environmental hazard for wild mammalian populations, while acknowledging that some exposure designs for laboratory rodent studies may be designed for specific human exposure scenarios. Specifically, results from rodent studies that utilized data quality evaluation methods for characterizing human health hazard (*Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#))) were considered by EPA to characterize toxicological effects in wild mammalian and avian populations resulting from ethylene dibromide exposure via inhalation. Inhalation was primarily evaluated because air exposure is considered to be the predominant route of exposure for terrestrial organisms due to the release profile of ethylene dibromide, potential for long-range transport, photolytic half-life, and general low bioaccumulation potential according to the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)).

3.3.1.1 Mammalian Species

EPA used ecologically-relevant endpoints from human health laboratory rodent model organisms to establish a hazard threshold for terrestrial mammals. Toxicological effects observed in mammalian taxa resulting from ethylene dibromide are characterized and assessed across multiple health outcomes (e.g., reproduction, development, and mortality) and multiple exposure routes (e.g., oral, inhalation, and injection) and are summarized in Table 3-6 through Table 3-8. Additional endpoints from mammalian studies are further described above in Sections 2.3 and 2.4 for the characterization of human health hazard.

3.3.1.1.1 Oral Exposure

Acute

Although oral exposure is not considered by EPA to be a major exposure pathway due to low bioaccumulation potential (Section 4.6 in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#))), hazard effects resulting from the ingestion of ethylene dibromide were characterized and used for extrapolation of avian inhalation hazard thresholds (discussed below in Section 3.3.1.2). As shown in Table 3-6, mortality health outcomes were measured in male and female Fischer rats following a single oral dose of ethylene dibromide administered by gavage over a range of doses (40 to 320 mg/kg-bw) ([Dow Chemical, 1992a](#)). Effects of lethargy were observed for all animals across all doses over a 2-week observation period following exposure, and palpebral closure and rapid shallow breathing occurred in animals starting at exposure doses of 80 mg/kg-bw. Sex-specific mortality hazard values were reported by the authors, and EPA used the geometric mean to derive an LD50 hazard value of 124.2 mg/kg-bw (male LD50: 116 mg/kg-bw, female

LD50: 133 mg/kg-bw) ([Dow Chemical, 1992a](#)). EPA assigned an overall quality determination rating of high to this study. In additional acute gavage studies where rats were exposed to a similar concentration of ethylene dibromide (*i.e.*, 110 mg/kg) increased serum sorbitol dehydrogenase and increased relative liver weight were observed ([Nachtomí, 1980](#); [Nachtomí et al., 1968](#)), as well as liver lesions including granular degeneration of cytoplasm, sinusoidal dilation, and necrosis of the central and midzone liver lobules ([Broda et al., 1976](#)). In addition to significantly increased relative liver weight in both sexes, significantly increased adrenal weights for female rats were also observed at 110 mg/kg ethylene dibromide administered via gavage ([Nachtomí et al., 1968](#)).

Chronic

From the available chronic data for oral exposure of mammals to ethylene dibromide, a significant reproductive effect of testicular atrophy was observed in male Osborne-Mendel rats exposed to 38 mg/kg/day for 5 days/week for 49 weeks via gavage ([NCI, 1978](#)). Additional effects include squamous cell carcinoma of the stomach and degenerative lesions in the adrenal cortex and are discussed in further detail in Section 2.4.3, Section 2.4.7.1.2, and listed in Table_Apx A-16. EPA assigned an overall quality determination rating of medium to this study.

Although empirical data for potential hazard were characterized above, acute and chronic hazard thresholds were not established for mammalian taxa exposed to ethylene dibromide through oral exposure routes since environmental releases as characterized in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)) are unlikely to result in the presence of ethylene dibromide in food items. Trophic transfer of ethylene dibromide is not currently considered to be the predominant exposure route of concern.

Table 3-6. Terrestrial Mammalian Toxicity of Ethylene Dibromide via Oral Exposure

Test Organism	Route of Administration (Duration)	Endpoint	Hazard Value ^{a b}	Effect(s)	Citation (Overall Quality Determination)
Fischer rat	Gavage (single dose) (Acute)	1-day LD50	124.2 mg/kg-bw ^{a b}	Mortality	Dow Chemical (1992a) (High)
Rat	Gavage (single dose) (Acute)	20-hour LOAEL	110 mg/kg-bw	Liver weight, adrenal weight	Nachtomí et al. (1968) (Medium)
Rat	Gavage (single dose) (Acute)	No Statistical Analysis	110 mg/kg-bw	Histological (liver lesions including granular degeneration of cytoplasm, sinusoidal dilation, and necrosis of the central and midzone liver lobules)	Broda et al. (1976) (Low)
Osborne-Mendel rat	Gavage (multiple dose) (Chronic)	49-week (5 days/week) LOAEC	38 mg/kg-bw/day	Reproduction (testicular atrophy)	NCI (1978) (Medium)
Cattle	Oral via multiple routes (milk, oil, capsule) (Acute)	No statistical analysis was conducted	2–4 mg/kg-bw/day	Decreased sperm density and motility, sperm structural alterations	Amir and Volcani (1965) (Low)

Test Organism	Route of Administration (Duration)	Endpoint	Hazard Value ^{a b}	Effect(s)	Citation (Overall Quality Determination)
Cattle	Oral via capsule (Acute)	No statistical analysis was conducted	4 mg/kg-bw/day	Decreased motility, sperm structural alterations	Amir and Ben David (1973) (Uninformative)
LD50 = dose that is lethal to 50% of test organisms; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level ^a Geometric mean across sex. ^b EPA estimated hazard value used to derive avian inhalation hazard (for additional details see Appendix G).					

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3.3.1.1.2 Inhalation Exposure

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Acute

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From the available studies, mortality, reproductive, and developmental health outcomes were identified for mammalian species resulting from ethylene dibromide exposure via inhalation and are shown below in Table 3-7. Reproductive and developmental effects were identified in mice exposed to a range of measured doses (0, 20, 38, and 80 ppm) of ethylene dibromide via inhalation chamber for 23 hours/day starting day 6 of gestation and continuing for 10 days ([Short et al., 1978](#)). Fetal skeletal malformations and lower bodyweights were identified in pups exposed to 20 ppm of ethylene dibromide *in utero*. Dams exposed to 20 ppm also had significantly decreased bodyweights and increased late-gestation resorptions of fetuses. Mortality was observed in dams starting at 38 ppm of ethylene dibromide. The author-reported 20 ppm LOAEC was standardized by EPA to 150 mg/m³ by multiplying by the molecular weight of 187.86 g/mol of ethylene dibromide and dividing by the molar volume (assuming a molar volume of an ideal gas of 24.45 at 25 °C and 1 atm). EPA assigned an overall quality determination rating of high for this study. In addition to the study discussed above by Short et al. ([1978](#)), another study reviewed by EPA identified toxicity via inhalation for hepatic effects in rats exposed to 10 ppm of ethylene dibromide ([Nitschke et al., 1981](#)).

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Although an LC50 endpoint for mortality was not available for rodent studies, EPA was able to derive an acute 4-hour LC50 hazard value for inhalation of 2.12 mg/L from rats exposed to ethylene dibromide vapor based on author reported data ([Rowe et al., 1952](#)). In this study, rats were exposed to a range of concentrations (0.77–77 mg/L) over a range of exposure durations (1.2 minutes to 16 hours) where total number of deaths were recorded. At higher exposure concentrations, deaths usually occurred within 24 hours and resulted from cardiac or respiratory failure. At lower concentrations, delayed death was observed over a period of 12 days and were often the result of pneumonia. Weight loss was also observed. EPA assigned an overall quality determination rating of medium for this study. Using author reported inhalation data in Table 3 of Rowe et al. ([1952](#)), EPA was able to estimate a mortality hazard value. This was carried out in accordance with Haber's Law which states that for a concentration of a poisonous gas ($C^n \times t = k$, where C is the concentration of the gas, t depicts the time necessary to inhale the gas, and k is a constant dependant on both the gas and effect) ([Haber, 1924](#)). In cases where the relationship between concentration and time is not linear, n depicts a chemical-specific constant. To estimate mortality based on reported data, exposure concentration and duration were converted to a Ct value by multiplying concentration (C) by time (t), allowing a 4-hour LC50 for inhalation exposure to be interpolated. This was done using the drc R package for dose-response analysis ([Ritz et al., 2015](#)). For additional information see Appendix G.

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In addition to the acute studies discussed above for inhalation exposure to ethylene dibromide, EPA reviewed other acute mammalian studies which reported toxicity to ethylene dibromide via inhalation

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across a range of concentrations (0.43–80 ppm) and effects (*i.e.*, neurotoxicity, growth, reproduction) (Koptagel and Bulut, 1998; Smith and Goldman, 1983; Nitschke et al., 1981; Short et al., 1979; Rowe et al., 1952). These studies are discussed in more detail in Section 2.3.2.2.

Chronic

Chronic health outcomes were identified in mammals exposed to ethylene dibromide via inhalation, including a reproductive effect in F344 rats exposed to a range of concentrations (0, 10, or 40 ppm) for 6 hours/day, 5 days/week for 103 weeks (NTP, 1982). Testicular degeneration in male rats was observed to occur via inhalation at 10 ppm of ethylene dibromide. The author-reported 10 ppm LOAEC was standardized by EPA to 77 mg/m³ by multiplying by the molecular weight of 187.86 g/mol of ethylene dibromide and dividing by the molar volume (assuming a molar volume of an ideal gas of 24.45 at 25 °C and 1 atm). In addition to testicular degeneration, other effects identified include hepatic necrosis, retinal atrophy, adrenal cortical degradation, as well as adenocarcinomas and carcinomas of the nasal cavity. Please see Section 2.3.1 and Section 2.4.1 for further details. EPA assigned an overall quality determination rating of high for this study. In another study where F344 rats were exposed to 10 ppm ethylene dibromide for 6 hours/day, 5 days/week for 13 weeks, elevated absolute liver weight was observed in females, and hyperplasia of the respiratory epithelium of the nasal turbinates was observed in males and females (Nitschke et al., 1981), further supporting the above findings.

In addition to the chronic studies discussed above for inhalation exposure to ethylene dibromide, EPA reviewed other chronic rodent studies which report toxicity to ethylene dibromide via inhalation for a range of concentrations (3–1,660 ppm) and effects (*i.e.*, nutrition, growth, reproduction) (Adkins et al., 1986; NTP, 1982; Wong et al., 1982; Short et al., 1979). These studies are listed in Table 3-7 and discussed in more detail in Section 2.3.2.3.

Table 3-7. Terrestrial Mammalian Toxicity of Ethylene Dibromide via Inhalation Exposure

Test Organism	Duration	Endpoint ^a	Hazard Value ^{b c}	Effect(s)	Citation (Overall Quality Determination)
Rat	Acute	4-hour LC50	2.12 mg/L ^b	Mortality	Rowe et al. (1952) (Medium)
Mouse	Acute	10-day LOAEC	20 ppm ^c	Reproduction (fetal skeletal malformations, reduced body weight in dams and offspring, late-gestation resorptions of fetuses)	Short et al. (1978) (High)
Rat	Acute	18-day (4 hours/day, 3 day/week), NOEL	0.43 ppm	Neurological/behavioral	Smith and Goldman (1983) (High)
Rat	Acute	6 hours/ day, 5 days/week for 13 weeks, LOEL	10 ppm	Mechanistic (hepatic)	Nitschke et al. (1981) (High)
Rat	Acute	7 hours/day, 5 days/week for 10 weeks, LOAEL	89 ppm	Reproduction (reduced fertility, testes weight, testosterone serum concentration)	Short et al. (1979) (High)

Test Organism	Duration	Endpoint ^a	Hazard Value ^{b c}	Effect(s)	Citation (Overall Quality Determination)
Rat	Acute	7 hours/day, 5 days/week for 10 weeks, LOAEL	39 ppm	Nutrition/metabolic	Short et al. (1979) , (High)
Rat	Chronic	6 hours/day, 5 days/week for 103 weeks, LOAEC	10 ppm ^c	Reproduction (testicular degeneration, hepatic necrosis, retinal atrophy, adrenal cortical degradation, adenocarcinomas, carcinomas of the nasal cavity)	NTP (1982) (High)
Rat	Chronic	7 hours/day, 5 days/week for 18 months, LOAEL	20 ppm	Mortality, adenoma, fibroadenoma, carcinoma, adenocarcinoma	Wong et al. (1982) (High)
Mouse	Chronic	6 hours/day, 5 days/week for 6 months, LOAEC	20 ppm	Pulmonary adenoma	Adkins et al. (1986) (High)
Rat	Acute	3-hour LOAEL	1,660 ppm	Respiration	Koptagel and Bulut (1998) (Uninformative)
LC50 = concentration that is lethal to 50% of test organisms; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level; LOEL = lowest-observed-effect level; NOEL = no-observed-effect level ^a Inhalation route of administration was whole body chamber. ^b EPA estimated hazard value used to derive avian inhalation hazard ^c Bolded hazard values were used to establish mammalian hazard thresholds.					

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3.3.1.1.3 Other Exposure Routes

5503 Hazard was characterized for additional studies reviewed by EPA which utilized exposure routes other
5504 than oral or inhalation and are listed below in Table 3-8. Amir et al. (1983) observed reproductive
5505 toxicological effects in domesticated rams (*Ovis aries*) that received a single 1-mL peritesticular
5506 injection of 430 mg ethylene dibromide (LOEL). Following injection, the rams exhibited acute sperm
5507 abnormalities, including elongated and elongating spermatids, however pre-meiotic stages of
5508 spermatogenesis were not affected. Furthermore, a study conducted via subcutaneous injections of 7.8 to
5509 13.5 mg/kg/day of ethylene dibromide into 18- to 30-month-old rams over 12 days was found to induce
5510 transient teratospermia including acrosome abnormalities, however statistical significance was not
5511 determined (Eljack and Hrudka, 1979). Because injection is not a relevant exposure pathway for
5512 environmental exposure, these studies were considered for hazard characterization but were not used to
5513 establish hazard thresholds. EPA assigned an overall quality determination rating of medium to both
5514 studies.
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Table 3-8. Terrestrial Mammalian Toxicity of Ethylene Dibromide via Other Exposure Routes

Test Organism	Route of Administration (Duration)	Endpoint	Hazard Value ^a	Effect(s)	Citation (Overall Quality Determination)
Sheep	Injection (Acute)	No statistical analysis was conducted	13.5 mg/kg/day	Teratospermia, sperm structural abnormalities	Eljack and Hrudka (1979) (Medium)
Sheep	Injection (Acute)	Single-dose injection per testis LOEL	430 mg ^a	Reproduction (sperm structural abnormalities)	Amir et al. (1983) (Medium)
Cattle	Injection (Acute)	No statistical analysis was conducted	110–120 mg/animal	Decreased motility, sperm structural alterations	Amir and Ben David (1973) (Uninformative)
LOEL = lowest-observed-effect level					
^a Author-reported hazard values					

3.3.1.1.4 Mammalian Hazard Thresholds

EPA derived mammalian hazard thresholds based on inhalation exposure routes that are likely to result from environmental releases discussed in Sections 5 and 8 of the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)).

Mammalian inhalation studies were selected to derive hazard thresholds based on ecologically relevant hazard values that are also consistent with PODs identified for different exposure durations and routes for human health hazard. Oral exposure is unlikely to be a source of significant environmental exposure because ethylene dibromide is unlikely to undergo bioconcentration and bioaccumulation according to the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#)). Thus, mammalian acute and chronic oral hazard thresholds were not established, however, mammalian oral hazard values were used to derive an estimated avian inhalation LD50 (as discussed below).

Shown below in Table 3-9, mammalian inhalation hazard thresholds were 150 mg/m³ for acute exposure and 77 mg/m³ for chronic exposure. These hazard thresholds were identified based upon the relevancy of inhalation for environmental exposure, and available studies with overall quality determination ratings of high, indicating confidence in the weight of scientific evidence for these findings ([NTP, 1982](#); [Short et al., 1978](#)).

Table 3-9. Mammalian Hazard Thresholds for Ethylene Dibromide

Test Organism	Route of Administration (Duration)	Endpoint	Hazard Value ^a	Hazard Threshold ^b	Effect	Citation (Overall Quality Determination)
Mouse	Inhalation (Acute)	LOAEC	20 ppm	150 mg/m ³	Reproduction (fetal skeletal malformations, reduced body weight in dams and offspring, late-gestation resorptions of fetuses)	Short et al. (1978) (High)
Rat	Inhalation (Chronic)	LOAEC	10 ppm	77 mg/m ³	Reproduction (testicular degeneration)	NTP (1982) (High)
LOAEC = lowest-observed-adverse-effect concentration ^a Author-reported units ^b EPA standardized to units of mg/m ³						

3.3.1.2 Avian Species

EPA reviewed five studies that contained ecologically relevant endpoints resulting from ethylene dibromide exposure ([Náprstková et al., 2005](#); [Náprstková et al., 2003](#); [Dusek et al., 2001](#); [Westlake et al., 1981](#); [Alumot et al., 1968](#)) with overall quality determinations of high or medium and one study with an overall quality determination of low ([Broda et al., 1976](#)). Toxicological effects observed in avian taxa resulting from ethylene dibromide are characterized and assessed across multiple health outcomes (e.g., mortality, development, growth, and reproduction) and exposure routes (e.g., oral and injection) and are summarized in Table 3-10 and Table 3-11. Of these, two studies were most relevant for quantitative assessment.

3.3.1.2.1 Oral Exposure

Acute

Mortality health outcomes were identified in 28-day old female Japanese quail (*Coturnix japonica*) following oral exposure to ethylene dibromide via gavage administered over 72 hours, resulting in an LD50 of 130 mg/kg-bw (43.3 mg/kg/day across 72 hours) ([Westlake et al., 1981](#)). Dyspnea, diarrhea, lethargy, asthenia and reduced body weight were also observed in quail starting at 6 hours post exposure, with death occurring over 7 to 72 hours. Surviving quail returned to normal body weight and symptoms resolved 3 days post-exposure to ethylene dibromide. In an additional, range-finding study where ethylene dibromide was administered twice daily in pure corn oil via gavage, mortality health outcomes were reported by the authors at an LC50 hazard value of 11.1 mg/day (converted by EPA to LC50 = 141.3 mg/kg/day by dividing by average study-reported weight of the organism of 0.0786 kg) for a slightly longer duration of 5 days in 28-day old Japanese quail ([Westlake et al., 1981](#)). In addition to mortality studies, sublethal studies were conducted and body weight, relative liver weight (measured as g/100 g body weight), total lipid, total protein, glucose, glutamate dehydrogenase (GDH), cholinesterase (ChE), aspartate aminotransferase, CYP were measured in liver and plasma at exposure concentrations of 65 mg/kg-bw ethylene dibromide. Acetylcholinesterase (AChE) in the brain, sorbitol dehydrogenase (SDH) in plasma, and hemoglobin were also measured. Significantly decreased hepatic total lipid, total protein and aspartate aminotransferase activity were also observed in quail exposed to 65 mg/kg-bw ethylene dibromide via gavage 24 hours post-exposure, while aspartate aminotransferase activity was significantly elevated in plasma. EPA assigned an overall quality determination rating of medium to these studies.

Chronic

In addition to acute studies discussed above, Westlake et al. (1981) conducted chronic studies in Japanese quail exposed to 3.7 mg/day ethylene dibromide via gavage and found increased relative liver weight after 7 days, and a significant reduction in total lipid levels in liver, aspartate aminotransferase, and increased ChE after 21 days.

Alumot et al. (1968) observed chronic reproductive health outcomes in one-day-old chickens (*G. gallus domesticus*) exposed to ethylene dibromide via dietary exposure for approximately 25 weeks, specifically significantly reduced egg weight. The authors reported an approximate 25-week LOEL of 40 ppm diet which was converted by EPA to 2.68 mg/kg-bw/day by estimating an average body weight of a chicken (1.245 kg) based on Isa et al. (2020), and daily ingestion amounts of 0.067 kg/day based on ingestion rates for non-passerine birds (U.S. EPA, 1993b). Feed per body weight was calculated and then multiplied by 40 ppm. While the authors reported that feed intake of the treatment group was equal to that of the control group, and no growth depression was observed, the study only reported an approximate duration of exposure and the amount of ethylene dibromide in the fumigated mash that was fed to the birds was not adequately quantified, introducing uncertainty in the reported results. Because the chickens started the study as 1-day old chicks and the study ended when the chickens were approximately 25 weeks of age, the estimated values for conversion to standardized units does not account for changes in feed intake over time.

EPA assigned an overall quality determination rating of medium to this study. In addition, Alumot et al. (1968) examined the growth rate and sexual development of 3-day-old male chicks that were fed mash fumigated with 150 and 300 ppm ethylene dibromide *ad libitum* for 12 weeks. After 6 weeks, reduced feed intake resulted in significantly reduced weight gain starting at 150 ppm ethylene dibromide exposure, however after 12 weeks, this effect was only significant in the 300-ppm treatment group. In a separate trial where male chicks were exposed via diet for 12 weeks at 80 and 180 ppm ethylene dibromide and feed intake of the control group was normalized to the highest treatment group, there were no significant effects on weight gain at 6 and 12 weeks for both treatment groups, suggesting the effect on weight gain is due to reduced food intake rather than ethylene dibromide toxicity. The authors also measured bromine content of the testes, spermatozoa, and testes weight in male animals sacrificed at 3 months and reported no significant effects (but found high individual variation) on sexual development or sperm characteristics across treatment groups. For a subset of males in the treatment group exposed *ad libitum* to 150 and 300 ppm ethylene dibromide, exposure was continued until 12 months of age, at which point the animals were sacrificed. After 12 months of exposure, the authors reported significantly reduced comb weight—a secondary sexual characteristic and indicator of androgen function, which was dose-dependent.

In a separate dietary study, Alumot et al. (1968) evaluated reproductive effects in one-year-old, artificially inseminated hens fed fumigated mash containing 100 ppm ethylene dibromide for four weeks. The authors did not report feeding conditions (*ad libitum* or restricted) for this study. Although statistical analyses were not conducted, the authors reported a 71% reduction in egg number and 28% reduction in egg weight compared to controls. Eggs from treated hens were infertile, with a fertilization rate of 12.5% and no embryo survival, compared with an 85.7% fertilization rate in the control. In an additional, prolonged dietary exposure of mature males to 300 ppm (equivalent to 7 mg/kg-bw/day) ethylene dibromide for up to 10 weeks found no significant difference between control and treatment group in sperm volume, density, or motility. Semen was pooled and used to artificially inseminate laying hens, and no significant differences were observed in the fertilization rate or egg hatchability between hens inseminated with semen from control versus treated males. Collectively, the results of these studies suggest that 100 ppm ethylene dibromide dietary exposure in females may be associated with decreased

fertilization rate and embryo viability, whereas 300 ppm dietary exposure of males to ethylene dibromide has no effect on sperm viability. In addition, ethylene dibromide exposure may have sex-specific differences in reproductive sensitivity. The absence of observed effects on cock sperm at 7 mg/kg-bw/day contrasts with findings from mammalian studies, where changes in sperm characteristics were reported in bulls exposed to 2 mg/kg-bw/day ethylene dibromide via diet ([Amir and Volcani, 1965](#)).

Table 3-10. Terrestrial Avian Hazard Values for Ethylene Dibromide via Oral Exposure

Test Organism	Route of Administration (Duration)	Endpoint	Hazard Value	Effect(s)	Citation (Overall Quality Determination)
Japanese quail (<i>Coturnix japonica</i>)	Oral via capsule (single dose) (Acute)	72-hour LD50	43.3 mg/kg/day	Mortality	Westlake et al. (1981) (Medium)
	Gavage (multiple dose) (Acute)	5-day LC50	141.3 mg/kg/day	Mortality	
	Oral via capsule (single dose) (Acute)	24-hour LOEL	65 mg/kg bw	Hemoglobin, Aspartate aminotransferase	Westlake et al. (1981) (High, Medium)
	Gavage (multiple dose) (Chronic)	7-day LOEL	550 mg/kg diet	Increased relative liver weight	
	Gavage (multiple dose) (Chronic)	21-day LOEL	550 mg/kg diet	Decreased hepatic total lipid	
Chicken (<i>Gallus gallus domesticus</i>)	Gavage (single dose) (Acute)	Not reported	110 mg/kg-bw	Cellular (increased hepatic eosinophilic granulocytes)	Broda et al. (1976) (Low)
	Dietary, fumigated mash (Chronic)	≤25-week LOEL	2.68 mg/kg-bw/day	Reproduction (egg weight)	Alumot et al. (1968) (Medium)
LC50 = concentration that is lethal to 50% of test organisms; LD50 = dose that is lethal to 50% of test organisms; LOEL = lowest-observed-effect level					

3.3.1.2.2 Inhalation Exposure

Acute

No avian studies were available for acute toxicity from ethylene dibromide. Because of the physical and chemical properties of ethylene dibromide, inhalation is a likely route of environmental exposure for terrestrial organisms (Section 4.6 in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#))). Due to the lack of available empirical toxicity data, STIR was used to model acute inhalation hazard for avian taxa exposed to ethylene dibromide ([U.S. EPA, 2010](#)). Empirical mortality data consisting of an LD50 of 124.2 mg/kg-bw for rats exposed to ethylene dibromide orally and a single-dose oral exposure to Japanese quail of 130 mg/kg-bw were used as inputs into STIR ([Dow Chemical, 1992a](#); [Westlake et al., 1981](#)). Empirical mammalian data for acute inhalation toxicity (discussed above in Section 3.3.1.1.1) was used by EPA to derive an acute 4-hour LC50 hazard value for inhalation of 2.12 mg/L (converted by EPA to 2,120 mg/m³) from rats exposed to ethylene dibromide. This was done based on author-reported data presented in Rowe et al. ([1952](#)). STIR estimated an acute avian adjusted inhalation LD50 of 13.87 mg/kg-bw. Although mortality is not the most sensitive endpoint for assessing toxicity to ethylene dibromide, this endpoint was chosen for

predicting acute avian inhalation toxicity because of EPA's confidence in the data quality, congruence with available empirical oral mortality endpoints from rats and birds, and consistency of effect concentrations. Further details describing the methodology used to derive the LD50 for avian acute exposure via inhalation are available in Appendix G.

Chronic

No chronic inhalation studies for birds were reasonably available. The oral hazard values discussed above were not used to model and predict chronic avian inhalation hazard due to uncertainties in the duration of exposure and amount of ethylene dibromide in the fumigated mash that was fed to the birds. In addition, other endpoints for consistent effects across mammalian and avian species for chronic studies are lacking. Given the lack of chronic data and uncertainty in the existing study, EPA could not estimate a chronic hazard value for avian inhalation using STIR, which requires oral endpoints from both avian and mammals, as well as an inhalation endpoint from mammals.

3.3.1.2.3 Other Exposure Routes

Studies considered by EPA and characterized for hazard via other exposure routes (*i.e.*, injection) are listed below in Table 3-11. Ten-day-old chicken embryos were exposed to a single dose of ethylene dibromide via intraamniotic injection, resulting in a significant increase in mesonephroi malformation and significant decrease in mesonephroi weight (LOEL = 300 µg) (Náprstková et al., 2003). EPA assigned an overall quality determination rating of high to this study. Congruent with the previous study, nephrotoxic effects were observed in chick embryos injected at embryonic day 3 with ethylene dibromide at lowest observed effect levels of 300 µg (Náprstková et al., 2005). Nephrotoxicity was evidenced by significantly reduced mesonephric vascularization and delayed functional maturation of the embryonic kidney at embryonic day 10. EPA assigned an overall quality determination rating of medium to this study. In another study examining the effects of ethylene dibromide on chicken embryos found that intraamniotic injection of 100 µg administered as early as embryonic day 3 induced significant embryotoxicity (Dusek et al., 2001). Mortality and developmental effects (*e.g.*, malformation) occurred within 24-hours post exposure. EPA assigned an overall quality determination rating of high to this study. Although intraamniotic injection is not considered by EPA to be an environmentally relevant exposure pathway, the results of these studies indicate that ethylene dibromide exposure may induce significant adverse impacts on developing embryos for avian taxa.

In addition to the gavage studies characterized above, Westlake et al. (1981) exposed Japanese quail via interperitoneal injection of 65 mg/kg-bw ethylene dibromide and quail were killed via exsanguination after 24 hours. At 65 mg/kg-bw, significantly increased relative liver weight, increased hepatic glucose, and decreased GDH and total lipid were measured in quail. Effects measured in liver (total protein, aspartate aminotransferase, CYP), plasma (hemoglobin, total lipid, SDH, aspartate aminotransferase), and brain (AChE) were not significantly different.

5682 **Table 3-11. Terrestrial Avian Hazard Values for Ethylene Dibromide via Other Exposure Routes**

Test Organism	Exposure Route (Duration)	Endpoint	Hazard Value	Effect(s)	Citation (Overall Quality Determination)
Chicken (<i>Gallus gallus domesticus</i>)	Injection (Acute)	Single-dose injection, LOEL/NOEL	300 µg/egg / 100 µg/egg	Development (nephrotoxicity)	Náprstková et al. (2003) (High)
	Injection (Acute)	Single-dose injection, LOEL	300 µg/egg	Growth (delayed functional maturation of the embryonic kidney)	Náprstková et al. (2005) (Medium)
	Injection (Acute)	Single-dose injection, LOAEL	100 µg/egg	Development (embryotoxicity)	Dusek et al. (2001) (High)
Japanese quail (<i>Coturnix japonica</i>)	Injection (Acute)	24-hour LOEL	65 mg/kg-bw	Liver (increased relative liver weight, glucose, decreased GDH, total lipid)	Westlake et al. (1981) (High, Medium)
		24-hour NOEL	65 mg/kg-bw	Liver (total protein, AT, cytochrome P-450), plasma (hemoglobin, total lipid, glucose, SDH, AT), brain (AChE)	

LOAEL = lowest-observed-adverse-effect level; LOEL = lowest-observed-effect level; NOEL = no-observed-effect level

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5684 3.3.1.2.4 Avian Hazard Thresholds

5685 In accordance with the methods outlined in Section 3.1.2.2, allometric scaling conducted using STIR
5686 was used to estimate acute avian inhalation toxicity from empirical avian oral and mammalian inhalation
5687 and oral toxicity values. Based on these estimates, a hazard threshold for mortality was derived of
5688 13.87 mg/kg-bw. This hazard threshold was converted to 2.0 µg/m³ for comparison to air release values
5689 using Equation 3-1, where inhalation rate is calculated based on guidance reported in the *Wildlife*
5690 *Exposure Factors Handbook for non-passerine birds* ([U.S. EPA, 1993b](#)), a continuous exposure
5691 duration is assumed over one year of 8,760 hours (based on daily air releases estimated in the *Draft*
5692 *Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* ([U.S. EPA, 2026b](#))), and
5693 using an average body weight for Japanese quail of 0.0786 kg as reported by Westlake et al. ([1981](#)). The
5694 assumptions for calculating an inhalation rate for Japanese quail are shown in Table 3-12, and the
5695 estimated hazard threshold is shown in Table 3-13.

5696 Equation 3-1. Converting Hazard Value Units

$$\text{HED (mg/kg)} = \text{HEC (mg/m}^3\text{)} \times ([\text{hourly inhalation rate (m}^3\text{/hour)} \times \text{exposure duration (hours)}]) \div \text{body weight [kg]}$$

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Table 3-12. Assumptions for Estimating Inhalation Rates for Japanese Quail

Test Organism	Assumption	Calculation	Value	Source
Japanese quail (<i>Coturnix japonica</i>)	Exposure duration	Continuous exposure = 365 days × 24 hours	8,760 hours	N/A
	Hourly inhalation rate (IR) for non-passerine birds	IR = 0.4089 (0.0786 ^{0.77})	0.058 m ³ /hour	U.S. EPA (1993b)
	Body weight	Author-reported	0.0786 kg	Westlake et al. (1981)

Table 3-13. Avian Hazard Threshold for Ethylene Dibromide

Test Organism	Exposure Route	Endpoint	Hazard Value ^a	Hazard Threshold ^b	Effect	Citation (Overall Quality Determination)
Japanese Quail (<i>Coturnix japonica</i>)	Inhalation (Acute)	LD50	13.87 mg/kg-bw	2.0 µg/m ³	Mortality	N/A
LD50 = dose that is lethal to 50% of test organisms ^a Units reported as modeled by STIR ^b EPA standardized units to be consistent with how air concentrations of ethylene dibromide are presented in the <i>Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide</i> (U.S. EPA, 2026b).						

3.3.1.3 Weight of Scientific Evidence for Terrestrial Vertebrate Hazard Thresholds

For the overall confidence in the hazard thresholds, EPA considers the evidence for acute and chronic terrestrial mammals robust, and the evidence for acute terrestrial birds to be moderate. Table_Apx F-1 summarizes the confidence for each environmental hazard threshold for exposure to ethylene dibromide. The Agency considered all terrestrial studies characterized in this technical support document; however, the hazard thresholds (terrestrial vertebrates and invertebrates) were derived using ecologically-relevant endpoints that were of sufficient quality with overall quality determination ratings of high or medium as rated by the systematic review data quality evaluation. For a more detailed explanation of the weight of scientific evidence, uncertainties, and overall confidence levels, see Appendix F.

Mammals

In lieu of available terrestrial wildlife mammalian studies, human health model organisms (*e.g.*, rat, mouse, rabbit) were used to determine the most sensitive and environmentally relevant ethylene dibromide concentrations that affected apical endpoints (*e.g.*, mortality, reproduction, growth) which could serve as an indication of hazard effects in wild mammalian populations resulting from ethylene dibromide releases being characterized in this draft assessment/TSD.

In weighing scientific evidence, the available data suggests that ethylene dibromide poses acute inhalation hazard to terrestrial mammals at 150 mg/m³. EPA has robust overall confidence in this hazard threshold because the quality and consistency of the database included four high-quality studies (using human health animal model organisms) for two terrestrial species (rats and mice) across similar endpoints (*i.e.*, NOAEC/NOAEL, LOAEC/LOAEL) ([Smith and Goldman, 1983](#); [Nitschke et al., 1981](#); [Short et al., 1979](#); [Short et al., 1978](#)). Effect concentrations were measured from 10 to 80 ppm ethylene dibromide. All the studies were conducted with reasonable dose-response designs and results, and effect concentrations were within one order of magnitude, indicating consistency in results. As this hazard threshold represents an unbounded LOAEC (*i.e.*, no corresponding NOAEC was identified), it may

underestimate the hazard threshold for mammals via inhalation, introducing uncertainty in whether the acute inhalation threshold for mammals is sufficiently protective. For the acute mammalian assessment, the apical endpoints used were mortality, reproduction, development, growth effects from available data. Although the studies were conducted in the laboratory environment, EPA considered studies where ethylene dibromide was administered as a fumigant, which is representative of an environmentally relevant pathway of inhalation. Furthermore, an acute study in rams in which ethylene dibromide was administered via peritesticular injection reported reproductive effects including sperm abnormalities ([Amir et al., 1983](#)). Although this study was not used quantitatively, it corroborates evidence from rodent studies demonstrating that ethylene dibromide can induce reproductive toxicity.

The weight of scientific evidence suggests that ethylene dibromide poses chronic inhalation hazard to terrestrial mammals at 77 mg/m³. EPA has robust confidence in this hazard threshold because the quality of the database of studies included five high quality studies with similar endpoints (*i.e.*, NOAEL, LOAEC, LOAEL) ([Adkins et al., 1986](#); [NTP, 1982](#); [Wong et al., 1982](#); [Nitschke et al., 1981](#); [Short et al., 1979](#)). Effect concentrations were measured from 10 to 39 ppm ethylene dibromide. Four of the studies were conducted with reasonable dose-response designs and results, while the study by Wong et al. ([1982](#)) reported only one exposure concentration. The effect concentrations were within one order of magnitude, indicating consistency in results. As this hazard threshold represents an unbounded LOAEC (*i.e.*, no corresponding NOAEC was identified), it may not provide a hazard threshold that is truly protective of mammals exposed to ethylene dibromide via air releases, introducing uncertainty in the chronic inhalation threshold for mammals. Chronic apical endpoints (*i.e.*, mortality, reproduction) were used for quantitative assessment. Although the studies were conducted in the laboratory environment, EPA considered studies where ethylene dibromide was administered as a fumigant, which is biologically relevant as it is representative of an environmental pathway of inhalation.

Avian

The weight of scientific evidence suggests that ethylene dibromide poses acute inhalation hazard to terrestrial birds at a hazard threshold of 2.0 µg/m³. EPA has moderate confidence in this hazard threshold. Empirical data for avian toxicity to ethylene dibromide via inhalation were not reasonably available. Although four terrestrial avian studies were identified as containing potentially relevant environmental toxicity data, two of the studies utilized egg injections as the exposure pathway, which is not considered by EPA to be an environmentally relevant route of exposure to ethylene dibromide and so were not used for quantitative assessment. The remaining two studies utilized gavage as the main exposure pathway. The Agency used available empirical oral exposure data for birds, in addition to empirical oral and inhalation toxicity data from rats, to predict an inhalation hazard threshold for acute exposure for birds. Therefore, EPA has slight confidence in the quality of the database used to predict avian inhalation toxicity due to the lack of avian inhalation studies.

Across exposure routes in birds and mammals, there is consistency in endpoints and sex-specific sensitivities to ethylene dibromide. For oral exposure studies used to predict the avian inhalation hazard threshold, there is congruence in mortality LC50, ranging from 130 mg/kg-bw in Japanese quail ([Westlake et al., 1981](#)) to 124.2 mg/kg-bw (geometric mean of LD50s of 116 mg/kg-bw for males and 133 mg/kg-bw for females) in rats ([Dow Chemical, 1992a](#)). Two studies indicate sex-specific differences in sensitivity in rats ([Dow Chemical, 1992a](#); [Rowe et al., 1952](#)). Mortality, as an apical endpoint, was used for quantitative assessment both because of data availability but also because of its potential impact on population level effects. Because of the robust consistency of the database across mammalian studies, EPA is confident in using mammalian oral and inhalation toxicity data for read across in estimating the avian inhalation threshold. The avian inhalation hazard threshold was predicted using Japanese quail as a surrogate species. While species-specific sensitivity to ethylene dibromide may

vary across avian taxa, confidence in the threshold is supported by STIR modeling and consistent empirical evidence from rat inhalation and oral studies and avian oral toxicity data.

3.3.2 Terrestrial Invertebrates

Terrestrial invertebrate hazard data for ethylene dibromide were identified for 12 medium- and high-rated studies in arthropods and nematodes for a range of effects (*i.e.*, mortality, reproduction, development, growth) and exposure routes (*i.e.*, fumigation, ground injection) and are listed below in Table 3-14. In addition to the invertebrate studies listed in Table 3-14, studies in which EPA assigned an overall quality determination rating of low or uninformative are listed in Appendix I. EPA reviewed two high-quality studies and seven studies with overall quality determination ratings of medium using varying arthropod species. Terrestrial invertebrate hazard data identified for nematode species consisted of two high-quality studies and one medium-quality study. Five additional studies were identified but were not used due to confounding variables. The focus of the studies were crop growth due to the historical use of ethylene dibromide as a pesticidal agent targeting invertebrate pests and/or ethylene dibromide was presented as a part of a mixture making it difficult to discern ethylene dibromide-specific effects to terrestrial invertebrates ([Johnson and Leonard, 1995](#); [McDonald and De Waele, 1987](#); [Minton et al., 1985](#); [Touhcton and Rodriguez-Kabana, 1985](#); [Broadley, 1979](#)). The studies used for hazard characterization and analysis were based on exposure to ethylene dibromide alone; studies where ethylene dibromide was administered as part of a mixture were not considered further.

As shown in Table 3-14, terrestrial invertebrate hazard data for ethylene dibromide identified by EPA for invertebrate arthropods included reproductive and mortality health outcomes. In a high-quality study, reproductive health outcomes, including reduced productivity, were observed in adult lesser grain borers (*Rhyzopertha dominica*) at a LOEL of 1.4 mg/L after a 24-hour exposure ranging from nominal doses of 0.40 to 1.60 mg/L via fumigation to ethylene dibromide and was not observed to stabilize by the end of the 35-day post-exposure observation period ([Rajendran and Shivaramaiah, 1985](#)). In addition, mortality was observed for eight arthropod studies with LD50 hazard values across a range of 0.11 to 143.9 mg/L, as shown below in Table 3-14. The most sensitive hazard concentration, an LD50 of 0.11 mg/L, was measured after a 2-hour exposure of Caribbean fruit fly, *Anastrepha suspensa*, eggs to ethylene dibromide via fumigation, where egg hatch was observed for 48 hours following exposure with and without the presence of grapefruit rind ([Brueck and Burditt, 1977](#)). The presence of the rind in the fumigation chamber decreased the sensitivity of the eggs to ethylene dibromide. EPA assigned this study an overall quality determination rating of medium.

In rust-red flour beetle eggs (*Tribolium castaneum*), mortality occurred in organisms fumigated with ethylene dibromide (ranging across nominal concentrations of 0.20–0.80 mg/L) for 24-hours at a LD50 hazard value of 0.736 mg/L (LD95 = 1.114 mg/L) for 1-day old eggs, LD50 hazard values of 0.519 mg/L (LD95 = 0.776 mg/L) for 2-day old eggs, and LD50 hazard values of 0.476 mg/L (LD95 = 0.638 mg/L) for 3-day old eggs ([Rajendran and Muthu, 1989](#)). Surviving organisms were followed until they reached the adult life stage to examine potential toxic effects for subsequent metamorphic stages. EPA assigned an overall quality determination rating of high to this study. Additional studies of medium quality, which identified mortality in arthropod species via fumigation exposure, include studies of cowpea weevils (*Callosobruchus chinensis*), where egg and larval lifestages were found to be the most sensitive (LD50 = 0.243 mg/L for eggs, 0.499 mg/L for larvae, 1.047 mg/L in pupae, and 5.649 mg/L in adults) after a 24-hour exposure duration; however, exposure concentrations were not reported in the study ([Adu and Muthu, 1985](#)). LD90 hazard values of 23.67 and 23.25 mg/L inside and above a grain mass, respectively, were measured in adult lesser grain borers (*Rhyzopertha dominica*) and 24.66 and 26.76 mg/L inside and above a grain mass, respectively, were found for adult rice moths (*Corcyra cephalonica*), where both species were fumigated with nominal concentrations (10–30 mg/L) of

ethylene dibromide ([Bowry, 1985b](#)). Mortality in 5-hour fumigation exposures of adult rusty grain beetles (*Cryptolestes ferrugineus*) ranged from LD50 hazard values of 0.245 mg/L in males to 0.475 mg/L in females indicating potential sex-specific differences, however exposure concentrations were not reported by the authors ([Barker, 1976](#)).

Bains et al. ([1976](#)) measured mortality effects (LD50 = 143.9 mg/L) in skin beetle (*Trogoderma granarium*) larvae in diapause and fumigated with ethylene dibromide for 7 days, indicating that larvae in diapause are much more resistant to ethylene dibromide fumigation than non-diapause larvae. In this study, skin beetle larvae were exposed to nominal concentrations of ethylene dibromide ranging from an author-reported 32.58 to 217.20 g/m³. Studies for two mite species (*Tyrophagus putrescentiae* and *Caloglyphus krameri*) indicated mortality at a LD50 of 0.3 mg/L for both species via 48-hour fumigation exposures, where five exposure concentrations were used although specific amounts were not reported by the authors ([Muthu et al., 1970](#)). In the adult weevil (*Sitophilus granarius*), using both a London wild normal strain and a London wild resistant strain (selected for 67 generations for resistance to ethylene dibromide fumigation), mortality was measured at predetermined time intervals following a 5-hour exposure to ethylene dibromide and ranged from LC50 hazard values of 1.46 µL/L (20-day post-exposure) in the normal strain to 3.97 µL/L (7-day post-exposure) in the resistant strain, though exposure concentration ranges were not reported by the authors ([Ellis, 1972a](#)). These author-reported LD values were converted by EPA to 3.17 and 5.97 mg/L, respectively, using a density of 2.172 g/mL for ethylene dibromide.

In addition to apical effects, mechanistic (*i.e.*, genotoxicity) effects were identified for terrestrial invertebrate taxa from supplemental references which did not undergo data evaluation and extraction. Fruit fly (*Drosophila melanogaster*) embryos were exposed to gaseous ethylene dibromide at concentrations ranging from 0.26 to 200 ppm. Mutations in fruit fly progeny were observed starting at 1 ppm ethylene dibromide ([Kale and Baum, 1983](#)). Sex-linked recessive lethal mutations were induced in males ([Fouremen et al., 1994](#); [Kramers et al., 1991](#); [Kale and Baum, 1979b](#)), and there is evidence that premeiotic stages may be more sensitive than postmeiotic ([Kale and Baum, 1979a](#)). In female fruit flies, effectiveness for the induction of interchromosomal recombination was found to be decreased, and the glutathione-mediated pathway was identified as a major cause of genotoxicity upon exposure to ethylene dibromide ([Ballerling et al., 1993](#)). Ballerling et al. ([1994](#)) found evidence for genotoxic effects through modification at ring nitrogens in DNA, specifically, the N-adducts could be directly miscoding resulting in non-coding lesions and/or misrepair.

Terrestrial invertebrate hazard data for nematode taxa identified health outcomes of development/growth and are shown below in Table 3-14. Lack of standardized units, likely due to studies being conducted in the field environment, prevented some comparative and quantitative analysis among studies. In a multi-year study, peanut root-knot nematodes (*Meloidogyne arenaria*) infesting peanut (*Arachis hypogaea* L.) crops were exposed to a yearly application of two nominal doses of ethylene dibromide, 8.4 and 16.8 L/ha, via injection at a depth of 20 cm into natural soil ([Rodríguez-Kábana and King, 1985](#)). Following exposure, larval nematode populations were significantly reduced (LOEL = 8.4 L/ha) at peanut maturity compared to the untreated control. EPA assigned an overall quality determination rating for this study of high. In another study, soybean cultivars infested with the root-knot nematode (*Meloidogyne* spp.) and the nematode (*Heterodera glycines*) were exposed to nominal 0.68 mL/m of ethylene dibromide via injection into natural soil at the time of planting, resulting in significantly reduced root-knot nematode juvenile populations for some of the cultivars but did not affect juvenile nematodes (*H. glycines*) in a 167-day study ([Rodríguez-Kábana et al., 1987](#)). EPA assigned an overall quality determination rating for this study of high. Northern root-knot nematode populations (*Meloidogyne hapla*) were found to be significantly decreased when exposed to nominal concentrations of ethylene dibromide starting at 70

5879 kg/ha; however, soil depth and composition were not reported ([Stirling and Wachtel, 1985](#)). EPA
5880 assigned an overall quality determination rating of medium for this study.
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Table 3-14. Terrestrial Invertebrate Toxicity of Ethylene Dibromide

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Lesser grain borer (<i>Rhyzopertha dominica</i>)	24-hour LOEL/NOEL	1.4 mg/L / 1.2 mg/L	Reproduction	Rajendran and Shivaramaiah (1985) (High)
Caribbean fruit fly (<i>Anastrepha suspensa</i>)	2-hour LD50 / LD95	0.11 mg/L (0.10–0.12) ^{a b} / 0.21 mg/L (0.19–0.24) ^a	Mortality (egg; without fruit rind)	Brueck and Burditt (1977) (Medium)
	2-hour LD50 / LD95	0.31 mg/L (0.22–0.37) ^a / 0.69 (0.53–1.77) ^a	Mortality (egg; with fruit rind)	
Rust-red flour beetle (<i>Tribolium castaneum</i>)	24-hour LD50 / LD95	0.736 mg/L (0.69–0.78) ^{a b} / 1.114 mg/L (0.99–1.25) ^a	Mortality (1-day old eggs)	Rajendran and Muthu (1989) (High)
	24-hour LD50 / LD95	0.519 mg/L (0.50–0.54) ^{a b} / 0.776 mg/L (0.74–0.81) ^a	Mortality (2-day old eggs)	
	24-hour LD50 / LD95	0.476 mg/L (0.42–0.54) ^{a b} / 0.638 mg/L (0.54–0.77) ^a	Mortality (3-day old eggs)	
Cowpea weevil (<i>Callosobruchus chinensis</i>)	24-hour LD50 / LD95	0.243 mg/L (0.205–0.287) ^{a b} / 0.525 mg/L (0.395–0.697) ^a	Mortality (egg)	Adu and Muthu (1985) (Medium)
	24-hour LD50 / LD95	0.499 mg/L (0.404–0.594) ^{a b} / 1.109 mg/L (0.780–1.578) ^a	Mortality (larvae)	
	24-hour LD50 / LD95	1.047 mg/L (0.762–1.629) ^{a b} / 3.715 mg/L (2.951–4.677) ^a	Mortality (pupae)	
	24-hour LD50 / LD95	5.649 mg/L (5.483–5.821) ^{a b} / 7.798 mg/L (7.328–8.299) ^a	Mortality (adult)	
Lesser grain borer (<i>Rhyzopertha dominica</i>)	7-day LD90	23.67 mg/L (19.36–28.92) ^a	Mortality (inside grain mass)	Bowry (1985b) (Medium)
		23.25 mg/L (20.07–27.08) ^a	Mortality (above grain mass)	
Rice moth (<i>Corcyra cephalonica</i>)	7-day LD90	24.66 mg/L (22.13–31.70) ^a	Mortality (inside grain mass)	
		26.76 mg/L (21.79–34.00) ^a	Mortality (above grain mass)	
Rusty grain beetle (<i>Cryptolestes ferrugineus</i>)	5-hour LD50 / LD95	0.245 mg/L^b / 0.316 mg/L	Mortality (adult males)	Barker (1976) (Medium)
		0.475 mg/L^b / 0.655 mg/L	Mortality (adult females)	
		0.273 mg/L^b / 0.397 mg/L	Mortality (adult males)	
		0.472 mg/L^b / 0.572 mg/L	Mortality (adult females)	

Test Organism	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Skin beetle (<i>Trogoderma granarium</i>)	7-day LD50 / LD95	143.9 mg/L (118.9–174.2) ^{a,b} / 229.7 mg/L (164.1–321.6) ^a	Mortality (larvae in diapause)	Bains et al. (1976) (Medium)
Copra mite (<i>Tyrophagus putrescentiae</i>)	2-hour LD50 / LD95	0.3 mg/L^b / 0.6 mg/L	Mortality (adult)	Muthu et al. (1970) (Medium)
Mite (<i>Caloglyphus krameri</i>)	2-hour LD50 / LD95	0.3 mg/L^b / 1.2 mg/L	Mortality (adult)	
Granary weevil (<i>Sitophilus granarius</i>)	5-hour LC50	3.17 mg/L^b	Mortality (adult London wild normal strain)	Ellis (1972a) (Medium)
		5.97 mg/L^b	Mortality (adult London wild resistant strain)	
Peanut root-knot nematode (<i>Meloidogyne arenaria</i>)	2–5 growing seasons LOEL	8.4 L/ha	Population abundance	Rodríguez-Kábana and King (1985) (High)
Root-knot nematode (<i>Meloidogyne</i> spp.)	127-days LOEL	0.68 mL/m (Ransom, Centennial, Forrest, Leflore soybean cultivars)	Population abundance	Rodríguez-Kábana et al. (1987) (High)
	127-days NOEL	0.68 mL/m (Braxton, Gordon, Kirby soybean cultivars)		
Nematode (<i>Heterodera glycines</i>)	127-days NOEL	0.68 mL/m		
Northern root-knot nematode (<i>Meloidogyne hapla</i>)	6-months LOEL	70 kg/ha	Population abundance	Stirling and Wachtel (1985) (Medium)
LC50 = concentration that is lethal to 50% of test organisms; LD50 = dose that is lethal to 50% of test organisms; LD90 = dose that is lethal to 90% of test organisms; LD95 = dose that is lethal to 95% of test organisms; LOEL = lowest-observed-effect level; NOEL = no-observed-effect level ^a 95% confidence interval around the LD50 as reported by the study authors. ^b Bolded hazard values were used in SSD. See Appendix I and Table_Apx I-1 for information from studies with overall quality determinations of low and uninformative.				

3.3.2.1 Acute Terrestrial Invertebrate Hazard Threshold

The acute terrestrial invertebrate hazard threshold for ethylene dibromide was derived from an SSD that contained 2-hour to 7-day LD/LC50 values for eight arthropod species identified in systematic review and shown in Table 3-14. SSDs were derived using EPA's SSD Toolbox (v1.1) ([Etterson, 2020b](#)). All studies included in the SSD were rated high or medium quality. After reviewing the possible statistical distributions for the SSD, the multiple distributions with the Maximum Likelihood fit method had acceptable p values. The Gumbel distribution was statistically the best fit, but the Normal, Logistic, and Triangular distributions appeared to fit the data equally well at the low end of the model; therefore EPA chose to use the modeled average of these four distributions to integrate the uncertainty about which distribution is best in the calculation of confidence limits around the hazard concentration estimates. The HC05 for this modeled average distribution is 0.07 mg/L. After taking the lower 95th percentile of this HC05 as an alternative to the use of assessment factors and after unit standardization and accounting for

5895 significant figures, the acute inhalation hazard threshold for terrestrial invertebrates is 0.03 mg/L or 30
5896 mg/m³ (Figure 3-4). For additional details please see Appendix E.2.

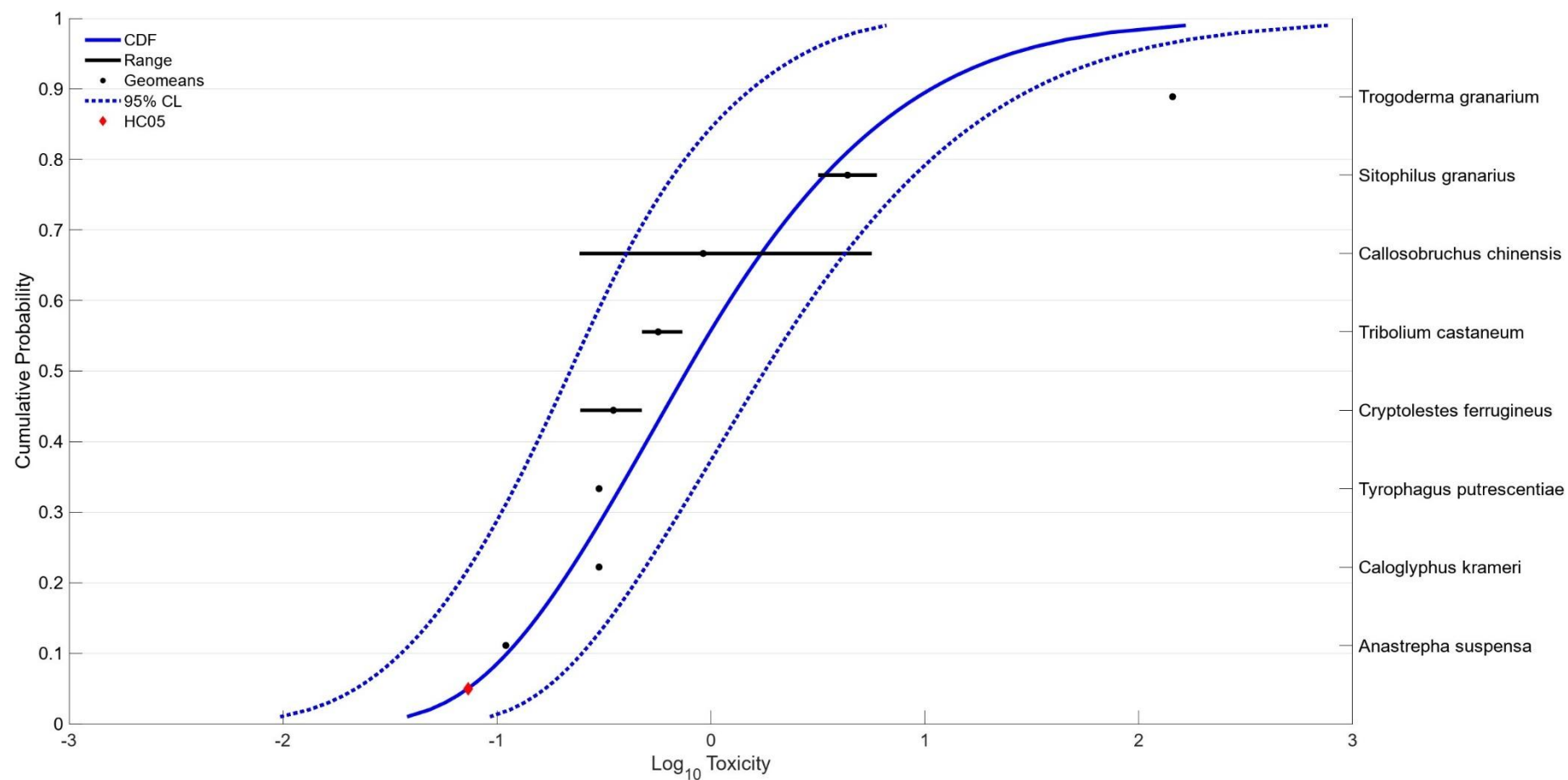


Figure 3-4. Species Sensitivity Distribution (SSD) of Acute Hazard Effects of Ethylene Dibromide on Terrestrial Invertebrates

The x-axis displays log-transformed empirical toxicity values (*i.e.*, LC50 or LD50 in mg/L). The y-axis displays cumulative probability representing the cumulative proportion of terrestrial invertebrate species affected by ethylene dibromide exposure. The horizontal black lines indicate the range of toxicity values for each species, with the black data points on that line indicating the geometric mean of the toxicity values. The dotted blue lines indicate the 95% confidence interval; the red dot indicates the 5% hazard concentration (HC05 = 0.07 mg/L). Plot created using SSD Toolbox v1.5.

3.3.2.2 Weight of Scientific Evidence for Acute Terrestrial Invertebrates

The weight of scientific evidence suggests that ethylene dibromide poses acute hazard to terrestrial invertebrates, particularly arthropod species, via fumigation exposure of 30 mg/m³. EPA has robust confidence in this hazard threshold based on a database of eight high or medium quality studies that consistently reported LD/LC50 endpoints across eight arthropod species. However, effect concentrations spanned more than three orders of magnitude, ranging from 0.11 mg/L ([Brueck and Burditt, 1977](#)) to 143.9 mg/L ethylene dibromide ([Bains et al., 1976](#)), reducing confidence in the overall consistency of the database. This variability is attributable, in part, to differences in tested lifestages, including egg, larva, pupae, and adults. Notably, Bains et al. ([1976](#)) reported that larvae in diapause were highly resistant to ethylene dibromide, measuring mortality at 143.9 mg/L, a concentration much higher than the highest LC50 reported for adults (5.649 mg/L). Despite this variability, the HC05 (0.07 mg/L) is very similar to the most sensitive identified hazard value of 0.11 mg/L ethylene dibromide for fumigated Caribbean fruit fly eggs. The eight studies containing empirical data were conducted with reasonable dose-response designs and results, which enabled precise LD/LC50 calculations.

EPA used a probabilistic technique (SSD) to derive a hazard threshold that is protective of 95% of the terrestrial invertebrates in a community by incorporating hazard values across species, lifestages, and habitats. EPA has robust confidence in the SSD with empirical data from eight species, which is the minimum number of species necessary for SSD ([Ettersson, 2020b](#)). Limitations of an SSD include its reliance on model species that may not exist or interact in the same ecological community and are weighted equally. Also, 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](#)). Another assumption that may limit the scope of SSD inference is whether the number of species used is adequate. EPA's Web-ICE Model could not be used to add surrogate mortality data from additional species to the SSD distribution because models are not available for terrestrial invertebrate taxa. Notwithstanding the limitations of SSD analyses, this method is widely used and accepted in risk assessments ([Raimondo et al., 2010](#)). Although the Gumbel distribution was the best statistical fit for the invertebrate data, utilizing the model average across Gumbel, Logistic, Normal, and Triangular distributions allows EPA to incorporate the uncertainty around the distributions and the calculation of confidence limits of the hazard concentration. The Gumbel distribution carried the majority of the Akaike Information Criterion (AICc) weight (64%), however the Logistic (16%), Normal (11%), and Triangular (9%) distributions also contributed to the average modeled hazard concentration. EPA has robust overall confidence in the quality, consistency, strength and precision, and relevance of the studies used in determining the acute terrestrial invertebrate hazard threshold (30 mg/m³ ethylene dibromide).

3.3.3 Terrestrial Plants and Fungi

For terrestrial fungi and vascular plants, EPA identified three studies with overall quality determination ratings of medium, one study had endpoints associated with medium and low overall quality determination ratings, and two studies received overall quality determination ratings of low. As noted above, because ethylene dibromide was historically used primarily as a pesticide, many studies investigating its effects on plants and fungi implemented experimental designs specific to pesticidal applications (*e.g.*, fumigation studies) and are characterized below. In addition, five studies containing information for terrestrial fungi and vascular plants in which EPA assigned an overall quality determination rating of uninformative are included in Table 3-15. Although these studies were considered by EPA, they were not used for quantitative assessment due to insufficiencies in study design or lack of statistical analysis. For additional information on low and uninformative studies, please see Appendix I.

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As shown below in Table 3-15, exposures of rice (*Oryza sativa*) to 100, 200, and 300 ppm ethylene dibromide for 4 hours resulted in significantly increased genotoxicity (chlorophyll mutation frequency) at a LOEL of 100 ppm in plants, and at a LOEL of 200 ppm in the panicle and seedling ([Suryakumari and Vaidyanath, 1989](#)). In addition, fresh weight, dry weight, and protein content of tissue culture callus (an *in vitro* assay) were significantly reduced after ethylene dibromide treatment for four weeks over a concentration range of 0.005 to 0.05%, suggesting potential effects on cellular growth and metabolism. EPA assigned an overall quality determination rating of medium to this study.

In fungi, EPA evaluated studies which included developmental (*e.g.*, growth) effects. Minimal growth retardation in three fungal species (*Aspergillus niger*, *Cladosporium herbarum*, and *Rhizopus arrhizus*) was observed at a LOEL of 15 µL/L, while no effects (NOEL = 15 µL/L) were observed in four species (*Alternaria alternata*, *Botrytis cinerea*, *Epicoccum purpurescens*, and *Monilinia fructicola*) after fungi were fumigated with ethylene dibromide for 4 hours and colony diameter was measured ([Sholberg et al., 1986](#)). EPA assigned an overall quality determination rating of medium to this study. In another study, significantly depressed development (*e.g.*, growth) was observed at a LOEL of 500 ppm (NOEL = 400 ppm) in *Arthrobotrys arthrobotryoides*, *Arthrobotrys conoides*, and *Arthrobotrys oligospora* exposed to ethylene dibromide in culture media for 15 days ([Mankau and Imbriani, 1971](#)). EPA assigned an overall quality determination rating of medium to this study. In a study of medium overall quality rating, ethylene dibromide killed 97% of microsclerotia of *Verticillium dahlia* in dry soil after a 16-day incubation at 7.5 µg a.i./g, although no statistical analysis was conducted ([Benyephet et al., 1981](#)).

In conclusion, EPA did not identify key studies for terrestrial plants and fungi for the derivation of a hazard threshold due to the lack of applicable exposure routes or pathways for environmental exposure of ethylene dibromide.

Table 3-15. Terrestrial Plants and Fungi Toxicity of Ethylene Dibromide

Test Organism	Exposure Route	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Rice (<i>Oryza sativa</i>)	Dipped or soaked	4-week LOEL	0.005–0.05%	Growth (tissue culture callus)	Suryakumari and Vaidyanath (1989) (Medium)
		4-hour LOEL	100 ppm (plants), 200 ppm (panicle, seedling)	Genotoxicity (mutation frequency)	
Fungus (<i>Aspergillus niger</i>)	Fumigation (Acute)	4-hour LOEL	15 µL/L	Growth (culture diameter)	Sholberg et al. (1986) (Medium)
Fungus (<i>Cladosporium herbarum</i>)					
Fungus (<i>Rhizopus arrhizus</i>)					
Fungus (<i>Alternaria alternata</i>)	Fumigation (Acute)	4-hour NOEL	15 µL/L	Growth (culture diameter)	
Fungus (<i>Botrytis cinerea</i>)					
Fungus (<i>Epicoccum purpurescens</i>)					
Fungus (<i>Monilinia fructicola</i>)					

Test Organism	Exposure Route	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Fungus (<i>Arthrobotrys arthrobotryoides</i> , <i>Arthrobotrys conoides</i> , <i>Arthrobotrys oligospora</i>)	Culture Medium (Chronic)	15-day NOEL/LOEL	400 ppm/500 ppm	Growth (dry weight)	Mankau and Imbriani (1971) (Medium)
Fungus (<i>Verticillium dahliae</i>)	Fumigation	No statistical analysis was conducted	7.5 µg a.i./g dry soil ^a	Reproduction (microsclerotia germination)	Benyephet et al. (1981) (Medium)
Tomato (<i>Solanum lycopersicum</i>)	Fumigation	No statistical analysis was conducted	8–16 g/m ³	Physiology (damage/injury to skin of fruit)	Spalding et al. (1978) (Uninformative)
Fungi (<i>Fusarium</i> , <i>Alternaria</i> , <i>Helminthosporium</i>)	Fumigation	No statistical analysis was conducted	32–96 mg/L	Growth (number of colonies)	Raghunathan et al. (1969) (Uninformative)
Grain (<i>sorghum bicolor</i> ssp. <i>bicolor</i>)			32–96 mg/L	Reproduction (viability)	
Aubergine (<i>Solanum melongena</i>)	Direct application	No statistical analysis was conducted	10–1,000 ppm	Growth (plumule and radicle length, number of leaves), reproduction (germination)	Tayal and Agarwal (1982) (Low)
			500 ppm	Mechanistic (amylase activity)	
Pigeonpea (<i>Cajanus cajan</i>)	Fumigation	7-day LOEL	0.29 µL/mL	Nutrition, Metabolic (protein content)	Pandey et al. (2013) (Uninformative)
		7-day LOEL	0.58 µL/mL	Reproduction (germination)	
Fungi		No statistical analysis was conducted	0.29–0.58 µL/mL	Growth (population abundance)	
Common onion (<i>Allium cepa</i>)	Hydroponic	3-hour LOEL	0.025%	Genotoxicity (DNA repair)	Suryakumari and Vaidyanath (1989) (Low)
Barley (<i>Hordeum vulgare</i>)	Direct Application (Acute)	1-day LC50	1.1 mM	Mortality	Ehrenberg et al. (1974) (Low)
		No statistical analysis was conducted	1.5 mM	Genotoxicity (chromosomal aberration, mutation)	

Test Organism	Exposure Route	Endpoint	Hazard Value	Effect	Citation (Overall Quality Determination)
Fungi ^b	Fumigation	No statistical analysis was conducted, no duration or exposure concentration were reported	Not reported	Growth	Misra et al. (1989) (Uninformative)
Purple nutsedge (<i>Cyperus rotundus</i>)	Fumigation	No statistical analysis was conducted, confounding variables	18 mL/m ²	Growth (population abundance)	Hussaini (1989) (Uninformative)

LC50 = concentration that is lethal to 50% of test organisms; LOEL = lowest-observed-effect level; NOEL = No-observed-effect level;

^a a.i. stands for active ingredient. In this study, the chemical exposure was to 12.5% ethylene dibromide.

^b *Acremonium persicinum*, *Acrophialophora fusicapna*, *Alternaria alternata*, *Aspergillus chevalieri*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus nidulans*, *Aspergillus niger niger*, *Aspergillus ochraceus*, *Aspergillus sydowii*, *Aspergillus tamarii*, *Aspergillus terreus*, *Aspergillus versicolor*, *Chaetomium biapiculatum*, *Chaetomium globosum*, *Cladosporium oxysporum*, *Cochliobolus lunatus*, *Dichotomopilus indicus*, *Gibberella moniliformis*, *Penicillium citrinum*, *Penicillium oxalicum*, *Pseudocochliobolus pallescens*, *Rhizopus oryzae*, *Talaromyces funiculosus*, and *Talaromyces purpureogenus*

3.4 Summaries and Conclusions of Environmental Hazard Assessment

3.4.1 Summary of Environmental Hazard Thresholds

After weighing scientific evidence, EPA selected a toxicity value from the integrated data to use for hazard thresholds to identify potential concerns to aquatic and terrestrial species (Table 3-16).

Table 3-16. Environmental Hazard Thresholds for Ethylene Dibromide

Receptor Group	Exposure Duration	Hazard Value	Assessment Factor	Hazard Threshold	Reference	Hazard Threshold Confidence
Aquatic vertebrates	Acute	See Table_Apx E-1 and Table_Apx E-2	N/A	550 µg/L ^b	SSD (see Section 3.2.1.1)	Robust
	Chronic	4.3 mg/L ^a	10	43 µg/L ^b	Kszos et al. (2003) (see Section 3.2.3.2)	Slight
Aquatic invertebrates	Acute	See Table_Apx E-1 and Table_Apx E-2	N/A	190 µg/L ^b	SSD (see Section 3.2.2.1)	Robust
	Chronic	3.61 mg/L ^a	10	36.1 µg/L ^b	Kszos et al. (2003) (see Section 3.2.4.1)	Slight
Terrestrial mammal (inhalation)	Acute	150 mg/m ³	N/A	150 mg/m ³	Short et al. (1978)	Robust
	Chronic	77 mg/m ³	N/A	77 mg/m ³	NTP (1982)	Robust

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Receptor Group	Exposure Duration	Hazard Value	Assessment Factor	Hazard Threshold	Reference	Hazard Threshold Confidence
Terrestrial avian (inhalation)	Acute	See Table 3-11 and Table 3-12	N/A	2.0 µg/m ³	STIR (See Section 3.3.1)	Moderate
Terrestrial invertebrates	Acute	See Table_Apx E-6	N/A	30 mg/m ³	SSD (See Section 3.3.2)	Robust
SSD = species sensitivity distribution; STIR = Screening Tool for Inhalation Risk ^a Hazard value was obtained from an acute study. An acute-to-chronic ratio (ACR) of 10 was also used to arrive at the hazard threshold, and the units were converted to µg/L. ^b Hazard threshold for aquatic organisms is called a concentration of concern (COC).						

3.4.2 Summary of Weight of Scientific Evidence for Environmental Hazard Assessment

EPA determined that ethylene dibromide poses hazards from acute and chronic exposures to aquatic vertebrates, acute and chronic exposures to aquatic invertebrates, chronic dietary exposure to terrestrial mammals, acute and chronic inhalation exposure to terrestrial mammals, acute inhalation exposure to birds, and acute and chronic inhalation exposure to terrestrial invertebrates. Table_Apx F-1 summarizes how the weight of scientific evidence considerations (quality of the database, consistency, strength and precision, biological gradient, and relevance) listed in Section 3.1.2.3 were determined for each environmental hazard threshold. Criteria for assessing confidence is described in Appendix F. EPA has robust confidence in the weight of scientific evidence in these hazard thresholds for acute aquatic invertebrates, acute aquatic vertebrates, acute and chronic terrestrial mammals, and acute terrestrial invertebrates. EPA has moderate confidence for the terrestrial avian threshold due to the number of reasonably available studies. The Agency has slight confidence in aquatic chronic exposures for both vertebrate and invertebrate species. Although there are many uncertainties due to the general lack of data for characterizing chronic vertebrate and invertebrate hazard resulting from ethylene dibromide exposure, the use of an ACR and assessment factor was a conservative screening hazard approach used to determine whether there may be potential environmental risk. The application of an ACR and assessment factor is routinely conducted for new chemical risk assessments conducted under TSCA section 5, when the database supporting a specific hazard threshold is not particularly strong in terms of data availability.

As described above in Section 3.2.3.2, there was only one chronic aquatic vertebrate study available where the effects observed for Japanese medaka were determined to not be sensitive enough to base a chronic COC for all aquatic vertebrates since the acute data demonstrated that other fish species (*i.e.*, fathead minnows) are likely to be more sensitive to ethylene dibromide exposures. There were no chronic aquatic invertebrate data identified, as explained in Section 3.2.4.1, therefore EPA also applied an ACR and assessment factor to derive a chronic aquatic invertebrate COC.

3.4.3 Environmental Hazard Assessment Conclusions

EPA considered the quality, consistency, strength and precision, biological gradient/dose response, and relevance of the reasonably available data to weigh the scientific evidence in determining the environmental hazards of ethylene dibromide. EPA determined that ethylene dibromide poses hazards from acute and chronic exposures to aquatic vertebrates, acute and chronic exposures to aquatic invertebrates, acute and chronic dietary exposure to terrestrial mammals, acute and chronic inhalation exposure to terrestrial mammals, acute inhalation exposure to birds, and acute and chronic inhalation exposure to terrestrial invertebrates (Table 3-17).

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Receptor Group and Exposure Duration	Organism Hazard	Hazard Threshold (COC or HV)	Assessment Medium	Citation (Study Quality)	Hazard Confidence
Acute aquatic vertebrates (Section 3.2.1)	Mortality	550 µg/L	Water column	From SSD	Robust
Acute aquatic invertebrates (Section 3.2.2)	Mortality and Immobility	43 µg/L	Water column	Kszos et al. (2003) (High)	Slight
Chronic aquatic vertebrates (Section 3.2.3)	Acute-to-chronic ratio and assessment factor applied to acute fathead minnow mortality data	190 µg/L	Water column	From SSD	Robust
Chronic aquatic invertebrates (Section 3.2.4)	Acute-to-chronic ratio and assessment factor applied to acute <i>C. dubia</i> mortality data	36.1 µg/L	Water column	Kszos et al. (2003) (High)	Slight
Acute terrestrial mammals (Section 3.3.1.1)	Inhalation exposure to terrestrial mammals (developmental deformities)	150 mg/m ³	Air	Short et al. (1978) (High)	Robust
Chronic terrestrial mammals (Section 3.3.1.1)	Inhalation exposure to terrestrial mammals (testicular degeneration)	77 mg/m ³	Air	NTP (1982) (High)	Robust
Acute terrestrial birds (Section 3.3.1.2)	STIR was used to estimate avian inhalation mortality	2.0 µg/m ³	Air	From STIR	Moderate
Acute terrestrial invertebrates (Section 3.3.2)	Exposure in air of eight arthropod species resulting in mortality	30 mg/m ³	Air	From SSD	Robust
COC = concentration of concern; HV = hazard value; SSD = species sensitivity distribution; STIR = Screening Tool for Inhalation Risk					

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APPENDICES

APPENDIX A CRITICAL NON-CANCER AND CANCER HEALTH OUTCOMES: NOT CONSIDERED FURTHER FOR POD DERIVATION

As described above in Sections 2.3 and 2.4, all studies identified through systematic review were considered for potential POD derivation and used to inform the weight of scientific evidence (Section 2.5) for the human health hazard assessment. This appendix focuses on additional study summaries and endpoint discussions for critical non-cancer and cancer health outcomes but were not considered further for POD derivation due to various study limitations and uncertainties. Although dermal and ocular irritation studies were not identified as critical endpoints in Section 2.3, the draft ethylene dibromide risk evaluation does quantitatively assess dermal hazard due to the likelihood of dermal exposure to ethylene dibromide in various exposure scenarios characterized in the *Draft Chemistry, Fate, Release, and Exposure Assessment for Ethylene Dibromide* (U.S. EPA, 2026b), and the route-to-route extrapolation approach used to assess dermal hazard are discussed above in Sections 2.3.2.5 and 2.4.7.4, for non-cancer and cancer, respectively. Adrenal toxicity is also addressed below in this appendix, because there were co-critical adrenal endpoints noted above for non-cancer in Sections 2.3.2.4 and 2.5.1.2

A.1 Dermal and Ocular Irritation

A.1.1 Human Evidence

EPA identified references that reported adverse ocular and dermal outcomes occurring after acute exposure to ethylene dibromide in humans (Osterloh, 1986; Letz et al., 1984a, b; Peoples et al., 1978). None of these epidemiology studies were found to have sufficient data for dose-response assessment. Therefore, all epidemiological references identified where dermal and ocular outcomes were observed are characterized below. These studies are described in Table_Apx A-1, and did not undergo data quality evaluation because they were screened as supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). These studies provide slight evidence of adverse dermal and ocular outcomes potentially occurring following acute exposure to ethylene dibromide, but do not provide sufficient dose information for quantitative assessment.

Table_Apx A-1 characterizes dermal and ocular outcomes observed in human studies.

Case reports of acute dermal exposure include reports of first and second degree burns and blisters, dermatitis, and erythema (Osterloh, 1986; Letz et al., 1984a, b; Peoples et al., 1978). Case reports of acute ocular exposure include an individual who developed conjunctivitis and another individual who developed corneal abrasions (Peoples et al., 1978).

EPA identified two studies that reported dermal and ocular outcomes associated with ethylene dibromide exposure: one reference that reported on occupational cases in California (Peoples et al., 1978) and three linked references that reported on an occupational incident in which two workers collapsed in a tank containing ethylene dibromide (Osterloh, 1986; Letz et al., 1984a, b).

There were six incidents in 1975 and 10 incidents in 1976 of acute ethylene dibromide exposure reported by physicians to the California Department of Food and Agriculture (Peoples et al., 1978). The exposures in these cases included several different formulations containing ethylene dibromide, including three individuals exposed to Dowfume W-85, two exposed to Terr-O-Cide, two exposed to

Namco S-T-D, two exposed to Dowfume 75, two exposed to Dawson Fumigant #73, two exposed to “ethylene dibromide”, one exposed to “ethylene dibromide, ethylene dichloride, and carbon tetrachloride”, one exposed to Telone C and subsequently to Dowfume W-85, and one exposed to Dowfume MC2 ([Peoples et al., 1978](#)). The percentage of ethylene dibromide and the other ingredients in these formulations were not specified in the report ([Peoples et al., 1978](#)). These 16 cases had several routes of exposure, including one case with both ocular and dermal exposure, three other cases with ocular exposure, seven other cases with dermal exposure, and the remaining five cases reported as having systemic illness associated with various exposure routes ([Peoples et al., 1978](#)). One of the individuals with ocular exposure developed conjunctivitis and one developed bilateral corneal abrasions ([Peoples et al., 1978](#)). There was limited information on the other two individuals with ocular exposure, but both had eyes flushed and one was reported to have received emergency medical treatment ([Peoples et al., 1978](#)).

The 1975 cases included three cases of dermal exposure to Dowfume W-85, which was a pesticide containing ethylene dibromide, including one individual who had Dowfume W-85 spill on his pants and then showered immediately after experiencing burning and had slight erythema, and two individuals with spills on footwear, one associated with a chemical burn with cellulites, and the other who put a contaminated boot back on and developed contact dermatitis and a chemical burn ([Peoples et al., 1978](#)). The five cases of acute dermal injuries in 1976 included a case of Dawson Fumigant #73 exposure including putting contaminated clothes back on after washing, which was associated with first and second degree burns, swelling, and itching; a dermal exposure treated by a physician; a worker with first and second degree burns; a case of fumigating using Terr-O-cide for approximately one hour, which was associated with development of a rash and acute dermatitis, which a physician diagnosed as an acute allergic reaction; and a case of erythema ([Peoples et al., 1978](#)).

Two workers collapsed in a tank of ethylene dibromide at a facility in California and had extensive dermal exposure to ethylene dibromide ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)). These exposures were fatal and several systemic issues were reported along with burning eyes and throat in one case and erythema and blisters in the other case ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)). Although there is some uncertainty, these might be two of the cases of systemic illness that were reported as occurring in 1976 in the paper on cases in California ([Peoples et al., 1978](#)).

These studies are described in Table_Apx A-1, and did not undergo data quality evaluation because they were screened as supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)). These studies provide slight evidence of adverse dermal and ocular outcomes potentially occurring following acute exposure to ethylene dibromide, but do not provide sufficient dose information for quantitative assessment.

Table_Apx A-1. Summary of Studies Reporting on Ethylene Dibromide Exposure and Dermal and Ocular Irritation Outcomes in Humans

Reference	Study Description	Dermal and Ocular Outcome(s) Reported	Overall Quality Determination
Peoples et al. (1978)	Occupational case reports for California in 1975 and 1976	Dermal: First and second degree burns, dermatitis, and erythema Ocular: conjunctivitis and corneal abrasions	N/A
Osterloh (1986); Letz et al. (1984a, 1984b)	Case report of acute ethylene dibromide exposure resulting in death in two workers who collapsed in a tank containing ethylene dibromide	Dermal: Erythema and blisters Ocular: Burning eyes	N/A
Overall Quality Determinations are N/A for supplemental studies such as case studies, case series, and mechanistic studies.			

A.1.2 Laboratory Animal Evidence

EPA identified six animal studies that explore acute irritation effects following dermal exposure to ethylene dibromide and two studies exploring acute irritation effects of eye exposure. No subchronic or chronic studies were identified with irritation outcomes. All data identified by EPA for irritation endpoints in animal toxicity studies are outlined below and characterized in Table_Apx A-2.

Acute Dermal

In the first study, 17 guinea pigs were reported to have been utilized across six independent chemical studies ([Kronevi et al., 1981](#)). The number of animals utilized for the study of ethylene dibromide is not clearly reported, nor is sex of the animals utilized. Glass rings were glued to the clipped skin of each guinea pig, where 1 mL of pure ethylene dibromide was applied within the ring, occluded under a glass cover. After 15 minutes, 1 hour, 4 hours, and 16 hours, the exposed skin sites were cut out and fixed for histological study, as was the adjacent non-exposed skin of the same animal as a negative control. At 1, 4, and 16 hours, ethylene dibromide induced degenerative changes in the epidermis, junctional separation, and cellular infiltration of the dermis. At one-hour, slight karyopyknosis in the basal and suprabasal epidermis, slight perinuclear oedema in epithelial cells, and focal junctional separation with tendency to small vesicles was observed. Despite the described limitations, EPA assigned this study a medium overall quality determination rating during systematic review, due to adequate experimental design and data analysis. The outcomes of this study were considered when characterizing the effects of dermal contact with ethylene dibromide, alongside the remaining pool of dermal irritation evidence described in this section.

Acute percutaneous absorption was conducted on male and female New Zealand white rabbits (2/sex/group) ([Dow Chemical, 1992a](#)). Rabbits were treated with 63, 50, 130, 200 or 320 mg/kg of undiluted ethylene dibromide. Topical responses observed included slight to marked redness, swelling, and slight necrosis. No treatment related lesions were noted at gross necropsy examination. EPA assigned this study a high overall quality determination rating during systematic review.

In an acute dermal toxicity study that also followed the Draize method, ethylene dibromide was dermally applied to the skin of rabbits at doses of 0.21 (n = 15), 0.30, 0.65, and 1.1 g/kg (n = 5) for 24 hours under occlusion ([Rowe et al., 1952](#)). At the end of the exposure period, the impervious sleeves were removed, and the area was cleansed with soap and water. The animals were observed for two

7219 weeks. The test material resulted in moderate to severe erythema, edema, and necrosis "in all cases".
7220 Healing occurred with scar formation. EPA assigned this study a medium overall quality determination
7221 rating during systematic review.
7222

7223 In a dermal toxicity study, New Zealand white rabbits (2/sex/group) were dermally exposed to ethylene
7224 dibromide (purity not reported) doses of 109, 218, 436, or 872 mg/kg by application of undiluted test
7225 material to the unabraded back of each animal ([Withheld, 1979](#)). The trunk of the animal was covered
7226 with vinylite sheeting, which was removed along with residual test material after 24 hours. No signs of
7227 toxicity were observed other than skin irritation. Skin erythema was noted in all test animals. Edema was
7228 reported in all test animals exposed to at least 218 mg/kg ethylene dibromide. EPA assigned this study a
7229 high overall quality determination rating during systematic review.
7230

7231 In an acute study, rabbits (1/group) were exposed to ethylene dibromide by single dermal application at
7232 300 mg/kg, 430 mg/kg, 480 mg/kg, 750 mg/kg, 1,090 mg/kg, or 2,000 mg/kg ([Kettering Laboratory, 1943](#)).
7233 No immediate reactions were observed following test substance application. EPA assigned an
7234 uninformative overall quality determination rating as only one animal was exposed to each
7235 concentration tested.
7236

7237 In a study of dermal absorption of ethylene dibromide, glass rings with a cover slip were glued to shaven
7238 skin on the backs of guinea pigs (number of test animals not clearly reported), and 1 mL neat ethylene
7239 dibromide was applied for an exposure of 6 or 12 hours ([Jakobson et al., 1982](#)). Four guinea pigs were
7240 reported to be exposed for six hours and had 1 exposure site. An additional four guinea pigs were
7241 reported to be exposed for 12 hours and had two exposure sites. 0.5 mL blood samples were collected
7242 every 5 to 20 minutes. 0.6 mL MacroDEX was injected after every blood draw to compensate for blood
7243 loss. Ethylene dibromide levels were measured in blood samples via gas chromatography. Ethylene
7244 dibromide was absorbed rapidly through the skin of guinea pigs and reached maximal blood levels
7245 within an hour. Guinea pigs that had one dermal exposure site, ethylene dibromide was measured in
7246 blood at 1.4 µg/mL after 30 minutes, and 3.8 µg/mL after 6 hours. In guinea pigs with two exposure
7247 sites, ethylene dibromide was measured in blood at 4.9 µg/mL after 30 minutes, and 7.1 µg/mL after 6
7248 hours. The overall quality determination of this study per EPA's systematic review is uninformative due
7249 to lack of information to support or dismiss the suggestion of animal attrition. Ultimately, absorption
7250 estimates were not determined by authors and effects of exposure other than levels of test substance in
7251 blood were not reported.
7252

7253 In a study of elimination of ethylene dibromide in test animal blood following exposure to ethylene
7254 dibromide, glass rings with a cover slip were glued to shaven skin on the backs of guinea pigs (number
7255 of test animals not clearly reported), and 1 mL neat ethylene dibromide was applied for an exposure of
7256 four hours before the test agent was removed and the exposure site was dried ([Jakobson et al., 1982](#)).
7257 Blood was drawn from these animals every 5 to 20 minutes for 2 hours, beginning after the removal of
7258 the exposure to study elimination of ethylene dibromide. 0.6 mL MacroDEX was injected after every
7259 blood draw to compensate for blood loss. Quantitative measurement of elimination from the blood of
7260 test animals is not clearly reported. The overall quality determination of this study per EPA's systematic
7261 review is uninformative due to lack of information to support or dismiss the suggestion of animal
7262 attrition. Effects of exposure other than levels of test substance in blood were not reported.
7263

7264 ***Short-Term Dermal***

7265 In a short-term irritation study, a 1% topical application of ethylene dibromide in butyl carbitol acetate
7266 was applied 10 times in 14 days to the rabbit ear and bandaged onto shaven belly ([Rowe et al., 1952](#)).
7267 The number of rabbits was not reported, and it is unclear whether the same rabbits were used for ear and

abdominal exposures. The 1% solution on the ear caused slight irritation, characterized by erythema and exfoliation, while application to the shaven abdomen resulted in marked irritation. Erythema and edema progressing to necrosis and sloughing of the superficial layers of skin were observed. Healing was complete without scarring within seven days after termination of exposure. No irritation scores were provided. EPA assigned this study an uninformative quality determination rating due to lack of clarity in exposure schedule and methods and test material volume.

Acute and Short-Term Ocular

In an eye irritation study, New Zealand white rabbits (3/sex) were exposed by instillation into the conjunctival sac of the right eye to 0.1 mL undiluted ethylene dibromide ([Withheld, 1979](#)). The left eye was not exposed, and the eyes were not washed after instillation. The cornea, iris, and conjunctiva were examined one hour after exposure, and then again 1, 2, 3, 4, and 7 days after instillation and scored using the Draize method. Corneal opacity was determined by fluorescein staining. No corneal or iris injuries were observed. Conjunctival redness and discharge were observed in all test animals at one hour and resolved by 48 hours. The authors classified ethylene dibromide as “practically non-irritating” to “minimally irritating” based on these findings. EPA assigned this study a high overall quality determination rating during systematic review.

In a final eye irritation study, neat, 10%, or 1% ethylene dibromide in propylene glycol was introduced into both eyes of rabbits ([Rowe et al., 1952](#)). After 30 seconds, one eye was flushed three times with running water. Eyes were examined after washing at 2, 24, and 48 hours post-exposure. In unwashed eyes, the neat test material caused pain and conjunctival irritation, with a slight amount of superficial necrosis of the cornea, all of which resolved within 48 hours. The 10% dilution produced a more severe reaction; conjunctival irritation and corneal injury, both of which were moderate in intensity, were observed within two hours and persisted for 48 hours. No effects on the iris or the lens were observed. Healing was complete within 12 days. The study reported that washing slightly reduced the intensity of all responses and shortened healing time. It is unclear whether the propylene glycol alone acted as an eye irritant. EPA assigned this study an uninformative overall quality determination rating due to lack of clarity in test material volume and the lack of a propylene glycol control group.

Table_Apx A-2. Summary of Ethylene Dibromide Studies Evaluating Dermal and Ocular Effects in Animals

Reference	Study Description	Effect(s)	Overall Quality Determination
Acute (dermal)			
Dow Chemical (1992a)	Acute percutaneous exposure on male and female New Zealand white rabbits (2/sex/group) of either 63, 50, 130, 200 or 320 mg/kg of undiluted ethylene dibromide.	No lesions reported at necropsy	High
Kronevi et al. (1981)	An unclear number of guinea pigs had glass rings were glued to the clipped skin where 1-mL of pure ethylene dibromide was applied within the ring, occluded under a glass cover. After 15 minutes, 1 hour, 4 hours, and 16 hours, the exposed skin sites were excised and fixed for histological study, as was the adjacent non-exposed	<u>1 hour:</u> ↑ Degenerative epidermis ↑ Junctional separation ↑ Cellular infiltration ↑ Focal junctional separation with tendency to small vesicles Slight karyopyknosis in the basal and supra-basal epidermis	Medium

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Reference	Study Description	Effect(s)	Overall Quality Determination
	skin of the same animal as a negative control.	- Slight ↑ perinuclear oedema - Slight ↑ in epithelial cells <u>4 hours:</u> ↑ Degenerative epidermis ↑ Junctional separation ↑ Cellular infiltration <u>16 hours:</u> ↑ Degenerative epidermis ↑ Junctional separation ↑ Cellular infiltration	
Jakobson et al. (1982)	Guinea pigs had glass rings with a cover slip glued to shaven skin on their backs (number of test animals not clearly reported), and 1 mL neat ethylene dibromide was applied for an exposure of 6 (n = 4; 1 exposure site) or 12 hours (n = 4; 2 exposure sites). 0.5 mL blood samples were collected every 5 to 20 minutes. 0.6 mL MacroDEX was injected per blood draw to compensate volume loss. Ethylene dibromide levels were measured in blood samples via gas chromatography. In a separate study, glass rings with a cover slip glued to shaven skin on their backs (number of test animals not clearly reported), and 1 mL neat ethylene dibromide was applied for an exposure of 4 hours before it was removed dried. Blood was drawn every 5–20 minutes for 2 hours, beginning after removal of the exposure to study elimination of ethylene dibromide. 0.6 mL MacroDEX was injected per blood draw to compensate volume loss.	<u>One Exposure Site:</u> - Level in Blood (30 min) = 1.4 µg/mL - Level in Blood (6 hr) = 3.8 µg/mL <u>Two Exposure Sites:</u> - Level in Blood (30 min) = 4.9 µg/mL - Level in Blood (6 hr) = 7.1 µg/mL <u>Ethylene Dibromide Elimination Recovery:</u> Elimination from blood is not clearly reported	Uninformative
Withheld (1979)	New Zealand white rabbits (2/sex/group) were dermally exposed to ethylene dibromide (purity not reported) doses of 109, 218, 436, or 872 mg/kg by application of undiluted test material to the unabraded back of each animal. The trunk of the animal was covered with vinylite sheeting, which was removed along with residual test material after 24 hours.	↑ Erythema at all doses ↑ Edema at doses ≥ 218 mg/kg	High
Rowe et al. (1952)	Ethylene dibromide was dermally applied, according to Draize method, to the skin of rabbits at doses of 0.21 (n = 15), 0.30, 0.65, and 1.1 g/kg (n = 5) for 24 hours under occlusion. At the end of the exposure period, the impervious sleeves were removed, and the	↑ Erythema (moderate to severe) ↑ Edema (moderate to severe) ↑ Necrosis (moderate to severe)	Medium

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Reference	Study Description	Effect(s)	Overall Quality Determination
	area was cleansed with soap and water. The animals were observed for two weeks.		
Kettering Laboratory (1943)	Rabbits (1/group) were exposed to ethylene dibromide by single dermal application at 300 mg/kg, 430 mg/kg, 480 mg/kg, 750 mg/kg, 1,090 mg/kg, or 2,000 mg/kg	No immediate reactions were observed following application	Uninformative
Short-term (dermal)			
Rowe et al. (1952)	A 1% topical application of ethylene dibromide in butyl carbitol acetate was applied 10 times in 14 days to the rabbit ear and bandaged onto shaven belly. The number of rabbits was not reported, and it is unclear whether the same rabbits were used for ear and abdominal exposures.	<u>Ear exposure:</u> ↑ Erythema ↑ Exfoliation <u>Abdominal exposure:</u> ↑ Edema ↑ Erythema Sloughing of superficial layers of skin <u>Healing:</u> Occurred within 7 days following exposure and left no noticeable scar	Uninformative
Acute and short-term (ocular)			
Withheld (1979)	New Zealand white rabbits (3/sex) exposed by instillation into the conjunctival sac of the right eye to 0.1 mL undiluted ethylene dibromide while the left eye was not exposed (no eye wash after instillation). The cornea, iris, and conjunctiva were examined one hour after exposure, and then again 1, 2, 3, 4, and 7 days after instillation and scored using the Draize method. Corneal opacity was determined by fluorescein staining.	↑ Conjunctival redness ↑ Discharge - Resolved by 48 hours - Practically non-irritating/Minimally irritating - No corneal or iris injuries were reported	High
Rowe et al. (1952)	Neat, 10%, or 1% ethylene dibromide in propylene glycol was installed into both eyes of rabbits. After 30 seconds, 1 eye was flushed 3 times with running water. Eyes were examined after washing at 2, 24, and 48 hours post-exposure. It is unclear whether the propylene glycol alone acted as an eye irritant.	<u>Neat:</u> ↑ Pain ↑ Conjunctival irritation Slight superficial corneal necrosis Resolved within 48 hours <u>10% in propylene glycol:</u> - Moderate conjunctival irritation - Moderate corneal damage - Resolved within 12 days Washing eyes resulted in ↓ intensity and ↓ healing times	Uninformative

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A.1.3 Evidence Integration and Summary

EPA's conclusion regarding ethylene dibromide is that it is irritating to skin and eyes, but not corrosive. The epidemiology evidence of acute dermal and ocular toxicity is slight. The quality of the small database consisting of case reports and case series describing a small number of individuals decreases the strength of the evidence. Because these cases occurred in humans, the biological plausibility and relevance of the data to humans increases the strength of the evidence.

Ethylene dibromide is a dense liquid at room temperature that may easily pass through skin, cloth, and protective materials like rubber and leather ([ATSDR, 2007](#)). Much of the evidence on systemic effects of dermal exposure to ethylene dibromide that EPA reviewed comes from animal studies. Epidemiological studies that assessed the association between dermal exposure to ethylene dibromide and health outcomes are limited. Specifically, EPA identified case reports and case series that reported severe irritation outcomes including first and second degree burns and blisters, dermatitis, and erythema ([Osterloh, 1986](#); [Letz et al., 1984a, b](#); [Peoples et al., 1978](#)). These reports involved a small number of individuals and have limitations in exposure characterization. One study specifically is cited by ([ATSDR, 2018](#)), as being key for dermal hazard characterization is a case report of an occupational accident in which two male workers collapsed in a tank containing ethylene dibromide. Both workers died within 3 days following exposure to ethylene dibromide; although there is some uncertainty as the authors noted that "the patients could have inhaled or swallowed" ethylene dibromide and there were other chemicals identified in the liquid in the tank, the report on the incident concluded that the adverse outcomes were due to ethylene dibromide exposure, and that the primary route of exposure was dermal. The measured concentration of ethylene dibromide in air ranged between 15 and 41 ppm and the concentration of ethylene dibromide in the liquid the two workers were lying in at the bottom of the tank was ppm ([Letz et al., 1984a](#)). As a case report of two individuals with uncertainties regarding exposure characterization, the Letz ([1984a](#)) paper is insufficient for quantifying the effects of dermal exposure to ethylene dibromide. EPA did not identify any additional studies through the systematic review process that reported exposure data on the absorption of ethylene dibromide in humans.

Dermal as a result of ethylene dibromide exposure was reported in several animal studies. One study reported that absorption of ethylene dibromide was demonstrated in guinea pigs whose blood levels were monitored during dermal exposure to ethylene dibromide. The study reported that ethylene dibromide was absorbed rapidly through the skin of guinea pigs and reached maximal blood levels within an hour ([Jakobson et al., 1982](#)). Application of ethylene dibromide to rabbits where the exposure site was not covered resulted in a range of outcomes (e.g., light to marked redness, swelling, and slight necrosis) ([Dow Chemical, 1992a](#)) whereas Kettering Laboratory ([1943](#)) reported no observed dermal effects. In studies where the exposure site was covered following application of ethylene dibromide, rabbits experienced moderate to severe erythema, edema, and necrosis, and skin healing following exposure resulted in scar formation ([Withheld, 1979](#); [Rowe et al., 1952](#)). Repeated dermal exposure in rabbits, 10 times in 14 days, resulted in slight irritation characterized by erythema and exfoliation at uncovered sites, and marked irritation characterized by erythema, exfoliation, necrosis, and sloughing of superficial skin layer at covered sites, which healed with scarring within 7 days of exposure cessation ([Rowe et al., 1952](#)). Of the nasal-respiratory epithelium was observed with inhalation exposure in rats and mice, providing additional evidence related to dermal irritation. Of note, a respiratory study in mice reported nasal epithelium hyperplasia in animals exposed to ethylene dibromide for 1 to 13 weeks, where the nasal epithelium in animals of all exposure groups returned to a healthy state following a 3-month recovery period ([Nitschke et al., 1981](#)). Animal studies exploring eye irritation show relatively mild outcomes including conjunctival redness ([Withheld, 1979](#); [Rowe et al., 1952](#)), as well as pain in test animals and slight, non-permanent corneal damage ([Rowe et al., 1952](#)). Overall, there is slight evidence of acute dermal or ocular irritation endpoints as a result of ethylene dibromide exposure in

animals. Overall, there is slight evidence of acute dermal or ocular irritation endpoints as a result of ethylene dibromide exposure in animals.

The available evidence indicates that ethylene dibromide may cause severe irritation, but there is insufficient evidence to indicate corrosivity. Thus, EPA's conclusion regarding ethylene dibromide is that it is irritating to skin and eyes (where the effects are non-destructive and reversible), but not corrosive. This conclusion by EPA is consistent with the findings of agencies in Europe ([European Chemicals Agency \(ECHA\) Classification Labeling and Packaging \(CLP\) Annex VI](#)), Canada ([Workplace Hazardous Materials Information System \(WHMIS\)](#)), Japan ([National Institute of Technology and Evaluation \(NITE\)](#) of Japan), and Malaysia ([Department of Occupational Safety and Health Ministry of Human Resources Malaysia](#); all preceding hyperlinks accessed May 21, 2026), which all have classified ethylene dibromide as Globally Harmonized System (GHS) Category 2 (H315), which indicates "causes skin irritation" but does not indicate corrosion, which would be GHS Category 1 (H314). Thus, although the evidence indicates that ethylene dibromide may cause severe irritation, this irritation may be reversible (in contrast to irreversible corrosion). Furthermore, reproductive toxicity epidemiology studies conducted by NIOSH have reported "moderate" chronic dermal exposure based on observation of the workers and a TWA inhalation exposure of 88 ppb (peak 262 ppb) based on breathing zone air sampling in a sample of papaya workers and "extensive" acute or short-term dermal exposure based on observation of the workers and a TWA inhalation exposure of 60 ppb (peak 2,165 ppb) based on breathing zone air sampling in a sample of forestry workers ([Schrader et al., 1988](#); [Ratcliffe et al., 1987](#); [Schrader et al., 1987](#)), which indicates that longer term dermal exposures may occur. Based on slight evidence in both humans and animals, evidence suggests but is not sufficient to conclude that acute ethylene dibromide exposure is associated with adverse ocular and dermal outcomes in humans. Given the mixed results and identified limitations of the available database for this endpoint, ethylene dibromide is considered to be a skin and eye irritant, where the local irritation effects are non-destructive and reversible.

A.2 Reproductive and Developmental Toxicity

Although reproductive and developmental toxicity is recognized as a critical health outcome for ethylene dibromide, the studies summarized in this section were not selected for quantitative dose-response analysis or as points of departure (PODs). This is primarily due to limitations such as insufficient data quality, lack of adequate dose-response information, absence of NOAELs, or other uncertainties. For example, many of the human epidemiology studies in this section were cross-sectional or case series with small sample sizes, limited exposure characterization, or potential confounding by co-exposures, making them unsuitable for quantitative risk assessment ([Gong and Zhan, 2022](#); [Larsen et al., 1998](#); [Schrader et al., 1988](#); [Ratcliffe et al., 1987](#); [Schrader et al., 1987](#); [Takahashi et al., 1981](#); [Turner and Barry, 1979](#); [Wong et al., 1979](#); [Equitable Environmental Health Inc, 1977](#)). Similarly, several animal studies lacked multiple dose groups, did not report critical endpoints in a manner that allowed for dose-response modeling, or had methodological limitations such as high mortality at lower doses or inadequate reporting of control data ([NTP, 1982](#); [Teramoto et al., 1980](#); [Short et al., 1979](#); [NCI, 1978](#); [Short et al., 1978](#); [Rowe et al., 1952](#)). As a result, while these endpoints inform the overall weight of evidence for reproductive and developmental toxicity, only studies meeting higher standards for methodological rigor and quantitative utility were carried forward for POD derivation in the main narrative.

A.2.1 Human Evidence

EPA identified studies that evaluated the association between ethylene dibromide exposure and reproductive/developmental outcomes in humans as described in Section 2.3.1.1.1. None of these epidemiology studies were found to have sufficient data for dose-response assessment. Therefore, all

epidemiological references identified where reproductive/developmental outcomes were observed are characterized below. Table_Apx A-3 characterizes all reproductive/developmental outcomes observed in human studies.

NIOSH conducted a cross-sectional study of papaya workers, which was reported in three publications ([Schrader et al., 1988](#); [Ratcliffe et al., 1987](#); [Schrader et al., 1987](#)). One of these publications ([Schrader et al., 1988](#)) also reported on a longitudinal study of forestry workers. These studies assessed and quantified ethylene dibromide in breathing zone air samples using gas chromatography. The cross-sectional study examined the association between ethylene dibromide exposure and semen and sperm characteristics in an exposed group of 46 male workers from six papaya packing and fumigation plants in Hawaii compared to 43 unexposed men from a nearby sugar refinery. The exposed workers had an average employment duration of approximately five years (4.9 ± 3.6 years). The exposed group included workers in three job categories: sorter/packers with average full-shift ethylene dibromide breathing zone inhalation exposures ranging from 36 to 148 ppb (based on measurements from 6 plants), forklift drivers with average full-shift ethylene dibromide breathing zone inhalation exposures ranging from 16 to 175 ppb (based on measurements from 5 plants), and fumigators with average full-shift ethylene dibromide breathing zone inhalation exposures of 116 ppb (based on measurements from 1 plant) ([Ratcliffe et al., 1987](#)). The overall time-weighted average geometric mean level of ethylene dibromide from breathing zone air samples was 88 ppb, and exposures ranged from 12 to 262 ppb ([Ratcliffe et al., 1987](#)). Dermal exposure in this group was reported as “moderate” based on observation of the workers ([Schrader et al., 1988](#)). Statistically significant decreases were reported in sperm count per ejaculate and the percentage of viable and motile sperm in exposed workers compared to unexposed workers. Additionally, statistically significant increases were observed in the proportion of sperm with specific morphological abnormalities (*i.e.*, tapered heads, absent heads, and abnormal tails). No statistically significant associations were observed for sperm velocity, the overall proportion of sperm with normal morphology, or two fluorescent bodies (*i.e.*, YFF bodies) ([Ratcliffe et al., 1987](#); [Schrader et al., 1987](#)).

The NIOSH study of papaya workers was a well-conducted study that assessed relevant biomarkers of effect (semen volume, semen pH, sperm count, sperm velocity, sperm motility, sperm viability, sperm concentration, sperm abnormalities, sperm YFF bodies) utilizing mobile field laboratories and found associations between ethylene dibromide exposure and adverse outcomes as indicated by these biomarkers. The study has some limitations including potential residual confounding due to differences in characteristics or co-exposure confounding due to differences in exposures to other substances between papaya workers (exposed group) and sugar workers (comparison group). Another limitation is that temporality could not be determined due to the cross-sectional study design, although no other occupational exposures were noted. Additionally, the relatively small sample size might have limited the sensitivity to detect an association. EPA assigned this study a medium overall quality determination rating.

Another NIOSH study ([Schrader et al., 1988](#)) assessed the association between acute or short-term ethylene dibromide exposure and semen and sperm characteristics in forestry workers in Colorado. This prospective cohort included 12 exposed and six unexposed male workers. The time-weighted average geometric mean ethylene dibromide exposure level based on personal breathing zone air samples was 60 ppb, with peak exposures up to 2,165 ppb. Peak exposures were assessed using samples “collected over durations of 15 minutes to one hour”. Dermal exposure in this group was reported to be “extensive” based on observation of the workers ([Schrader et al., 1988](#)). Statistically significant decreases were observed in semen volume ($p = 0.03$) and sperm distance velocity ($p = 0.004$) among exposed workers compared to unexposed workers. No statistically significant associations were observed for sperm pH, sperm concentration, or sperm viability. Although the sample size was small resulting in potentially

limited sensitivity to detect an association, this study was a well-conducted longitudinal study of associations between ethylene dibromide exposure and semen and sperm characteristics. EPA assigned this study a medium overall quality determination rating.

The 2018 ATSDR Toxicological Profile for 1,2-Dibromoethane (a synonym of ethylene dibromide) ([ATSDR, 2018](#)) reported the 88 ppb geometric mean time-weighted average exposure from the NIOSH cross-sectional study of papaya workers as the “lowest LOAEL” across human and animal studies. The California Office of Environmental Health Hazard Assessment (OEHHA) also reported the 88 ppb as a “LOAEL” and used that value to derive a chronic reference exposure level (REL) ([CalEPA, 2001](#)). Of note, the study of forestry workers, which had a more relevant longitudinal design, had a lower time-weighted average of 60 ppb of ethylene dibromide (measured using gas chromatography) in the exposed group that was associated with adverse outcomes ([Schrader et al., 1988](#)). Furthermore, in both studies the time-weighted average in the exposed group is not a typical lowest observed adverse effect level (LOAEL) because comparisons were not made between multiple quantitative exposure levels. In both the papaya worker and the forestry worker studies, although more detailed measurements of exposure were obtained, including personal-breathing zone air samples, the main statistical analyses in these studies compared only two exposure levels: exposed and unexposed. Some analyses were performed by job and duration of exposure. However, these analyses by job type were potentially limited by small sample sizes and were not reported in sufficient detail for data extraction. Although the mean inhalation exposure level was 88 ppb in the papaya workers and 60 ppb in the forestry workers, peak inhalation exposures reached 262 ppb and 2,165 ppb, respectively, and there was simultaneous “moderate” or “extensive” dermal exposure ([Schrader et al., 1988](#)). Thus, although the NIOSH studies provide insufficient information for dose-response analysis, it is relevant to note that adverse outcomes were observed for male reproductive biomarkers in workers with average exposure levels that were substantially lower than levels associated with adverse reproductive outcomes in animals, and therefore potential risk of adverse reproductive outcomes at these lower exposure levels cannot be ruled out.

Takahashi et al. ([1981](#)) assessed the relationship between ethylene dibromide exposure and semen and sperm characteristics in a cross-sectional pilot study in Hawaii. Analyses were performed on semen samples from 13 pineapple field workers and a reference group of 19 men from the general population of Molokai, Hawaii. In the exposed group of pineapple workers, drip irrigators applied ethylene dibromide for 6 days and field research workers used ethylene dibromide for 5 days. Sperm counts were lower in the pineapple workers and the frequency distribution was statistically significantly different compared to the reference group ($p < 0.02$) and compared to a fertile Honolulu population from a previous study. No statistically significant differences in semen volume or sperm morphology were observed in the pineapple workers compared to either the reference group or to the fertile Honolulu population. There are substantial concerns with exposure measurement and potential co-exposure confounding in this study. Exposure to ethylene dibromide was not measured directly and could not be separated from exposure to other pesticides, particularly dibromochlorophane (DBCP), which was used simultaneously with ethylene dibromide in the pineapple field. Additionally, other exposures may differ between pineapple workers and the general population. Due to the comparison to men from the general population, there also is the potential for healthy worker effect, which would bias the results towards the null hypothesis of no association. Thus, EPA assigned this study a low overall quality determination rating.

In addition to these studies of male reproductive biomarkers, other studies assessed male fertility using birth rates. Male workers from four ethylene dibromide manufacturing plants in Texas and Arkansas were included in a study that investigated the association between ethylene dibromide exposure and male fertility via the assessment of birth rate of workers’ spouses ($n = 297$ couples) ([Wong et al., 1979](#)).

Exposure to ethylene dibromide ranged from less than 0.5 to 5.0 ppm. The birth rate among the partners of male workers was compared with national birth rates considering maternal age, parity, and race. Based on the analysis of each plant, a statistically significant decreased in birth rate was observed among workers in one of the four plants ([Wong et al., 1979](#)). When considering all the plants combined, a statistically significant association between ethylene dibromide exposure and birth rate was not observed ([Wong et al., 1979](#)). This study had several limitations, including inadequate covariate characterization. Furthermore, birth rate was used as a measure of male fertility without sufficient consideration of potential fertility variables of the female partners. EPA assigned this study a low overall quality determination rating.

Turner and Barry ([1979](#)) conducted a survey study investigating inferred fertility (measured as the number of children fathered while employed) in male workers in two ethylene dibromide manufacturing plants in Great Britain. Factory A started production of ethylene dibromide in 1940 and continued until 1970; factory B started production in 1954. The process involved the extraction of bromine from sea water and its subsequent reaction with ethylene to form ethylene dibromide. The potential exposure was categorized into four categories: “None” (n = 41), “Regular Process” (n = 13), “Irregular Process” (n = 17), and “Irregular Maintenance” (n = 11). When concern over the potential effect of ethylene dibromide on fertility arose, only factory B was operational with 82 employees, and only factory B was included in the analyses. The average length of employment at the time of the survey was 15 years for those exposed and unexposed. The average number of children born per man during their time of employment was 0.95 in the unexposed group, 0.62 in the Regular Process group, 0.82 in the Irregular Process group, and 1.18 in the Irregular Maintenance group. Statistical hypothesis testing was not performed. This study lacked quantitative exposure measurements. Furthermore, the study did not adequately consider potential confounding factors including the fertility of the female partners of the study participants. EPA assigned this study a low overall quality determination rating.

The cohorts from Wong et al. ([1979](#)) and Turner and Barry ([1979](#)) also were assessed by EEH ([1977](#)), with similar findings and similar limitations. Wong et al. ([1979](#)) and EEH ([1977](#)) appear to be partial duplicates of each other, as both papers reported similar analyses of the U.S. data. The British data were analyzed differently in Turner and Barry ([1979](#)) and EEH ([1977](#)), but neither analysis found a substantial association between ethylene dibromide exposure and the birth outcomes assessed. EEH ([1977](#)) did not find a statistically significant association. Turner and Barry ([1979](#)) did not perform statistical hypothesis testing, but the magnitude of the outcomes assessed were not substantially different between exposure groups. EPA assigned the EEH ([1977](#)) study a low overall quality determination rating.

Larsen et al. ([1998](#)) in a retrospective study investigated the relationships between pesticide use (including ethylene dibromide) in the prior year and conception and fecundability among 904 Danish farmers selected from the Danish Ministry of Agriculture. No statistically significant difference in fecundability was found between traditional farmers compared to organic farmers. However, ethylene dibromide specific exposure was not directly assessed. Farmers reporting pesticide use were asked about the number of hectares they sprayed themselves, type of spraying and protective equipment used, and type of crops. Farmers were given a list of the most used pesticides during the past 10 years and asked to check off the ones they had used. However, ethylene dibromide was not mentioned as being included in the list and ethylene dibromide-specific exposure was not assessed. Thus, a substantial limitation of this study was that the exposure of interest was pesticides, not specifically ethylene dibromide. Ethylene dibromide was banned in the European Union approximately a decade before this study took place, so substantial ethylene dibromide exposure is unlikely to have occurred in these Danish farmers.

Additionally, fecundability is not a direct measure of male fertility. Due to these substantial limitations, EPA assigned this study an overall quality determination rating of uninformative.

Overall, multiple studies suggest an association between ethylene dibromide exposure and adverse semen or sperm outcomes ([Schrader et al., 1988](#); [Ratcliffe et al., 1987](#); [Schrader et al., 1987](#); [Takahashi et al., 1981](#)). Because these studies only compared exposed and unexposed groups, there is not sufficient data for dose-response assessment across different exposure levels. However, associations with biomarkers of effect were found in exposed groups with time-weighted average exposure levels as low as 60 ppb ([Schrader et al., 1988](#)). Studies of birth rates generally did not find statistically significant associations ([Turner and Barry, 1979](#); [Wong et al., 1979](#); [Equitable Environmental Health Inc, 1977](#)), but these studies were of lower quality, due in part to inadequate consideration of female fertility factors, and there was an indication of an association in at least one cohort ([Wong et al., 1979](#)).

In addition to these studies of male reproductive toxicity, a case-control study of 470,530 women from across Texas by Gong ([2022](#)) examined the associations between maternal exposures to ambient air concentrations of hundreds of chemicals, including ethylene dibromide, and low birth weight (defined <2,500 g) in offspring from 1996 to 2008. The Texas Commission on Environmental Quality (TCEQ) collected ambient concentrations of 367 non-criteria air pollutants, sampled every 3 or 6 days. The authors reported that “exposures were assessed based on the residence location of a mother relative to the locations of the air quality monitoring sites during a given time window. In the analysis of this study, the exposure window started from 366 days, including 90-day exposure windows in 6-day increments, before the estimated date of conception associated with each case and control.” Although detailed exposure measurements were collected and assessed, only two exposure groups were used in the statistical analyses: high exposed group vs. low exposed group. During the 90-day exposure window prior to conception, there was a statistically significant association with low birth weight in offspring for the high ethylene dibromide exposed group compared to the low exposed group, with an odds ratio (OR) of 1.97 (95% CI: 1.24–3.15). This study was generally well-conducted and utilizes a novel method to identify critical windows of maternal air pollution exposures associated with low birth weight in offspring. The main limitation of this study is that measurements were assessed at the ambient level which do not fully account for exposures at the individual level so there is some potential for exposure misclassification. EPA assigned this study a medium overall quality determination rating.

Table_Apx A-3. Summary of Studies Evaluating the Association Between Ethylene Dibromide Exposure and Reproductive/Developmental Outcomes in Humans

Reference	Study Description	Reproductive/Developmental Outcome(s)	Overall Quality Determination
Ratcliffe et al. (1987) ; Schrader et al. (1987)	These references assessed the association between chronic ethylene dibromide exposure and semen and sperm characteristics in an exposed group of 46 male workers from 6 papaya packing and fumigation plants in Hawaii compared to 43 unexposed men from a nearby sugar refinery in a cross-sectional study.	Statistically significant associations between ethylene dibromide exposure and adverse semen and sperm outcomes were reported in: <u>Papaya workers:</u> ↓ Sperm Count ↓ Viable and Motile sperm ↑ Tapered and Absent Heads and Abnormal Tails	Medium
Schrader et al. (1988)	This paper describes a longitudinal study that assessed the association between acute or	<u>Forestry workers:</u> ↓ Semen volume	Medium

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Reference	Study Description	Reproductive/Developmental Outcome(s)	Overall Quality Determination
	short-term ethylene dibromide exposure and semen and sperm characteristics in forestry workers in Colorado; and also includes additional reporting on the Ratcliffe et al. (1987) ; Schrader et al. (1987) studies.	↓ Sperm distance velocity	
Takahashi et al. (1981)	Investigated the relationships between ethylene dibromide exposure and semen and sperm characteristics among 13 pineapple field workers and a reference group of 19 men from the general population of Molokai, Hawaii	Statistically significant association between ethylene dibromide exposure and ↓ Sperm Count	Low
Wong et al. (1979)	Male workers from four ethylene dibromide manufacturing plants in Texas and Arkansas were included in a study that investigated the association between ethylene dibromide exposure and male fertility via the assessment of birth rate of workers' spouses (n = 297 couples)	↓ in birth rate was observed among workers in one of the four plants No other statistically significant associations were reported.	Low
Turner and Barry (1979)	Conducted a survey study investigating inferred fertility (measured as the number of children fathered while employed) in male workers in two ethylene dibromide manufacturing plants in Great Britain	Statistical hypothesis testing was not performed	Low
Equitable Environmental Health Inc (1977)	This study and Wong et al. (1979) appear to be partial duplicates of each other, as both papers reported similar analyses of the U.S. data. It assessed the association between ethylene dibromide exposure and birth outcomes.	No statistically significant associations were observed	Low
Larsen et al. (1998)	Retrospective study investigated the relationships between pesticide use in the prior year and conception and fecundability among 904 Danish farmers selected from the Danish Ministry of Agriculture. A substantial limitation of this study was that the exposure of interest was pesticides, not specifically ethylene dibromide.	No statistically significant difference in fecundability was found between traditional farmers compared to organic farmers	Uninformative
Gong and Zhan (2022)	Case-control study based on birth data (94,106 low birth weight cases and 376,424 controls) and air quality monitoring data (367 chemicals including ethylene dibromide) in Texas during 1996–2008. This study examined the associations between maternal exposures to ambient air concentrations of hundreds of chemicals, including ethylene dibromide, and low birth weight.	Reported a positive association between maternal ethylene dibromide exposure and low birth weight, with an odds ratio (OR) of 1.97 (95% CI: 1.24–3.15).	Medium

A.2.2 Laboratory Animal Evidence

EPA identified six animal studies (3 short-term, 2 subchronic, and 1 chronic) that evaluated the effects of ethylene dibromide inhalation on reproductive and developmental outcomes. Additionally, two short-term and one chronic animal oral gavage study were identified. References that were considered further as POD candidates are described in Section 2.3.1, while references that were not considered further as

POD candidates can be found below. Table_Apx A-4 and Table_Apx A-5 characterize all reproductive/developmental endpoints that results from inhalation and oral exposure, respectively.

Short-Term Inhalation

Pregnant rats were exposed to ethylene dibromide by inhalation chamber for 23 hours/day for 10 days, starting on gestational day six. Exposure groups were 0 ppm (n = 17), 20 ppm (n = 15), 38 ppm (n = 16), 80 ppm (n = 16) and 0 ppm with feed restriction (n = 16) ([Short et al., 1978](#)). Rats were sacrificed on gestational day 20 for fetal assessment of soft tissue and skeletal abnormalities. Significantly fewer fetuses had normally ossified centra at 20 ppm, though the 38 ppm group did not see a significant change and the 80 ppm group had significantly more normally ossified centra than was observed in the 20 ppm group. Significant dam body weight change was observed during exposure at 38 ppm, where the feed-restricted control group consumed similar amounts of food. Fetal weights were also significantly lower in the 38 ppm group. The 80 ppm group saw reduced implantation and no viable fetuses and significant mortality in dams. Due to an inverse-dose-effect in fetal ossification and a large reduction in food ingested by dams, a NOAEC of 20 ppm was assigned. EPA assigned this study a high overall quality determination rating.

Female CD rats (20/group) were exposed to 0, 20, 39, or 80 ppm ethylene dibromide 7 hours/day, 7 days/week for three weeks ([Short et al., 1979](#)). The exposed females were then bred with untreated males and sacrificed mid-gestation (3 weeks post-exposure) to assess implants, viable implants, resorptions, and reproductive histopathology. Females exposed to 80 ppm consumed less food than controls, lost weight during the study, and had significant mortality (20%). No reproductive or histopathological effects were observed at the two lowest doses. Females in the 80 ppm group experienced diestrus and did not cycle normally for 3 to 4 days following exposure, resulting in fewer matings. On histopathological examination, females in the 80ppm group had increased incidence of mild vacuolated degeneration of uterine epithelium (with or without necrosis) and ovarian cysts. A LOAEL of 80 ppm was assigned for reproductive effects, though this dose also resulted in significant dam mortality. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

Subchronic Inhalation

In a subchronic duration exposure study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for as many as 63 exposures in 91 days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Hematological examinations were conducted “periodically” in “representative” rats. Animals were necropsied at the time of sacrifice, where testes were weighed and microscopically examined. More than 50% of the males died due to pneumonia and infections in the upper respiratory tract. A LOAEC of 50 ppm was determined for significant decrease in absolute weight of testes. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a low overall quality determination rating during systematic review.

Chronic Inhalation

F344 rats (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide 6 hours per day, 5 days per week, for 2 years ([NTP, 1982](#)). Throughout the study, mean body weights of high-dose rats of either sex were lower than those of the corresponding untreated controls. Survival of the high-dose rats of either sex was significantly shorter than that in the corresponding controls. A LOAEC

of 10 ppm was identified following 103 weeks of exposure, where testicular degeneration in male rats occurred. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

Table_Apx A-4. Summary of Ethylene Dibromide Studies Evaluating Reproductive/Developmental Effects in Animals (Inhalation)

Reference	Study Description	Reproductive/Developmental Outcome(s)	Overall Quality Determination
Short-term			
Short et al. (1978)	Pregnant mice were exposed to ethylene dibromide in an inhalation chamber for 23 hours/day for 10 days, starting on GD 6. Exposure groups were 0 ppm (n = 18), 20 ppm (n = 20), 38 ppm (n = 20), 80 ppm (n = 22), and 0 ppm with feed restriction (n = 18). Fetal assessments of soft tissue and skeletal abnormalities conducted on gestation day 18.	<u>20 ppm:</u> ↑ Late resorptions ↓ Fetal weight Fetal skeletal abnormalities including incomplete supraoccipital and incus ossification were also observed <u>38 ppm:</u> ↑ Mortality in dams ↓ Percentage of viable fetuses ↑ number of runts ↑ Skeletal abnormalities in fetuses (e.g., enlarged fontanel occipital; unossified phalanges; incompletely ossified or split sternebrae; and an unossified or incompletely ossified hyoid bone, supraoccipital, or incus), compared to those observed at 20 ppm. LOAEC of 20 ppm was assigned for maternal and developmental effects.	High
Short et al. (1978)	Pregnant rats were exposed to ethylene dibromide by inhalation chamber for 23 hours/day for 10 days, starting on gestational day six. Exposure groups were 0 ppm (n = 17), 20 ppm (n = 15), 38 ppm (n = 16), 80 ppm (n = 16) and 0 ppm with feed restriction (n = 16). Fetal assessments of soft tissue and skeletal abnormalities conducted on gestation day 18.	<u>20 ppm:</u> ↓ Fetuses had normally ossified centra <u>38 ppm:</u> ↓ Fetal weights at 38 ppm Significant dam body weight change at 38 ppm, where the feed-restricted control group consumed similar amounts of food <u>80 ppm:</u> ↑ Normally ossified centra at ↓ Implantation and no viable fetuses ↑ Mortality in dams Due to an inverse-dose-effect in fetal ossification and a large reduction in food ingested by dams, a NOAEC of 20 ppm was assigned	High
Short et al. (1979)	Female CD rats (20/group) were exposed to 0, 20, 39, or 80 ppm ethylene dibromide 7 h/day, 7 days/week for 3 weeks (Short et al., 1979). The exposed females were	<u>Females (80 ppm):</u> ↓ Matings ↑ Incidence of mild vacuolated degeneration of uterine epithelium (with or without necrosis) and ovarian cysts	High

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Reference	Study Description	Reproductive/Developmental Outcome(s)	Overall Quality Determination
	then bred with untreated males and sacrificed mid-gestation (3 weeks post-exposure) to assess implants, viable implants, resorptions, and reproductive histopathology	- No reproductive or histopathological effects observed at the two lowest doses - Females experienced diestrus and did not cycle normally for 3–4 days LOAEL of 80 ppm was assigned for reproductive effects	
Subchronic			
Short et al. (1979)	Male CD rats (18-20/group) were exposed to 0, 19, 39, or 89 ppm ethylene dibromide 7 hours/day, 5 days/week for 10 weeks via inhalation chamber.	↓ Fertility ↓ Testis weight ↓ Serum testosterone	High
Rowe et al. (1952)	Rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for as many as 63 exposures in 91 days. The study included 2 groups of controls: 1 unexposed and 1 air-exposed control (numbers not specified). Not that this reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment.	↑ Mortality (more than 50% of males) due to pneumonia and infections in the upper respiratory tract ↓ Testis weight LOAEC of 50 ppm was determined for significant decrease in absolute weight of testes.	Low
Chronic			
NTP (1982)	F344 rats (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide 6 hours per day, 5 days per week, for 2 years.	↓ Survival of the high-dose rats of either sex LOAEC of 10 ppm was identified following 103 weeks of exposure, where testicular degeneration in male rats occurred.	High
LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level; NOAEC = no-observed-adverse-effect concentration			

Short-Term Oral

Ethylene dibromide was administered in Sprague-Dawley rats (15 males/group) at a dose of 10 or 30 mg/kg/day for 5 days via gavage ([Teramoto et al., 1980](#)). Additional groups of rats (15 males/group) received 1.2 mg/kg olive oil by mouth daily for 5 days, or a 200 mg/kg dose of ethyl methanesulfonate (EMS) via i.p. (intraperitoneal) injection once, where these animals served as concurrent vehicle and positive controls. Following exposure, each male rat was mated with one untreated female in the pro-estrus stage, overnight. The next morning, females were checked for signs of pregnancy (*i.e.*, vaginal plug, semen at vaginal opening) and were separated from the males. This pattern of mating experimental males with an untreated female was repeated once per week, for 10 total weeks. Evaluators measured number of females with implants, number of corpora lutea, number of implantations, number of embryos, and number of dead implants in the mated females. The frequency of induced dominant lethal

mutations was calculated weekly by the Röhrborn method. The mating performance of exposed males was not affected based on these metrics when compared to controls. Mating behavior was also not affected by exposure. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a medium overall study quality determination rating.

Ethylene dibromide was administered in BDF1 mice (7–9 males/group) at a dose of 100 or 150 mg/kg/day for 5 days via gavage ([Teramoto et al., 1980](#)). It is stated that the experiment in mice was completed two times for a total of 16 males in each exposure group. Additionally, a group of seven male rats received a 300 mg/kg dose of ethyl methanesulfonate (EMS) via i.p. injection once, to serve as a positive control. Experimental data shows that additional mice were utilized as a vehicle control group, but the number of animals and method of dosing is not stated. Following exposure, each male rat was mated with two untreated females in the pro-estrus stage for seven days. Each morning, females were checked for signs of pregnancy (*i.e.*, vaginal plug, semen at vaginal opening) and were separated from the males if assumed to be pregnant. At the end of the 7-day mating period, any remaining non-pregnant females were removed and replaced with two new females. This pattern of mating experimental males with two untreated female was repeated for 6 total weeks. Females were then sacrificed 12 to 14 days after conception and the embryos examined for viability. Evaluators measured number of females with implants, number of corpora lutea, number of implantations, number of embryos, and number of dead implants in the mated females. The frequency of induced dominant lethal mutations was calculated weekly by the Röhrborn method. The mating performance of exposed males was not affected based on these metrics when compared to controls. Mating behavior was also not affected by exposure. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a medium overall quality determination rating due to a relatively small number of animals per test group, and a lack of reported details related to chemical purity, and statistical analysis. The outcomes of this study were considered when characterizing the reproductive/developmental effects of ethylene dibromide exposure, alongside additional evidence described in this section.

Chronic Oral

Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil five days/week in a chronic cancer bioassay (50/sex/groups receiving treatment) ([NCL, 1978](#)). Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group were 0, 38, 41 mg/kg/day for male rats, 0, 37, 39 mg/kg/day for female rats. High-doses were suspended at 17 weeks due to deaths of 18 high-dose males and 20 high-dose females; at week 30, treatments resumed for the remaining rats in high-dose groups at the same dose the low-dose rats were receiving. At week 42, all treatments in rats were paused for a week then resumed for an additional four weeks. The study was discontinued at 49 weeks in male rats due to excessive deaths in both treatment groups. The study was discontinued for female rats at week 61. In the corn oil gavage vehicle group, male gavage doses were stopped at week 49 and animals were observed for an additional 14-week recovery period; females gavage doses were stopped at week 61 followed by a 2-week observation period (vehicle controls sacrificed at week 63). In the untreated control group, five males were sacrificed in week 59 and the remaining four in week 107. Endpoints evaluated included mortality (daily); clinical signs of toxicity, body weight, food consumption and palpation for tissue masses (weekly); and histopathological examination of testis, prostate, seminal vesicle, uterus, mammary gland, and ovary.

Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included reddened ears and hunched appearance in all treated groups by week five”, and firm distended abdomens and abdominal urine stains in all treated groups by week 38 (incidence data not reported). Body weights were decreased in males and females after 10 weeks of treatment; however, the study authors note that this decrease in mean weight may reflect may be due to

mortality. Significant increased incidences of atrophy in the testes were reported in the low-dose (14/49) and high-dose (18/50) compared to vehicle control (0/20). A POD was not reported by study authors. A LOAEL of 38 mg/kg/day was determined in males for increased incidence of atrophy in the testes. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a medium overall quality determination rating.

Table_Apx A-5. Summary of Ethylene Dibromide Studies Evaluating Reproductive/Developmental Effects in Animals (Oral)

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
Short-term			
Teramoto et al. (1980)	Sprague-Dawley rats (15 males/group) at a dose of 10 or 30 mg/kg/day for 5 days via gavage, mated for 10 weeks. BDF1 mice (7–9 males/group) at a dose of 100 or 150 mg/kg/day for 5 days via gavage.	No effects on mating performance or behavior in rats or mice	Medium
CHRONIC			
NCI (1978)	Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil five days/week in a chronic cancer bioassay (50/sex/groups receiving treatment). Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). TWA doses achieved in each group were 0, 38, 41 mg/kg/day for male rats, 0, 37, 39 mg/kg/day for female rats	↑ Atrophy in the testes were reported in the low dose (14/49) and high dose (18/50) compared to controls (0/20) LOAEL of 38 mg/kg/day was determined in males for increased incidence of atrophy in the testes	Medium
LOAEL = lowest-observed-adverse-effect level			

A.3 Hepatic Toxicity

Although hepatic toxicity is recognized as a critical health outcome for ethylene dibromide, the studies summarized in this section were not selected for quantitative dose-response analysis or as points of departure (PODs). This is primarily due to limitations in study design, data quality, or reporting that precluded their use for quantitative modeling. For example, many of the human case reports and case series describe acute hepatic effects following ingestion or dermal exposure, but lack quantitative exposure data, control groups, or sufficient detail for dose-response assessment ([U.S. EPA, 2021](#); [Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Osterloh, 1986](#); [Letz et al., 1984a, b](#)). Similarly, several animal studies either lacked multiple dose groups, did not report critical endpoints in a manner that allowed for BMD modeling, or had methodological limitations such as high mortality at lower doses, inadequate reporting of control data, or inconsistent exposure durations ([Singh et al., 2007](#); [Prakash et al., 1999](#); [Aragno et al., 1996](#); [Nii et al., 1993](#); [Aragno et al., 1989](#); [Danni et al., 1988](#); [Saraswat et al., 1986](#); [Moslen, 1984](#); [Moody et al., 1981](#); [Nitschke et al., 1981](#); [Nachtom, 1980](#); [Short et al., 1979](#); [Broda et al., 1976](#); [Nachtom, 1968](#); [Rowe et al., 1952](#); [Kettering Laboratory, 1943](#)). As a result, while these endpoints inform the overall weight of evidence for hepatic toxicity, only studies meeting higher standards for methodological rigor and quantitative utility were carried forward for POD derivation in the main narrative.

A.3.1 Human Evidence

EPA identified case reports and case series that reported on ethylene dibromide exposure and hepatic outcomes observed in humans as described in Section 2.3.1.2.1. None of these epidemiology studies were found to have sufficient data for dose-response assessment. Therefore, all epidemiological references identified where hepatic outcomes were observed are characterized below. Table_Apx A-6 characterizes all hepatic outcomes observed in human studies, regardless of the OQDs.

In a case series describing 64 cases of acute exposure to ethylene dibromide, hepatotoxicity was reported in 28 (43.8%) of the cases ([Singh et al., 2007](#)).

Hepatic toxicity has been documented in several cases of acute ingestion exposure, including in cases where individuals died ([Saraswat et al., 1986](#)), as well as several cases who were hospitalized but survived ([Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Prakash et al., 1999](#)).

Six cases of attempted suicide via ingestion of ethylene dibromide in Udaipur, India were reported from December 1982 to June 1984 ([Saraswat et al., 1986](#)), where each of the six people ingested one ampule of ethylene dibromide. Two of these cases died, and four were hospitalized but survived. Autopsies were performed on the two who died. In addition to other abnormalities, the autopsy of one case found “massive necrosis” of the liver, and the autopsy of the other case found centrilobular necrosis of the liver ([Saraswat et al., 1986](#)).

A case report described a 20-year-old weighing 56 kg who consumed a 3-mL ampule of Fumigrain containing 6,480 mg of ethylene dibromide ([Prakash et al., 1999](#)). He was reported to have toxic hepatitis and other issues, which were treated after surviving this acute exposure to ethylene dibromide ([Prakash et al., 1999](#)).

Similarly, a case report of a 16-year-old male who ingested one ampule (3 mL) of ethylene dibromide reported that the individual developed acute hepatic failure, including development of hepatic encephalopathy, as well as metabolic acidosis and coagulopathy ([Singh et al., 2000](#)). He was hospitalized for 20 days, and received hemodialysis and an anti-hepatic coma regime, and survived after this acute exposure to ethylene dibromide ([Singh et al., 2000](#)).

Another paper reported on two men, ages 29 and 20 years, who each ingested 3 mL of ethylene dibromide and were hospitalized ([Mehrotra et al., 2001](#)). They were reported to have developed jaundice, and hepatitis-like illness “without evidence of acute liver failure,” and survived after this acute exposure to ethylene dibromide ([Mehrotra et al., 2001](#)).

In addition to acute ingestion, other routes of acute exposure have been associated with adverse hepatic outcomes. Two workers who died after collapsing in a tank of ethylene dibromide had extensive acute dermal exposure, which was reported to be primarily dermal, but also likely included inhalation exposure ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)). Both cases had metabolic acidosis. An autopsy of the first case indicated liver damage as well as several other issues. The second case had hepatic failure and other issues ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)).

These studies provide evidence that acute exposure to ethylene dibromide, via oral ingestion and potentially other exposure routes, is associated with hepatic toxicity, which may be severe and may contribute to fatalities. These studies did not undergo data quality evaluation because they were screened as Supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review

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Protocol ([U.S. EPA, 2021](#)). However, these studies provide slight evidence of adverse hepatic outcomes potentially occurring following acute exposure to ethylene dibromide.

Table_Apx A-6. Summary of Studies Evaluating the Association Between Ethylene Dibromide Exposure and Hepatic Outcomes in Humans

Reference(s)	Study Description	Hepatic Outcome(s)	Overall Quality Determination
Singh et al. (2000)	Case study of a 16-year-old male who was hospitalized after ingestion of one ampule (3 mL) of ethylene dibromide	Developed acute hepatic failure, including hepatic encephalopathy, as well as metabolic acidosis and coagulopathy	N/A
Saraswat et al. (1986)	Six cases of attempted suicide via ingestion of ethylene dibromide in Udaipur, India, were reported from December 1982 to June 1984, where each of the 6 people ingested one ampule of ethylene dibromide	Two of these cases died, and 4 were hospitalized but survived. Autopsies were performed on the 2 who died. In addition to other abnormalities, the autopsy of 1 case found “massive necrosis” of the liver, and the autopsy of the other case found centrilobular necrosis of the liver.	N/A
Osterloh (1986); Letz et al. (1984a, 1984b)	Two workers who died after collapsing in a tank of ethylene dibromide had extensive acute exposure, which was reported to be primarily dermal, but also likely included inhalation exposure	Both cases had metabolic acidosis. An autopsy of the first case indicated liver damage as well as several other issues. The second case had hepatic failure and other issues.	N/A
Mehrotra et al. (2001)	Two men (aged 29 and 20 years) each ingested 3 mL of ethylene dibromide and were hospitalized and survived.	Developed jaundice, hepatitis-like illness “without evidence of acute liver failure.”	N/A
Prakash et al. (1999)	20-year-old weighing 56 kg who consumed a 3-mL ampule of Fumigrain containing 6,480 mg of ethylene dibromide was hospitalized and survived	Toxic hepatitis	N/A
Singh et al. (2007)	Case series describing 64 cases of acute exposure to ethylene dibromide	Hepatotoxicity was reported in 28 (43.8%) of the cases	N/A
Overall quality determinations are N/A for supplemental studies such as case studies, case series, and mechanistic studies.			

A.3.2 Laboratory Animal Evidence

EPA identified one acute, two short-term, five subchronic, and one chronic animal study that evaluated the effects of ethylene dibromide inhalation on hepatic outcomes. Additionally, 19 animal oral gavage studies in various animal species were identified: 12 acute, 5 short-term, and 1 chronic. References that were considered further as POD candidates are described in Section 2.3.1.2.2, whereas references that were not considered further as POD candidates can be found below. Table_Apx A-7 and Table_Apx A-8 characterize hepatic endpoints that results from inhalation and oral exposure, respectively.

Acute Inhalation

Rats were exposed, whole body, to ethylene bromide vapor concentrations of 200, 400, 1,600, 5,000, or 10,000 ppm for various durations ranging from 0.02 to 16 hours; the durations differed for each group ([Rowe et al., 1952](#)). Groups of 20 rats were also exposed to 100 ppm for 8.5, 12, or 16 hours. Finally, a

separate group of females only (20/group) were exposed to 50, 500, 200, or 800 ppm for 0.1, 0.7, 2.5, or 7 hours. Animals were observed for changes in behavior and body weight changes for 2-3 weeks, or until it was certain they had recovered from the effects of exposure. A subset of animals killed 16 to 24 hours after exposure showed increased liver weights and histopathological changes. A LOEL was not defined for liver endpoints, as the associated exposure levels were not specified. This study is uninformative for hepatic endpoints for this reason.

Short-Term Inhalation

In a short-term duration exposure study, rats (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, to seven 7-hour exposures in 9 days (the methods indicated a frequency of 5 days per week) ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each experiment. Generally, animals that received repeat exposures were monitored for mortality and changes in appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Livers were weighed and microscopically examined. In “some cases” frozen sections of liver were stained with Oil Red O. “In many cases” blood was collected for determination of BUN levels and plasma-prothrombin-clotting time was determined (only in animals exposed to 100 ppm). “In some cases” total lipid analysis was conducted on liver sections. Three out of 10 animals died after 1, 5, and 7 exposures. Surviving rats were thin and unkempt. Liver weights were purportedly significantly increased; however, the data table only shows the unexposed controls (n = 4). Air-only control responses were not reported, which would have been the more appropriate comparator. Histopathology showed cloudy swelling in the liver. The results are likely to represent a LOAEC of 100 ppm; however, based on reporting deficiencies and failure to use the more appropriate control, the study was considered uninformative and a reliable POD could not be determined.

In a short-term duration exposure study, rabbits (4 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, for up to four 7-hr exposures in four days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). Animals suffered severe intoxication and 2/4 animals died within two days and a third died during exposure on the third day. The last animal was sacrificed following the fourth exposure. Animals that died showed widespread central fatty degeneration of the liver and some necrosis. No control responses were reported, and it is unclear if controls were indeed included as there were no mention of controls in the text. Two additional rabbits were exposed to the same concentration for 7 hours on 2 consecutive days and then sacrificed. These animals lost weight (data not shown). Organ weights were comparable to controls (which controls not specified) and serum BUN levels and nonprotein nitrogen levels were normal. The liver showed slight cloudy swelling. The results are likely to represent a LOAEC of 100 ppm; however, based on reporting deficiencies and failure to use the more appropriate control, the study was considered uninformative and a reliable POD could not be determined.

Subchronic Inhalation

CDF (F344) rats (9 weeks old) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/ day, 5 days/week for 6 weeks (10 males/group) ([Nitschke et al., 1981](#)). Significantly decreased body weights were observed in male rats at 40 ppm ethylene dibromide dose. Relative liver weights in males exposed to 40 ppm were significantly elevated. These effects were not observed in female animals. A hepatic LOEL of 40 ppm was identified for male rats. EPA assigned this study a high overall quality determination rating.

CDF (F344) rats (9 weeks old) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 13 weeks (10/sex/group), or for 13 weeks plus an 88 to 89-day recovery period to evaluate lesion reversibility (10/sex/group) ([Nitschke et al., 1981](#)). In animals that were exposed for 13 weeks without the recovery period, significantly decreased body weights were observed in male rats at 40 ppm. By the end of the recovery period, weights returned to control levels. Relative liver weights in males exposed to 40 ppm were significantly elevated, persisting into the recovery period. Liver weights in females exposed to 10 ppm (absolute) or 40 ppm (absolute and relative) were also significantly different than control prior to the recovery period, where weights then returned to that of controls. Females in the 40 ppm group also had slight paleness of the liver. A LOEL of 10 ppm was identified for hepatic effects. EPA assigned this study a high overall quality determination rating.

In a subchronic duration exposure study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day, 5 days/week for as many as 63 exposures in 91 days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Hematological examinations were conducted “periodically” in “representative” rats. Animals were necropsied at the time of sacrifice. Lungs, heart, liver, kidneys, spleens, and testes were weighed and microscopically examined along with the adrenal glands and pancreas. In “some cases” frozen sections of liver and kidney were stained with Oil Red O. “In many cases” blood was collected for determination of BUN levels and plasma-prothrombin-clotting time was determined (only in animals exposed to 100 ppm). “In some cases” total lipid analysis was conducted on liver sections. More than 50% of the males died due to pneumonia and infections in the upper respiratory tract. Four treated females died. Treated animals showed reduced growth, but the difference was not statistically significant. Absolute liver weights increased in males and females. These changes were significant compared with the unexposed controls. The air-only control data were not reported and would have been a more appropriate comparator. No histopathological or clinical chemistry effects were observed. A LOAEC of 50 ppm was determined for significant organ weight changes. EPA assigned this study a low overall quality determination rating during systematic review.

In a subchronic duration exposure study, guinea pigs (8/group, unclear if 8/sex or 8 total) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day, 5 days/week for 80 days (57 exposures total) ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Livers were weighed and microscopically examined. In “some cases” frozen sections of liver and kidney were stained with Oil Red O. “In many cases” blood was collected for determination of BUN levels and plasma-prothrombin-clotting time was determined (only in animals exposed to 100 ppm). “In some cases” total lipid analysis was conducted on liver sections. Both male and female final body weights were significantly decreased compared to the unexposed controls (reductions of 26% in males and 24% in females). No comparisons were made to air-only controls, and these data were not provided. There are no other data within the reference indicating whether the guinea pig unexposed and air-only controls showed similar responses. The increases in absolute liver weights observed likely reflect the decreased body weights observed. Relative liver weights were not reported. Total lipid contents were comparable to controls. There was slight fatty degeneration in all of the livers and slight interstitial congestion and edema with slight parenchymatous degeneration of the tubular epithelium in 8/14 kidneys. Control

incidences and statistical significance were not reported. A tentative LOAEL of 50 ppm was determined based on decreased body weights and liver and kidney histopathology; however, there are reporting deficiencies, and the study did not use the most appropriate control group as a comparator. EPA assigned this study a low overall quality determination rating during systematic review. Young adult rabbits (1 female and 3 males) were exposed whole body to ethylene dichloride vapors at concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for 84 days (totaling 59 exposures) ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Livers were weighed and microscopically examined. In "some cases", frozen sections of liver and kidney were stained with Oil Red O. "In many cases", blood was collected for determination of BUN levels and plasma-prothrombin-clotting time was determined (only in animals exposed to 100 ppm). "In some cases", total lipid analysis was conducted on liver sections. No significant effects were observed in any of the endpoints examined except for a "slight increase in liver weights" (data and significance were not reported). Since the data were not provided, and the statement about significance is unclear, a reliable POD could not be determined. EPA assigned this study a low overall quality determination rating during systematic review.

Acute Oral

In an acute study evaluating the effects of exposure on microsomal responses, male Sprague-Dawley rats (3/group) were administered a dose of the test substance in mineral oil at 625 mg/kg via gavage ([Moody et al., 1981](#)). Animals were sacrificed one or 18 hours after dosing. Control rats were used, but details (untreated vs. vehicle control) were not provided. Systemic endpoints were limited to mortality, body weights, and relative liver weights. No mortality or loss of body weight was observed. Relative liver weights were reported to be elevated, compared with controls, but the data were not shown. No toxicity values were reported by the study author. A LOEL of 625 mg/kg was determined based on increased relative liver weights. EPA assigned this study a medium overall quality determination rating.

In an acute study evaluating the effects of exposure on microsomal responses, Male Sprague-Dawley rats (3/group) were administered a dose of the test substance in mineral oil at 220 mg/kg via gavage ([Moody et al., 1981](#)). Animals were sacrificed one or 18 hours after dosing. Control rats were used, but details (untreated vs. vehicle control) were not provided. Systemic endpoints were limited to mortality, body weights, and relative liver weights. No mortality was observed. Study authors reported that treated animals showed "appreciably greater loss of body weight than controls," but no additional information was provided. Relative liver weights were reported to be elevated compared with controls, but the data were not shown and it is unclear if the increase was reflective of body weight changes. No toxicity values were reported by the study author. A LOEL of 220 mg/kg was determined based on increased relative liver weights in male rats. EPA assigned this study a medium overall quality determination rating.

Male Sprague-Dawley rats were given an i.p. injection of 0.9% NaCl and a gavage of water; these were controls for other experiments performed in the study ([Aragno et al., 1996](#)). Six hours later, animals (3-8/group) were administered mineral oil or 87 mg/kg ethylene dibromide via gavage. Animals were sacrificed after 0.5, 4, or 12 hours post-treatment. Endpoints evaluated included serum SDH levels (12 hours), lipid peroxidation (4 hours) and total hepatic GSH levels (0.5 and 4 hours). Serum SDH levels were significantly increased (2-fold) compared to the control group 12 hours after treatment. Total GSH content was significantly decreased at 0.5 hour (58%) and 4 hours (34%) compared to the control group.

No significant difference in lipid peroxidation was observed compared to the control group. A LOEL of 87 mg/kg was determined based on increase in serum SDH levels. EPA assigned this study a medium overall quality determination rating.

Albino rats (both sexes, number per group not specified) were administered a single dose of 0 or 110 mg/kg body weight ethylene dibromide (purity not reported) in soybean oil, via gavage ([Nachtomi et al., 1968](#)). There is some uncertainty in the dose because the data tables reported the dose as 120 mg/kg. Liver weights, liver NADP, liver ascorbic acid, and alkaline phosphatase in liver and blood were evaluated. The study reported a significant increase in relative liver weights (19-20%) in both sexes 20 hours after dosing. Alkaline phosphatase was increased in female livers (but not serum), and in both the liver and serum of males. Changes in liver free sulfhydryl and ascorbic acid concentrations were plotted vs. time, and the data were not statistically analyzed. 110 mg/kg, the only dose tested, was identified as a LOAEL for increased relative liver weights with associated biochemical changes. EPA assigned this study a medium overall quality determination rating.

In a focused study, male Sprague-Dawley rats (at least 34 animals/group) were administered ethylene dibromide (purity 99%) at 75 mg/kg/dose via gavage in corn oil, as either one or two doses ([Moslen, 1984](#)). There were three exposure groups. Group one received corn oil (2.5 mL/kg) at 0 and 24 hr. Group 2: received corn oil at 0 hr and 75 mg/kg ethylene dibromide at 24 hr. Group 3: received 75 mg/kg ethylene dibromide at 0 and 24 hr. Animals from all groups underwent a partial (two-thirds) hepatectomy four to five hours after the final dose and a remaining one-third hepatectomy on study day 90. Starting on month 13, all animals were given 0.05% PBT as a promoter in drinking water, for the last 4 months of the study. Mitogenic indices of hepatocytes were determined from 10 animals per group at the time of the first hepatectomy. Body weights were determined after 90 days and at termination (16 months). Liver weights were recorded at the final sacrifice. Histology was done on liver samples collected at 90 days and 16 months, and GGT activity was assessed in saved liver specimens. There were no significant changes in body weights, although the authors noted that final body weights of 16% of the rats were >1,000 g and these animals were considered to be morbidly obese. It was not stated which group(s) these animals were in, whether the obesity was related to exposure, and it is unclear whether this may have influenced the mean body weights reported. Animals from both treatment regimens showed significant increases in the mitotic index of hepatocytes, compared with controls. Liver weights were not impacted by treatment. Treated animals had higher incidences of eosinophilic foci, and also higher numbers, larger sizes, and larger areas of γ -GGT foci than the control group. A LOAEL of 75 mg/kg, the only dose tested, was identified based on observed liver effects. EPA assigned this study a high overall quality determination rating for hepatic endpoints due to well-detailed descriptions of experimentation and data analysis. The outcomes of this study were considered when characterizing the hepatic effects associated with ethylene dibromide exposure, alongside the remaining evidence described in this section.

Adult male albino rats were administered 0 or 110 mg/kg ethylene dibromide in olive oil (1:50 v/v) via a single gavage ([Broda et al., 1976](#)). Animals (6-8/timepoint) were sacrificed at 2, 4, 8, 12, 17, and 22 hours after dosing. Livers were collected for histopathology. It is unclear if control animals were also killed at each time point. After four hours, the study reports that no detectable changes occurred. At 8 and 12 hours post-dosing centrisinusoidal dilations were observed (incidence data was not reported). At 17 hours post-dosing, study authors report "degenerative changes of hepatocytes were noticed in all preparations". These changes included granular degeneration of cytoplasm and marked sinusoidal dilation, and partly or completely degenerated nuclei. At 24 hours post-dosing, "necrosis was evident in the central and midzone of the liver lobules," balloon cells were "sometimes visible at the borders of the mid-zonal region". Centrilobular necrosis was observed at 24 hours (incidence data were not reported).

Study authors also reported that the test substance did not cause fat accumulation in the liver cells. The study authors did not report a POD. A LOAEL of 110 mg/kg was determined based on increased hepatic lesions. EPA assigned this study a medium overall quality determination rating.

Male CD rats (4/group) were exposed to 0, 10, or 100 mg/kg ethylene dibromide dissolved in corn oil via oral gavage ([Short et al., 1979](#)). Two and 4 hours following exposure, the non-protein sulfhydryl concentration was determined in the liver and right testis. In the 100 mg/kg group, the hepatic non-protein sulfhydryl concentration was significantly reduced. A hepatic LOEL of 100 mg/kg was identified. EPA assigned this study a medium overall quality determination rating.

Male CD rats (4/group) were exposed to 0, 10, or 100 mg/kg ethylene dibromide dissolved in corn oil via oral gavage ([Short et al., 1979](#)). Aortic blood was collected 24 hours later to measure serum SGOT, SGPT, and BUN. There were no significant treatment-related findings. A hepatic NOAEL of 100 mg/kg was identified. EPA assigned this study a medium overall quality determination rating.

Male Wistar rats weighing 180 to 200 g were to exposed to ethylene dibromide via gavage ([Danni et al., 1988](#)). Five to seven rats/group were treated with 1 or 2 μ L per 100 g body weight to ethylene dibromide. Liver enzyme SDH, AST and ALT were slightly elevated after (12 or 24 hours) treatment compared to the control group. Ethylene dibromide exposure led to a slight, yet significant liver GSH depletion at 30 minutes following exposure, with a rebound to normal GSH level 12 hours following exposure. A hepatic LOEL of 0.02 μ L/g was identified. EPA assigned this study a medium overall quality determination rating.

Male rats (strain not reported; referred to as “locally bred”) were fasted overnight and administered a single dose of 0 (n = 3–4/group) or 110 mg/kg ethylene dibromide (n = 4–6/group) via gavage in corn oil ([Nachtomí, 1980](#)). Groups 1 and 2 remained fasting after ethylene dibromide treatment for 24 or 48 hours, respectively and groups 3 and 4 were re-fed for the same periods, respectively. Two hours before sacrifice, rats were administered [methyl-3H]thymidine. Endpoints evaluated include serum GPT (ALT) and SDH, liver weight, and liver proliferation (assessed by incorporation of 3H-thymidine). In the group of rats that continued to be fasted, no significant changes in serum ALT, SDH or relative liver weight were seen compared to control at 24 hours. At 48 hours, significant, but not biologically relevant increase in serum ALT (<2-fold) and a significant increase in SDH (63%) were seen; no significant change in relative liver weights were reported. Increased hepatic cell proliferation (3H-thymidine incorporation) was measured after 24 hours (2.4-fold) and 48 hours (5.6-fold) in fasted rats compared to the control group. In the group of rats that were re-fed for 24 hours after dosing, no significant difference in serum ALT or SDH were measured; relative liver weight was significantly, but not biologically relevant, increased (5%) compared to the control group. After 48 hours of refeeding, no significant changes in serum ALT levels were measured but significant increases in serum SDH (71%) and relative liver weight (27%) were reported compared to the control group. Increased hepatic cell proliferation (3H-thymidine incorporation) was observed at 24 hours (2.7-fold) and 48 hours (2.2-fold) in re-fed rats compared to control. Study authors do not identify a POD. A LOAEL of 110 mg/kg was determined based on an increase in relative liver weight and serum SDH levels. A mechanistic LOAEL of 110 mg/kg was also determined based on increased hepatic cell proliferation. EPA assigned this study a medium overall quality determination rating.

Male rats (strain not reported; referred to as “locally bred”) were administered a single dose of 0 (n = 8) or 110 mg/kg (n = 15) ethylene dibromide via gavage in corn oil ([Nachtomí, 1980](#)). The rats were killed 24 hours after the ethylene dibromide dose and two hours after [methyl-3H]-thymidine treatment. Endpoints evaluated include serum GPT (ALT) and alkaline phosphatase (AP); liver weight; liver

calcium and AP levels; and liver proliferation (assessed by incorporation of 3H-thymidine). Another group of rats (15/group) was included that received diethyldithiocarbamate (DDC; 80 mg/kg body weight.) twice, once every other day, and one more dose 30 minutes before ethylene dibromide or oil treatment as described above. The same endpoints were evaluated as above. In rats that only received ethylene dibromide, no significant difference in serum ALT or AP levels were measured compared to the control group. No significant differences in liver weight, liver AP, or liver calcium levels were measured compared to the control group. Significantly increased hepatic cell proliferation (3H-thymidine incorporation) was observed (4.2-fold) compared to the control group. In control DDC-pretreated rats, significant decreases in the serum AP and significant increases in live calcium were measured compared to untreated control. No differences in serum ALP, relative liver weights, or liver AP levels were observed compared to untreated control. In rats pretreated with DDC and received ethylene dibromide, significant decreases in serum AP, increases in serum ALT, increases in liver AP and increases in liver calcium were observed compared to untreated control. No change in relative liver weights were observed compared to untreated control. Hepatic cell proliferation was increased 5-fold compared to untreated controls and 2.9-fold compared to the DDC alone group. The modulation effect of DDC was an enhancement of the toxic effect of ethylene dibromide, as reflected by increased activity of serum GPT, liver AP, and Ca²⁺ levels. The elevation of DNA specific activity seems to be an additive effect of both ethylene dibromide and DDC. The high [methyl-3H]thymidine incorporation to DNA in the DDC + ethylene dibromide group could result from both DNA repair and DNA replication. DDC may have the same side effect as that of ethylene dibromide on liver cells. Study authors did not identify a POD. A mechanistic LOEL of 110 mg/kg is proposed based on increased hepatic cell proliferation. EPA assigned this study a medium overall quality determination rating.

Rabbits (1/group) were exposed to ethylene dibromide by single oral gavage at 20 mg/kg, 25 mg/kg, 30 mg/kg, 50 mg/kg, 100 mg/kg, 250 mg/kg, 500 mg/kg, 1,000 mg/kg, 2,000 mg/kg, or 3,500 mg/kg ([Kettering Laboratory, 1943](#)). Rabbits given doses of 50, 100, and 250 mg/kg died at 34, 20 and 12-16 hours, respectively. No adverse clinical signs were observed in these rabbits. Pathological effects that occurred in animals that died include congestion in organs (not specified) and focal degeneration in cells of the liver. EPA assigned this study an uninformative overall quality determination rating for hepatic endpoints during systematic review as only one animal was used for each dose, and the dose level at which the liver effects were seen is not specified.

Short-Term Oral

Early effects of a high-dose of ethylene dibromide in rats pretreated with modulators was evaluated ([Nachtom, 1980](#)). Phenobarbitone (PB) was given in drinking water (1 mg/mL, equivalent to 50 mg/kg) in addition to either ethylene dibromide or oil (control). Diethyldithiocarbamate (DDC) (80 mg/kg body weight) was administered twice, once every other day, and one more dose 30 min before ethylene dibromide or oil treatment. The rats were fed or fasted 24 hours before ethylene dibromide administration (via gavage) and killed 2 hours thereafter. Study authors did not explicitly state the dose of ethylene dibromide that was administered. They stated that the experiment was with the "high ethylene dibromide dose." Based on descriptions of other study designs in this publication, it was assumed that the high-dose used was 110 mg/kg, but there is some uncertainty. Eight to nine rats were included in each treatment group. In fasted rats dosed with ethylene dibromide alone (*i.e.*, no PB or DDC pretreatment), no effects on liver weight, serum GPT and ALP, or liver ALP and CS²⁺ levels were reported. In PB-pretreated and fasted rats, relative liver-to-body-weight increased and the GPT activity decreased in the serum regardless of ethylene dibromide treatment. In DDC-pretreated and fasted rats, inhibition of serum GPT and AP activity was noticed with enhanced AP activity in the liver. The differences from control were more marked with DDC plus ethylene dibromide treatment in fasted than in fed animals. The study authors did not identify a POD. A NOAEL of 110 mg/kg is proposed based on

no effects observed in rats fasted and treated with a single dose of 110 mg/kg ethylene dibromide. EPA assigned this study a medium overall quality determination rating.

Female F344 rats (10/group) were orally exposed to 0 or 100 mg/kg ethylene dibromide in olive oil for two days ([Nii et al., 1993](#)). Half of each group (5/group) were then inoculated with Tyzzer's organism and all animals were sacrificed two days later. Ethylene dibromide treatment alone resulted in increased absolute (23%) and relative (24%) liver weights, compared with control animals. Body weight gain in treated animals was reduced by 13% compared with control animals. These endpoints were not statistically analyzed. There did not appear to be a significant change in serum GOT or GPT. There were a greater number of mitotic figures and an increase in swelling of hepatocytes (slight severity) relative to controls; incidences were not provided. A hepatic LOEL of 100 mg/kg was identified. EPA assigned this study a medium overall quality determination rating.

Male rats (n = 8, strain not reported; referred to as "locally bred") were administered a single dose of 0 or 10 mg/kg ethylene dibromide via gavage in corn oil for 12 days ([Nachtom, 1980](#)). The rats were killed 24 hours after the last treatment and 2 hours after [methyl-3H] thymidine injections. Endpoints evaluated included serum ALT and SDH, liver weight and hepatic cell proliferation ([3H]-thymidine incorporation). The study also investigated mechanisms involved in ethylene dibromide toxicity by studying effects of pentobarbitone (PB) or diethyldithiocarbamate (DDC) treatment on rats given ethylene dibromide. Four groups of rats (6/group) were used for this study. PB was given in drinking water (1 mg/mL) in addition to either ethylene dibromide or oil (control), the daily dose of PB being approximately 50 mg/kg body weight; DDC, 80 mg/kg body weight, was administered daily, by gavage, 30 minutes before ethylene dibromide or oil administration. The dose of ethylene dibromide was 10 mg/kg body weight/day. The rats were killed 24 hours after the last treatment and 2 hours after [methyl-3H]thymidine injection. Endpoints evaluated included serum ALT and SDH, liver weight and hepatic cell proliferation ([3H]-thymidine incorporation).

In rats exposed only to ethylene dibromide, significant, but not biologically relevant increase in serum ALT (<2-fold) and a significant increase in SDH (2.2-fold) were observed compared to control; no significant change in relative liver weights were seen. No significant effect on hepatic cell proliferation was observed compared to the control group. PB alone (*i.e.*, no treatment with ethylene dibromide) increased the relative liver weight significantly (5%) but did not affect the DNA concentration per gram and slightly depressed the specific radioactivity of DNA. PB protected against the elevation of serum enzymes caused by ethylene dibromide. DDC alone increased the liver weight, elevated the GPT in serum, and enhanced the DNA synthesis in ethylene dibromide-treated rats. DDC seems to act in a synergistic way with ethylene dibromide. The study authors did not propose a POD. A LOEL of 10 mg/kg/day was determined based on increased serum SDH in animals treated with ethylene dibromide alone. EPA assigned this study a medium overall quality determination rating.

Male Wistar rats were administered ethylene dibromide, carbon tetrachloride, or a mixture of the two chemicals ([Aragno et al., 1989](#)). The primary goal of this study was to determine if the mixture of the two chemicals induced a stronger effect on the liver than either chemical alone. The precise doses administered, and the number of doses administered cannot be determined. Four to 48 hours after administration of the final dose, various liver parameters were measured, including relative liver weight, dry liver weight, liver and serum triglycerides, circulating non esterified non-esterified fatty acids (NEFA), and liver triglyceride synthesis. Treatment with ethylene dibromide alone did not alter any of the measured parameters compared to control animals. A hepatic NOAEL of 2 µL /100 g bodyweight was identified. However, EPA assigned this study an uninformative overall quality determination rating during systematic review due to lack of clarity on ethylene dibromide administration frequency.

Male rats (strain not reported; referred to as “locally bred”) were fed fumigated diets containing 0, 100, or 200 ppm ethylene dibromide (study reports equivalent to 0 (n = 8), ≈ 10 (n = 6), and ≈ 20 (n = 6) mg/kg/day) for 18 days ([Nachtomí, 1980](#)). Rats were administered [methyl-3H]thymidine intraperitoneal daily throughout the 18 days of exposure. Endpoints evaluated included liver weight and hepatic cell proliferation ([3H]-thymidine incorporation). No significant difference in relative liver weights were observed compared to the control group. No significant difference in hepatic cell proliferation was seen compared to the control group. The study authors do not identify a POD. A NOAEL of 20 mg/kg/day was determined based on lack of observed effects. However, EPA assigned this study an uninformative overall quality determination rating during systematic review due to lack of reporting on diet preparation and storage.

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Table Apx A-7. Summary of Ethylene Dibromide Studies Evaluating Hepatic Effects in Animals (Inhalation)

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
Acute			
Rowe et al. (1952)	Rats were exposed, whole body, to ethylene bromide vapor concentrations of 200, 400, 1,600, 5,000, or 10,000 ppm for various durations ranging from 0.02–16 hours; the durations differed for each group. Groups of 20 rats were also exposed to 100 ppm for 8.5, 12, or 16 hours. Finally, a separate group of females only (20/group) were exposed to 50, 500, 200, or 800 ppm for 0.1, 0.7, 2.5, or 7 hours.	<u>16 to 24 hours post-exposure:</u> ↑ liver weights and histopathological changes. LOEL was not defined for liver endpoints, as the associated exposure levels were not specified	Uninformative
Short-term			
Rowe et al. (1952)	<u>Rats:</u> (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, to seven 7-hour exposures in 9 days (the methods indicated a frequency of 5 days per week). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each experiment. <u>Rabbits:</u> (4 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, for up to four 7-hour exposures in 4 days	<u>Rats (50 ppm):</u> Slight fatty degeneration of livers with edema and interstitial congestion. <u>Rats (100 ppm):</u> ↑ Organ weight and cloudy swelling of hepatocytes <u>Rabbits:</u> Widespread central fatty degeneration of the liver and some necrosis.	Uninformative
Subchronic			
Rowe et al. (1952)	<u>Rats:</u> n = 20/sex were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day, 5 days/week for as many as 6 exposures in 91 days <u>Guinea pigs:</u> 8/group, unclear if 8/sex or 8 total) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day, 5 days/week for 80 days (57 exposures total) <u>Rabbits:</u> Young adult rabbits (1 female and 3 males) were exposed whole body to ethylene dichloride vapors at	<u>Rats:</u> ↑ Absolute liver weights (significantly) in both males and females. The air-only control data not reported and would have been a more appropriate comparator LOAEC of 50 ppm was determined for significant organ weight changes <u>Guinea pigs:</u> ↑ absolute liver weights observed likely reflect the decreased body weights observed	Low

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
	concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for 84 days (totaling 59 exposures)	• Slight fatty degeneration of livers with edema and interstitial congestion at 50 ppm. • Relative liver weights were not reported. A tentative LOAEL of 50 ppm was determined based on decreased body weights and liver <u>Rabbits:</u> • No significant effects were observed in any of the endpoints examined except for a “slight increase in liver weights” (data and significance were not reported). Because the data were not provided, and the statement about significance is unclear, a reliable POD could not be determined	
Nitschke et al. (1981)	CDF (F344) rats (9 weeks old) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 13 weeks (10/sex/group), or for 13 weeks plus an 88- to 89-day recovery period	<u>Males (40 ppm):</u> ↑ relative liver weight 40 ppm <u>Females (10 ppm):</u> ↑ absolute liver weight (10 ppm) ↑ absolute and relative liver weights (40 ppm) • Females in the 40 ppm group also had slight paleness of the liver LOEL of 10 ppm was identified for hepatic effects	High
Chronic			
NTP (1982)	F344 rats (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide for 6 hours/day, 5 days/week for 2 years	• General hepatic necrosis was observed in males (2 control, 6 low-dose, 19 high-dose) and females (2 control, 3 low-dose, 13 high-dose), with significant occurrence seen in high-dose animals. • Localized centrilobular hepatic necrosis was significant in low-dose males (1/50 controls, 5/50 low-dose, 13/50 high-dose) LOAEC of 10 ppm was determined based on centrilobular liver necrosis in males	High
LOEL = lowest-observed-effect level; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level			

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Table Apx A-8. Summary of Ethylene Dibromide Studies Evaluating Hepatic Effects in Animals (Oral)

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
Acute			
Moody et al. (1981)	<u>Group 1:</u> Male Sprague-Dawley rats (3/group) were administered ethylene dibromide (625 mg/kg in mineral oil via gavage). <u>Group 2:</u> Male Sprague-Dawley rats (3/group) were administered ethylene dibromide (220 mg/kg in mineral oil via gavage).	<u>Group 1:</u> Relative liver weights were reported to be elevated, compared with controls, but the data were not shown. No toxicity values were reported by the study author A LOEL of 625 mg/kg was determined based on increased relative liver weights <u>Group 2:</u> Relative liver weights were reported to be elevated compared with controls, but the data were not shown and it is unclear if the increase was reflective of body weight changes. No toxicity values were reported by the study author LOEL of 220 mg/kg was determined based on increased relative liver weights in male rats	Medium
Aragno et al. (1996)	Male Sprague-Dawley rats (3–8/group) were administered mineral oil or 87 mg/kg ethylene dibromide via gavage.	• Significantly ↑ serum SDH levels (2-fold) 12 hours after treatment. Total GSH content was significantly decreased at 0.5 hours (58%) and 4 hours (34%) • No significant difference in lipid peroxidation was observed compared to the control group LOEL of 87 mg/kg was determined based on increase in serum SDH levels	Medium
Nachtoml (1980)	Albino rats (both sexes, number per group not specified) were administered a single dose of 0 or 110 mg/kg body weight ethylene dibromide (purity not reported) in soybean oil, via gavage	• Significant increase in relative liver weights (19–20%) in both sexes 20 hours • Alkaline phosphatase increased in female livers (but not serum), and in both the liver and serum of males • Changes in liver free sulphydryl and ascorbic acid concentrations were plotted vs. time, and the data were not statistically analyzed 110 mg/kg, the only dose tested, was identified as a LOAEL for increased relative liver weights with associated biochemical changes	Medium

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
Kettering Laboratory (1943)	Rabbits (1/group) were exposed to ethylene dibromide by single oral gavage at 20 mg/kg, 25 mg/kg, 30 mg/kg, 50 mg/kg, 100 mg/kg, 250 mg/kg, 500 mg/kg, 1,000 mg/kg, 2,000 mg/kg, or 3,500 mg/kg	Mortality at doses of 50, 100, and 250 mg/kg at 34, 20, and 12–16 hours, respectively Pathological effects that occurred in animals that died include congestion in organs (not specified) and focal degeneration in cells of the liver	Uninformative
Moslen (1984)	Male Sprague-Dawley rats were given the following oral treatment <u>Group 1:</u> received corn oil (2.5 mL/kg) at 0 and 24 hr <u>Group 2:</u> received corn oil at 0 hr and 75 mg/kg ethylene dibromide at 24 hr <u>Group 3:</u> received 75 mg/kg ethylene dibromide at 0 and 24 hours	• Significant increases in the mitotic index of hepatocytes, compared with controls. Liver weights were not impacted by treatment • Higher incidences of eosinophilic foci, and also higher numbers, larger sizes, and larger areas of γ-GGT foci than the control group LOAEL of 75 mg/kg, the only dose tested, was identified based on observed liver effects	High
Broda et al. (1976)	Adult male albino rats were administered 0 or 110 mg/kg ethylene dibromide in olive oil (1:50 v/v) via a single gavage Broda et al. (1976) . Animals (6–8/timepoint) were sacrificed at 2, 4, 8, 12, 17, and 22 hours after dosing.	<u>8 and 12 hours post-dosing:</u> • Centrisinusoidal dilations were observed (incidence data was not reported) <u>17 hours post-dosing:</u> • Study authors report “degenerative changes of hepatocytes were noticed in all preparations”. These changes included granular degeneration of cytoplasm and marked sinusoidal dilation, and partly or completely degenerated nuclei <u>24 hours post-dosing:</u> • Necrosis was evident in the central and midzone of the liver lobules • Balloon cells were sometimes visible at the borders of the mid-zonal region • Centrilobular necrosis was observed at 24 hours (incidence data were not reported) • Study authors also reported that the test substance did not cause fat accumulation in the liver cells. The study authors did not report a POD. LOAEL of 110 mg/kg was determined based on increased hepatic lesions.	Medium
Short et al. (1979)	Male CD rats (4/group) were exposed to 0, 10, or 100 mg/kg ethylene dibromide dissolved in corn oil via oral gavage	Hepatic non-protein sulfhydryl concentration was significantly reduced at 100 mg/kg	Medium

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
		Hepatic LOEL of 100 mg/kg was identified.	
Danni et al. (1988)	Male Wistar rats weighing 180 to 200 g were exposed to ethylene dibromide via gavage. Five to seven rats/group were treated with 1 or 2 µL per 100 g body weight to ethylene dibromide	• Liver enzyme SDH, AST and ALT were slightly elevated after (12 or 24 hours) treatment compared to the control group • Slight, yet significant liver GSH depletion at 30 minutes following exposure, with a rebound to normal GSH level 12 hours following exposure LOEL of 0.02 µL/g was identified	Medium
Nachtomi (1980)	Male rats (strain not reported; referred to as “locally bred”) were fasted overnight and administered a single dose of 0 (n = 3-4/group) or 110 mg/kg ethylene dibromide (n = 4-6/group) via gavage in corn oil. Groups 1 and 2 remained fasting after ethylene dibromide treatment for 24 or 48 hours, respectively and groups 3 and 4 were re-fed for the same periods, respectively	<u>Fasted group:</u> • No significant changes in serum ALT, SDH or relative liver weight were seen compared to control at 24 hours • At 48 hours, significant, but not biologically relevant increase in serum ALT (<2-fold) and a significant increase in SDH (63%) were seen; no significant change in relative liver weights were reported • Increased hepatic cell proliferation (3H-thymidine incorporation) was measured after 24 hours (2.4-fold) and 48 hours (5.6-fold) in fasted rats compared to the control group <u>Refed group:</u> • No significant difference in serum ALT or SDH were measured; relative liver weight was significantly, but not biologically relevant, increased (5%) • After 48 hours of refeeding, no significant changes in serum ALT levels were measured but significant increases in serum SDH (71%) and relative liver weight (27%) were reported compared to the control group ↑ Increased hepatic cell proliferation (3H-thymidine incorporation) was observed at 24 hours (2.7-fold) and 48 hours (2.2-fold) in re-fed rats compared to control. Study authors do not identify a POD. LOAEL of 110 mg/kg was determined based on an increase in relative liver weight and serum SDH levels	Medium
Nachtomi (1980)	Male rats (strain not reported; referred to as “locally bred”) were administered a single dose of 0 (n = 8) or 110 mg/kg (n = 15) ethylene dibromide via gavage in corn oil	↑ hepatic cell proliferation (3H-thymidine incorporation) was observed (4.2-fold) compared to the control group	Medium

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
		• In control DDC-pretreated rats, significant decreases in the serum AP and significant increases in live calcium were measured compared to untreated control • No differences in serum ALP, relative liver weights, or liver AP levels were observed compared to untreated control <u>In rats pretreated with DDC:</u> ↓serum AP ↑ serum ALT ↑ liver AP ↑ liver calcium • No change in relative liver weights • Hepatic cell proliferation was increased 5-fold compared to untreated controls and 2.9-fold compared to the DDC alone group • The modulation effect of DDC was an enhancement of the toxic effect of ethylene dibromide, as reflected by increased activity of serum GPT, liver AP, and Ca²⁺ levels • The elevation of DNA specific activity seems to be an additive effect of both ethylene dibromide and DDC • The high [methyl-³H]thymidine incorporation to DNA in the DDC + ethylene dibromide group could result from both DNA repair and DNA replication. DDC may have the same side effect as that of ethylene dibromide on liver cells • Study authors did not identify a POD. A mechanistic LOEL of 110 mg/kg is proposed based on increased hepatic cell proliferation	
Short-term			
Nachtomi (1980)	The rats (n = 8–9) were fed or fasted 24 hours before ethylene dibromide administration (via gavage) and killed 2 hours thereafter. Study authors did not explicitly state the dose of ethylene dibromide that was administered. They stated that the experiment was with the “high ethylene dibromide dose.” Based on descriptions of other study designs in this publication, it was	A NOAEL of 110 mg/kg is proposed based on no effects observed in rats fasted and treated with a single dose of 110 mg/kg ethylene dibromide	Medium

Reference	Study Description	Hepatic Outcome(s)	Overall Quality Determination
	assumed that the high-dose used was 110 mg/kg, but there is some uncertainty.		
Nii et al. (1993)	Female F344 rats (10/group) were orally exposed to 0 or 100 mg/kg ethylene dibromide in olive oil for two days Nii et al. (1993) . Half of each group (5/group) were then inoculated with Tyzzer's organism.	↑ absolute (23%) and relative (24%) liver weights LOEL of 100 mg/kg was identified	Medium
Nachtomí (1980)	Male rats (n = 8, strain not reported; referred to as "locally bred") were administered a single dose of 0 or 10 mg/kg ethylene dibromide via gavage in corn oil for 12 days	Significant, but not biologically relevant increase in serum ALT (<2-fold) and a significant increase in SDH (2.2-fold) LOEL of 10 mg/kg/day was determined based on increased serum SDH in animals treated with ethylene dibromide alone	Medium
Nachtomí (1980)	Male rats (strain not reported; referred to as "locally bred") were fed fumigated diets containing 0, 100, or 200 ppm ethylene dibromide (study reports equivalent to 0 (n = 8), ~10 (n = 6), and ~20 (n = 6) mg/kg/day) for 18 days. Rats were administered [methyl-3H]thymidine intraperitoneal daily throughout the 18 days of exposure.	No significant differences were observed NOAEL of 20 mg/kg/day was determined based on lack of observed effects.	Medium
Chronic			
NCI (1978)	Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/groups receiving treatment) Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group were 0, 38, 41 mg/kg/day for male rats, 0, 37, 39 mg/kg/day for female rats (target doses 40 and 80).	<u>Males:</u> - Liver peliosis in 0/40 control, 10/50 low-dose, and 9/50 high-dose groups. <u>Females:</u> - Peliosis in 0/40 control, 1/47 low-dose, and 5/48 high-dose groups. A POD was not reported by study authors. A LOAEL of 38 mg/kg/day was determined in males for increased incidence of liver peliosis.	Medium
LOEL = lowest-observed-effect level; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure			

A.4 Gastrointestinal Toxicity

Although gastrointestinal toxicity is recognized as a critical health outcome for ethylene dibromide, the studies summarized in this section were not selected for quantitative dose-response analysis or as points of departure (PODs). This is primarily due to limitations in study design, data quality, or reporting that precluded their use for quantitative modeling. For example, many of the human case reports and case series describe acute gastrointestinal effects following ingestion or inhalation exposure, but lack quantitative exposure data, control groups, or sufficient detail for dose-response assessment (U.S. EPA, 2021; Singh et al., 2007; Mehrotra et al., 2001; Prakash et al., 1999; Saraswat et al., 1986; Peoples et al., 1978). Similarly, several animal studies either lacked multiple dose groups, did not report endpoints in a manner that allowed for benchmark dose modeling, or had methodological limitations such as high mortality at lower doses, absence of NOAELs, or inconsistent dosing regimens (Ghanayem et al., 1986; NCI, 1978). As a result, while these endpoints inform the overall weight of evidence for gastrointestinal toxicity, only studies meeting higher standards for methodological rigor and quantitative utility were carried forward for POD derivation in the main narrative.

A.4.1 Human Evidence

EPA identified several case reports and case series that reported on acute ethylene dibromide exposure and gastrointestinal outcomes observed in humans as described in Section 2.3.1.3.1. None of these epidemiology studies were found to have sufficient data for dose-response assessment. Therefore, all epidemiological references identified where gastrointestinal outcomes were observed are characterized below. Table_Apx A-9 characterizes all gastrointestinal outcomes observed in human studies, regardless of the OQDs.

A report on 64 cases of acute exposure to ethylene dibromide found that all cases had symptoms of nausea, vomiting, and abdominal pain (Singh et al., 2007). A case series describing six cases of ethylene dibromide ingestion noted stomach wall congestion in case one; vomiting, nausea, and burning throat in cases two, three, four, and five; and vomiting in case six (Saraswat et al., 1986). A report on two cases of ingestion of 3 mL of ethylene dibromide stated that one case “developed generalized noncolicky abdominal pain” and the other case developed vomiting and “profuse watery diarrhea” (Mehrotra et al., 2001). A case report described a 20-year-old who weighed 56 kg and consumed a 3-mL ampule of Fumigrain containing 6480 mg of ethylene dibromide and “developed recurrent vomiting, which continued for five days” (Prakash et al., 1999). Another case report of ethylene dibromide ingestion noted vomiting (Singh et al., 2000). In addition to ingestion exposure, acute inhalation exposure also was reported to be associated with abdominal pain, diarrhea, and vomiting in one case and nausea in another case (Peoples et al., 1978). These studies did not undergo data quality evaluation because they were screened as Supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). However, these studies provide slight evidence of gastrointestinal outcomes potentially occurring following acute exposure to ethylene dibromide.

Table_Apx A-9. Summary of Studies Evaluating the Association Between Ethylene Dibromide Exposure and Gastrointestinal Outcomes in Humans

Reference	Study Description	Gastrointestinal Outcome(s)	Overall Quality Determination
Singh et al. (2007)	Case series describing 64 cases of acute exposure to ethylene dibromide	All cases had symptoms of nausea, vomiting, and abdominal pain	N/A
Saraswat et al. (1986)	A case series describing 6 cases of ethylene dibromide ingestion	Reported stomach wall congestion in case one; vomiting, nausea, and	N/A

Reference	Study Description	Gastrointestinal Outcome(s)	Overall Quality Determination
		burning throat in cases 2, 3, 4, and 5; and vomiting in case 6	
Mehrotra et al. (2001)	A report on two cases of ingestion of three mL of ethylene dibromide	One case “developed generalized noncolicky abdominal pain” and the other case developed vomiting and “profuse watery diarrhea”	N/A
Prakash et al. (1999)	A case report described a 20-year-old who weighed 56 kg and consumed a 3-mL ampule of Fumigrain containing 6,480 mg of ethylene dibromide	“Developed recurrent vomiting, which continued for five days”	N/A
Singh et al. (2000)	Case report of ethylene dibromide ingestion	Noted vomiting	N/A
Peoples et al. (1978)	A report on occupational cases in California in 1975 and 1976, including two cases of acute inhalation of ethylene dibromide	One case developed abdominal pain, diarrhea, and vomiting; the other presented nausea	N/A
Overall quality determinations are N/A for supplemental studies such as case studies, case series, and mechanistic studies.			

A.4.2 Laboratory Animal Evidence

EPA identified one short-term and two chronic animal studies that evaluated the effects of oral exposure to ethylene dibromide on gastrointestinal outcomes. References that were considered further as POD candidates are described in Section 2.3.1.3.2, while references that were not considered further as POD candidates can be found below. Table_Apx A-10 characterizes gastrointestinal endpoints that results from oral exposure.

Chronic Oral

Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil five days/week in a chronic cancer bioassay (50/sex/groups receiving treatment) ([NCI, 1978](#)). Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group were 0, 38, and 41 mg/kg/day for male rats and 0, 37, and 39 mg/kg/day for female rats. High-doses were suspended at 17 weeks due to deaths of 18 high-dose males and 20 high-dose females; at week 30, treatments resumed for the remaining rats in high-dose groups at the same dose the low-dose rats were receiving. At week 42, all treatments in rats were paused for a week then resumed for an additional four weeks. The study was discontinued at 49 weeks in male rats due to excessive mortality in both treatment groups. The study was discontinued for female rats at week 61. In the corn oil gavage vehicle group, male gavage doses were stopped at week 49, and animals were observed for an additional 14-week recovery period; females gavage doses were stopped at week 61 followed by a two-week observation period (vehicle controls sacrificed at week 63). In the untreated control group, five males were sacrificed in week 59 and the remaining four in week 107. Endpoints evaluated included mortality, clinical signs of toxicity, body weight, food consumption, and histopathological examination of salivary gland, esophagus, stomach, small intestine, and large intestine. Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included reddened ears and hunched appearance in all treated groups by week 5, and firm distended abdomens and abdominal urine stains in all treated groups by week 38 (incidence data not reported). Body weights were decreased in males and females after 10 weeks of treatment; however, the study authors note that

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this decrease in mean weight may reflect increased mortality. Incidences of hyperkeratosis and acanthosis in the forestomach were significantly increased in high-dose males (12/50) and females (18/50) compared to vehicle control (0/20 males; 0/20 females). A POD was not reported by the study authors. A gastrointestinal LOAEL of 41 mg/kg/day for males and 39 mg/kg/day for females was determined for increased incidence of forestomach hyperkeratosis and acanthosis. EPA assigned this study a medium overall quality determination rating.

B6C3F1 mice were exposed via gavage to ethylene dibromide in corn oil five days/week in a chronic cancer bioassay (50/sex/groups receiving treatment) (NCI, 1978). 20 control animals received corn oil vehicle, and 20 control animals were untreated. Time-weighted averaged doses achieved in each group were 0, 62, and 107 mg/kg/day in mice of both sexes. Dose levels were adjusted at several points during the study. Both doses increased during week 11 and were then returned to normal levels at week 13. At week 40, the high-dose group was reduced to 60 mg/kg/day, and all treatments were discontinued at week 54. All surviving male and females in the high-dose group were sacrificed at week 78. Low-dose females were sacrificed at week 91. Endpoints evaluated included mortality (daily); clinical signs of toxicity, body weight, food consumption and palpation for tissue masses (weekly); and histopathological examination of salivary gland, esophagus, stomach, small intestine, and large intestine. Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included alopecia in treated animals at week seven; soft feces, body sores in both dose groups at week 14; thin, hunched appearance in the high-dose group, and small inguinal nodules in some low-dose males at week 42 (incidence data not reported). Body weights were decreased in males and females after 10 weeks of treatment; however, the study authors note that this decrease in mean weight may reflect increased mortality. Incidences of forestomach hyperkeratosis were significantly increased in high-dose males (13/49) and high-dose females (12/50) compared to vehicle control animals (0/20 and 0/20, males and females, respectively), but not low-dose males (0/50) or females (1/49). A gastrointestinal LOEL for forestomach hyperkeratosis was identified at 107 mg/kg/day. However, EPA assigned an uninformative overall quality determination rating due to large inconsistencies in dosing levels over time.

Table_Apx A-10. Summary of Ethylene Dibromide Studies Evaluating Gastrointestinal Effects in Animals (Oral)

Reference	Study Description	Gastrointestinal Outcome(s)	Overall Quality Determination
Short-term			
Ghanayem et al. (1986)	Male F344 rats (8-16/group) were exposed to 0, 40, or 80 mg/kg/day of ethylene dibromide in corn oil vehicle 5 days/week for 2 weeks	<u>↑ cell proliferation:</u> Controls = 0/16 40mg/kg/day = 0/8 80mg/kg/day = 4/8 <u>Hyperkeratosis:</u> Controls = 0/16 40mg/kg/day = 1/8 80mg/kg/day = 6/8 NOAEL of 40 mg/kg/day and a LOAEL of 80 mg/kg-day were determined for gastrointestinal effects, based on increased incidence of cell proliferation and hyperkeratosis	High
Chronic			

Reference	Study Description	Gastrointestinal Outcome(s)	Overall Quality Determination
NCI (1978)	Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/group) Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group (males: 0, 38, and 41 mg/kg/day and females: and 0, 37, and 39 mg/kg/day)	High doses suspended at 17 weeks due to high mortality (male = 18; female = 20) <u>Hyperkeratosis and Acanthosis (Forestomach):</u> <u>Males:</u> Controls = 0/20 41mg/kg/day = 12/50 <u>Females:</u> Controls = 0/20 39mg/kg = 18/50 LOAEL of 41 mg/kg/day for males and 39 mg/kg/day for females was determined for increased incidence of forestomach hyperkeratosis and acanthosis	Medium
NCI (1978)	B6C3F1 mice were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/groups receiving treatment) 20 control animals received corn oil vehicle, and 20 control animals were untreated. Time-weighted averaged doses achieved in each group were 0, 62, and 107 mg/kg/day in mice of both sexes. Dose levels were adjusted at several points during the study.	Large inconsistencies in dosing levels <u>Forestomach hyperkeratosis: Males:</u> Control = (0/20) 62 mg/kg/day = (0/50) 107 mg/kg/day = (13/49) <u>Females:</u> high-dose females Control = (0/20) 62 mg/kg/day = (0/49) 107 mg/kg/day = (12/50) compared to vehicle control but not low-dose males (0/50) LOEL for forestomach hyperkeratosis was identified at 107 mg/kg/day	Uninformative
NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level; LOEL = lowest-observed-effect level			

A.5 Respiratory/Lung Toxicity

Although lung and respiratory toxicity is recognized as a critical health outcome for ethylene dibromide, the studies summarized in this section were not selected for quantitative dose-response analysis or as points of departure (PODs). This is primarily due to limitations in study design, data quality, or reporting that precluded their use for quantitative modeling. For example, many of the human studies, such as ([Hoppin et al., 2009](#)), were cross-sectional analyses with self-reported exposures and outcomes, limited quantitative exposure data, and potential confounding by co-exposures, making them unsuitable for quantitative risk assessment. Similarly, several animal studies either lacked multiple dose groups, did not report endpoints in a manner that allowed for benchmark dose modeling, or had methodological limitations such as high mortality at lower doses, absence of NOAELs, or inconsistent reporting of control data ([Koptagel and Bulut, 1998](#); [NTP, 1982](#); [Nitschke et al., 1981](#); [Rowe et al., 1952](#); [Kettering Laboratory, 1943](#)). As a result, while these endpoints inform the overall weight of evidence for lung and respiratory toxicity, only studies meeting higher standards for methodological rigor and quantitative utility were carried forward for POD derivation.

A.5.1 Human Evidence

EPA identified one study that evaluated the association between of ethylene dibromide exposure and respiratory outcomes in humans as described in Section 2.3.1.4.1. This study was not used for POD derivation and therefore is characterized below. Table_Apx A-11 characterizes all respiratory outcomes observed in human studies, regardless of the OQDs.

The study was a cross-sectional analysis of enrollment data from the Agricultural Health Study that assessed the associations between lifetime use of pesticides, including ethylene dibromide, and prevalent adult-onset asthma in male farm workers (n = 19,704) ([Hoppin et al., 2009](#)). Exposure was assessed using self-reported questionnaire data on lifetime use of pesticides including ever-use, frequency of use, number of years used and decade of first use of specific pesticides including ethylene dibromide. Additionally, participants reported if they ever experienced pesticide poisoning (self-report/doctor diagnosis) or high pesticide exposure events (based on response to the questionnaire question “Have you ever had an incident or experience while using any type of pesticide which caused you unusually high personal exposure?”). The study also compared outcomes between three exposure groups: two exposure levels defined based on the median of intensity-adjusted lifetime days of use (adjusted for application methods, mixing habits, repairs, and use of PPE), and a referent group of never-users of ethylene dibromide. Ever use of ethylene dibromide was significantly associated with a higher prevalence of allergic asthma compared to the referent group of never-users of ethylene dibromide (OR = 2.07; 95% CI: 1.02–4.20). A significant trend in the exposure-response model was also observed (p < 0.05). No statistically significant relationship was observed for non-allergic asthma (OR = 1.25; 95% CI: 0.73–2.15) ([Hoppin et al., 2009](#)). The study was generally well-conducted, but the cross-sectional design precludes determination of temporality. Another limitation is that exposure was based on self-reported data rather than direct measurements. EPA assigned this study a medium overall quality determination rating.

Table_Apx A-11. Summary of Studies Evaluating the Association Between Ethylene Dibromide Exposure and Respiratory Outcomes in Humans

Reference	Study Description	Respiratory Outcome(s)	Overall Quality Determination
Hoppin et al. (2009)	This cross-sectional analysis of enrollment data from the Agricultural Health Study assessed associations between lifetime use of pesticides, including ethylene dibromide, and prevalent adult-onset asthma in male farm workers (n = 19,704)	- Compared to a referent group of never-users of ethylene dibromide, a statistically significant association was found between ever use of ethylene dibromide and the prevalence of allergic asthma (OR = 2.07; 95% CI: 1.02–4.20). - A statistically significant trend was found in an exposure-response model (p < 0.05). - No statistically significant relationship was observed for non-allergic asthma (OR = 1.25; 95% CI: 0.73–2.15).	Medium

A.5.2 Laboratory Animal Evidence

EPA identified 9 animal studies (two acute, three short-term, three subchronic, and one chronic) that evaluate the respiratory effects resulting from exposure to ethylene dibromide via inhalation. Additionally, one acute animal gavage study was identified. References that were considered further as POD candidates are described in Section 2.3.1.4.2, while references that were not considered further as POD candidates can be found below. Table_Apx A-12 characterizes gastrointestinal endpoints that results from oral exposure.

Acute Inhalation

Koptagel et al. (1998) was aimed at investigating the rat tracheal structure following different types and concentrations of hydrocarbon exposure. While control group animals underwent no treatment, five experimental groups received different types of hydrocarbons saturated in air, including ethylene dibromide, at 1-, 3- and 6-hour intervals in isolated chambers. Control group consisted of five rats whereas the experimental groups contained four rats each (12 total animals were exposed to ethylene dibromide). Tracheal tissue samples were collected from the control and experimental group animals and were processed for light microscopy. Tracheal morphology underwent distinct alterations after 3 and 6 hours of ethylene dibromide exposure. After 1 hour exposure to ethylene dibromide, tissue retained a normal appearance with some inflammatory cell infiltration into the lamina propria and dilation of blood vessels. After 3 hours exposure, the tracheal epithelial cells were shorter with degenerated junctional complexes and increased cilia height. Hemorrhage was observed in the tracheal lumen. After 6 hours exposure, there was chronic inflammatory cell infiltration and increased collagen fiber accumulation in the lamina propria, as well as tracheal epithelial cell irregularities including bleb-like projections into the lumen. A LOAEL of 1660 ppm after 3 hours exposure was identified for tracheal epithelial damage, though EPA assigned this study an uninformative overall quality determination rating during systematic review due to lack of clarity on the inhalation chambers used having static or dynamic airflow.

Rats were exposed, whole body, to ethylene bromide vapor concentrations of 200, 400, 1,600, 5,000, or 10,000 ppm for various durations ranging from 0.02 to 16 hours; the durations differed for each group (Rowe et al., 1952). Groups of 20 rats were also exposed to 100 ppm for 8.5, 12, or 16 hours. Finally, a separate group of females only (20/group) were exposed to 50, 500, 200, or 800 ppm for 0.1, 0.7, 2.5, or 7 hours. Mortality was recorded, and animals were observed for changes in behavior and body weight changes for two to three weeks, or until it was certain they had recovered from the effects of exposure. Data were plotted showing vapor concentration (ppm) vs. duration of exposure (hours). Delayed deaths (up to 12 days after exposure) at lower concentrations were due to pneumonia that developed due to lung injury. Prior to death, animals showed evidence of weight loss, rough and unkempt fur, irritability, and blood-tinged fluid from the nose. A subset of animals killed 16 to 24 hours after exposure showed increased lung weight and histopathological changes. A LOEL is not defined for respiratory endpoints, as the associated exposure levels are not specified. This study is uninformative for respiratory endpoints for this reason.

Short-Term Inhalation

CDF (F344) rats (nine weeks old) were used for this study Nitschke (1981). Animals were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for one week (10 males/group) (Nitschke et al., 1981). Males in the 10-ppm group had hyperplasia of the nasal respiratory epithelium. One of these rats also had focal epithelial cell necrosis of the nasal respiratory epithelium. Males in the 40-ppm group had scattered to diffuse hyperplasia of the respiratory epithelium. A LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia. EPA assigned this study a high overall quality determination rating.

CDF (F344) rats (9 weeks old) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 6 weeks (10 males/group) (Nitschke et al., 1981). Significantly decreased body weights were observed in male rats at 40 ppm ethylene dibromide dose. Males in the 10 ppm group had isolated diffuse hyperplasia of the nasal respiratory epithelium. Males in the 40 ppm group had multifocal to diffuse hyperplasia and multifocal cell necrosis in the respiratory epithelium. A LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia. EPA assigned this study a high overall quality determination rating.

In a short-term duration exposure study, rats (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, to seven 7-hour exposures in 9 days (the methods indicated a frequency of 5 days/week) (Rowe et al., 1952). The studies included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Hematological examinations were conducted “periodically” in “representative” rats. Animals were necropsied at the time of sacrifice. Three out of 10 animals died after 1, 5, and 7 exposures. Surviving rats were thin and unkempt. Lung weights were purportedly significantly increased. Histopathology showed thickening of the alveolar walls with slight leucocytic infiltration of the lungs. Based on reporting deficiencies and failure to use the more appropriate control, the study was considered uninformative and a reliable POD cannot be determined.

Subchronic Inhalation

In a subchronic duration exposure study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day, 5 days/week for as many as 63 exposures in 91 days (Rowe et al., 1952). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Hematological examinations were conducted “periodically” in “representative” rats. Animals were necropsied at the time of sacrifice. More than 50% of the males died due to pneumonia and infections in the upper respiratory tract. Four treated females died. Treated animals showed reduced growth, but the difference was not statistically significant. Absolute organ weights changes included significantly increased lung weights in males. A LOAEC of 50 ppm is determined for significant lung weight changes in male rats. EPA assigned this study a low overall quality determination rating during systematic review.

In a subchronic range finding study, B6C3F1 mice (10 animals/sex/group) were exposed to 0, 3, 15, or 75 ppm ethylene dibromide for 6 hours/day, 5 days/week for 13 weeks (NTP, 1982). Animals were observed twice daily for mortality and for signs of toxicity or abnormal behavior, and after 13 weeks, representative tissues were examined microscopically. four male mice exposed to 3 ppm and one female mice exposed to the 75 ppm dose died. A dose-related depression in weight gain was observed for male (3, 21, 36% decrease across dose groups) and female (15, 15, 25% decrease across dose groups) mice. Megalocytic cells were found lining the bronchioles in three male mice and nine female mice exposed to the highest concentration. Control responses were not specified. Histopathological alterations observed in the nasal cavity at 75 ppm included cytomegaly (3 males and 9 females), focal hyperplasia (2 males and 8 females), squamous metaplasia (3 males and 9 females), and loss of cilia (3 males and 9 females). These lesions were not observed in the control mice or in the lower concentration groups Reznik et al. (1980). A respiratory LOAEC of 75 ppm was identified for changes in the nasal cavity and bronchioles. EPA assigned this study a high overall quality determination rating.

Chronic Inhalation: B6C3F1 mice (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide for 78 weeks to 2 years (NTP, 1982). Throughout the study, mean body weights of high-dose mice of either sex were lower than those of the corresponding untreated controls. Survival of the low- and high-dose female and male mice was significantly shorter than in the corresponding controls. The principal cause of early death in control and dosed male mice was ascending, suppurative urinary tract infection that resulted in necrotic, ulcerative lesions around the urethral opening, chronic or

suppurative cystitis (often with urinary tract obstruction), and ascending suppurative pyelonephritis. A separate publication further discusses the nasal lesion data presented in these animals ([Stinson et al., 1981](#)). Dose-related increases in the incidence of focal nasal epithelia hyperplasia were observed in male (Incidence: 0/45, 1/44, and 10/46 in control, low, and high-dose groups, respectively) and female (incidence: 0/50, 3/49, and 11/49, respectively) mice. A respiratory LOAEC of 40 ppm was identified for nasal epithelia inflammation. EPA assigned this study a high overall quality determination rating.

Acute Oral

Rabbits (1/group) were exposed to ethylene dibromide by single oral gavage at 20, 25, 30, 50, 100, 250, 500, 1,000, 2,000, or 3,500 mg/kg ([Kettering Laboratory, 1943](#)). The minimum lethal dose was determined to be between 30 and 50 mg/kg. Pathological effects that occurred in animals that died included pulmonary edema. A respiratory POD could not be assigned to the study because it is not specified in which animals' pulmonary edema was identified. When evaluated using data quality criteria for animal toxicity, EPA assigned this study an uninformative overall quality determination rating during systematic review because only one rabbit was tested per dose level and key experimental details were not reported, including gavage vehicle and volume.

Table_Apx A-12. Summary of Ethylene Dibromide Studies Evaluating Respiratory Effects in Animals (Inhalation)

Reference	Study Description	Respiratory Outcome(s)	Overall Quality Determination
Acute			
Koptagel and Bulut (1998)	While control group animals underwent no treatment, 5 experimental groups received different types of hydrocarbons saturated in air, including ethylene dibromide, at 1-, 3- and 6-hour intervals in isolated chambers. Control group consisted of 5 rats whereas the experimental groups contained 4 rats each (12 total animals were exposed to ethylene dibromide).	<u>Tracheal morphology:</u> Distinct alterations after 3 and 6 hours - Tissue retained a normal appearance with some inflammatory cell infiltration into the lamina propria and dilation of blood vessels - Tracheal epithelial cells were shorter with degenerated junctional complexes and increased cilia height at 3 hours - Hemorrhage was observed in the tracheal lumen - Chronic inflammatory cell infiltration and increased collagen fiber accumulation in the lamina propria, as well as tracheal epithelial cell irregularities including bleb-like projections into the lumen at 6 hours LOAEL of 1,660 ppm after 3 hours exposure was identified for tracheal epithelial damage	Uninformative
Rowe et al. (1952)	Rats were exposed, whole body, to ethylene bromide vapor concentrations of 200, 400, 1,600, 5,000, or 10,000 ppm for various durations ranging from 0.02 to 16 hours; the durations differed for each group. Groups of 20 rats were also exposed to 100 ppm for 8.5, 12,	A LOEL is not defined for respiratory endpoints, as the associated exposure levels are not specified	Uninformative

Reference	Study Description	Respiratory Outcome(s)	Overall Quality Determination
	or 16 hours. Finally, a separate group of females only (20/group) were exposed to 50, 500, 200, or 800 ppm for 0.1, 0.7, 2.5, or 7 hours.		
Short-term			
Rowe et al. (1952)	Rats (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, to seven 7-hour exposures in 9 days (the methods indicated a frequency of 5 days/week) (Rowe et al., 1952). The studies included 2 groups of controls, 1 unexposed and 1 air-exposed control (numbers not specified).	- This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. - Lung weights were purportedly significantly increased. Histopathology showed thickening of the alveolar walls with slight leucocytic infiltration of the lungs. - Reporting deficiencies and inappropriate control (air-exposed)	Uninformative
Nitschke et al. (1981)	Group 1: CDF (F344) rats (nine weeks old) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for one week (10 males/group) Group 2: Male CDF (F344) rats (nine weeks old) exposed via inhalation to 0, 3, 10 or 40 ppm (n = 10) ethylene dibromide 6 hours/day, 5 days/week for 6 weeks	Males (10 ppm): - Hyperplasia of the nasal respiratory epithelium. - One of these rats also had focal epithelial cell necrosis of the nasal respiratory epithelium Males (40 ppm): - Scattered to diffuse hyperplasia of the respiratory epithelium LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia.	High
Nitschke et al. (1981)	Nine week old CDF (F344) rats (40 males and 20 females) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 6 weeks (10 males/group)	Males (10 ppm): - Isolated diffuse hyperplasia of the nasal respiratory epithelium Males (40 ppm): - Multifocal to diffuse hyperplasia and multifocal cell necrosis in the respiratory epithelium LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia	High
Subchronic			
Nitschke et al. (1981)	Nine week old CDF (F344) rats (40 males and 20 females) were exposed via inhalation to 0, 3, 10 or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 6 weeks (10 males/group) for 13 weeks (10/sex/group), or for 13 weeks plus an 88-89 day recovery	Males and females (10 ppm): - Isolated multifocal hyperplasia of the nasal respiratory epithelium - One female also had epithelial cell necrosis of the nasal respiratory epithelium - Animals that underwent a recovery period following 13-week exposure to 10 ppm showed no nasal epithelium changes Males and females (40 ppm):	High

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Reference	Study Description	Respiratory Outcome(s)	Overall Quality Determination
		- Diffuse or focal nonkeratinizing squamous metaplasia - Hyperplasia of the respiratory epithelium, and focal necrosis of the respiratory epithelium - One female rat in the recovery period had histological abnormalities – an isolated focus of epithelial hyperplasia in the respiratory epithelium of the nasal turbinates LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia in animals that did not undergo the recovery period.	
NTP (1982)	In a subchronic range finding study, B6C3F1 mice (10 animals/sex/group) were exposed to 0, 3, 15, or 75 ppm ethylene dibromide for 6 h/day, 5 days/week for 13 weeks.	- Megalocytic cells lining the bronchioles in 3 male mice and 9 female mice exposed to the highest concentration - Control responses were not specified <u>Histopathological alterations observed in the nasal cavity at 75 ppm included:</u> - Cytomegaly (3 males and 9 females) - Focal hyperplasia (2 males and 8 females) - Squamous metaplasia (3 males and 9 females) - Loss of cilia (3 males and 9 females) LOAEC of 75 ppm was identified for changes in the nasal cavity and bronchioles	High
Rowe et al. (1952)	Rats (20/sex) exposed to ethylene dibromide vapor concentrations (0 and 50 ppm 7 hours/day, 5 days/week for as many as 63 exposures in 91 days). Two groups of controls, 1 unexposed and 1 air-exposed control (numbers not specified). This reference reported multiple experiments, it is not clear which endpoints were definitively assessed in each separate experiment	Significantly ↑ absolute lung weights in males LOAEC of 50 ppm is determined for significant lung weight changes in male rats	Low
Chronic			
NTP (1982)	B6C3F1 mice (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide for 78 weeks to 2 years	<u>Focal nasal epithelia hyperplasia:</u> <u>Males:</u> ↑ incidence (0/45, 1/44, and 10/46 in control, low, and high dose respectively) <u>Females:</u> ↑ incidence (0/50, 3/49, and 11/49 in control, low, and high dose respectively)	High

Reference	Study Description	Respiratory Outcome(s)	Overall Quality Determination
		LOAEC of 40 ppm for nasal epithelia inflammation.	
LOAEL = lowest-observed-adverse-effect level; LOAEC = lowest-observed-adverse-effect concentration			

A.6 Adrenal Toxicity

EPA did not identify epidemiological studies that evaluated any potential adrenal hazards for ethylene dibromide in humans. While adrenal toxicity is recognized as a critical health outcome for ethylene dibromide, the animal studies summarized in this section were not selected for quantitative dose-response analysis or as points of departure (PODs) in the main risk assessment. This is primarily due to limitations in study design, data quality, or reporting that precluded their use for quantitative modeling. For example, several animal studies, such as (NTP, 1982), identified adrenal cortical cell changes in rats, but these studies often lacked multiple dose groups, did not report endpoints in a manner that allowed for benchmark dose modeling, or had methodological limitations such as high mortality at lower doses or insufficient reporting of control data. Other studies, including (Nachtomi et al., 1968), reported increased adrenal weights and biochemical changes following acute oral exposure, but were limited by small sample sizes, absence of NOAELs, or incomplete reporting of critical endpoints. As a result, while these endpoints inform the overall weight of evidence for adrenal toxicity, only studies meeting higher standards for methodological rigor and quantitative utility were carried forward for POD derivation.

A.6.1 Laboratory Animal Evidence

EPA identified three animal studies that evaluates the adrenal effects resulting from exposure to ethylene dibromide. As described in Section 2.3.1.3.2, while co-critical effects evaluated in NTP (1982) references were identified, it was not considered further as a POD candidate and a discussion regarding study details can be found below.

Subchronic Inhalation: In a subchronic range finding study, 4 to 5 male F344 rats and 5 to 6 female F344 rats were exposed to 0, 3, 15, or 75 ppm ethylene dibromide for 6 hours/day, 5 days/week for 13 weeks (NTP, 1982). Animals were observed twice daily for mortality and for signs of toxicity or abnormal behavior, followed by microscopic examination of representative tissues at 13 weeks. No deaths occurred in rats at any of the exposure concentrations tested. There was a dose-related depression in weight gain for male rats at all doses (8, 27, and 42% decrease at 3, 15, and 75 ppm, respectively). In female rats, weight gain compared with the controls was depressed only in the 75-ppm dose group. In rats exposed to 75 ppm, swelling and/or vacuolation of the adrenal cortical cells of the zona fasciculata were detected in 8/10. An adrenal LOEL of 75 ppm was identified. EPA assigned this study a high overall quality determination rating.

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Table_Apx A-13. Summary of Ethylene Dibromide Studies Evaluating Adrenal Effects in Animals (Inhalation)

Reference	Study Description	Adrenal Outcome(s)	Overall Quality Determination
Subchronic			
NTP (1982)	In a subchronic range finding study, 4–5 male F344 rats and 5–6 female F344 rats were exposed to 0, 3, 15, or 75 ppm ethylene dibromide for 6 h/day, 5 days/week for 13 weeks	<u>Males:</u> ↓ weight gain for male rats at all doses (8, 27, and 42% decrease at 3, 15, and 75 ppm, respectively) <u>Females:</u> ↓ weight gain compared with the controls only at 75 ppm In rats exposed to 75 ppm, swelling and/or vacuolation of the adrenal cortical cells of the zona fasciculata were detected in 8/10 LOEL of 75 ppm identified	High
LOAEL = lowest-observed-adverse-effect level			

Acute Oral: Albino rats (both sexes, number per group not specified) were administered a single dose of 0 or 110 mg/kg body weight ethylene dibromide (purity not reported) in soybean oil, via gavage ([Nachtomi et al., 1968](#)). There is some uncertainty in the dose because the data tables reported the dose as 120 mg/kg body weight. Adrenal weights and adrenal ascorbic acid were evaluated. Relative adrenal weights were increased in both sexes 20 hours after ethylene dibromide administration. Adrenal ascorbic acid levels were significantly decreased in females only, although there was a large variation in the controls; the decrease coincided with adrenal enlargement. Absolute organ weights and body weights were not reported. 110 mg/kg, the only dose tested, was identified as a LOAEL for increased relative adrenal weights with associated biochemical changes. EPA assigned this study a medium overall quality determination rating.

Chronic Oral: Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/group) ([NCL, 1978](#)). Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). TWA doses achieved in each group were 0, 38, and 41 mg/kg/day for male rats and 0, 37, and 39 mg/kg/day for female rats. High-doses were suspended at 17 weeks due to deaths of 18 high-dose males and 20 high-dose females; at week 30, treatments resumed for the remaining rats in the high-dose group at the same dose the low-dose rats were receiving. At week 42, all treatments in rats were paused for a week then resumed for an additional four weeks. The study was discontinued at 49 weeks in male rats due to excessive deaths in both treatment groups. The study was discontinued for female rats at week 61. In the corn oil gavage vehicle group, male gavage doses were stopped at week 49 and animals were observed for an additional 14-week recovery period; female gavage doses were stopped at week 61 followed by a 2-week observation period (vehicle controls sacrificed at week 63). In the untreated control group, five males were sacrificed in week 59 and the remaining four in week 107. Endpoints evaluated included mortality (daily); clinical signs of toxicity, body weight, food consumption and palpation for tissue masses (weekly); and histopathological examination of the adrenal. Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included reddened ears and hunched appearance in all treated groups by week 5, and firm distended abdomens and abdominal urine

stains in all treated groups by week 38 (incidence data not reported). Body weights were decreased in males and females after 10 weeks of treatment; however, the study authors note that this decrease in mean weight might be due to increased mortality. Incidences of degenerative changes in adrenal cortex were significantly increased in males (13/48 and 9/47 in the low- and high-dose, respectively), compared to the vehicle control (0/20). A POD was not reported by the study authors. A LOAEL of 38 mg/kg/day was determined in males for increased incidence of degenerative lesion in the adrenal cortex. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a medium overall quality determination rating.

Table_Apx A-14. Summary of Ethylene Dibromide Studies Evaluating Adrenal Effects in Animals (Oral)

Reference	Study Description	Adrenal Outcome(s)	Overall Quality Determination
Acute			
Nachtomi et al. (1968)	Albino rats (both sexes, number per group not specified) were administered a single dose of 0 or 110 mg/kg body weight ethylene dibromide (purity not reported) in soybean oil, via gavage. Uncertainty in dose. Adrenal weights and adrenal ascorbic acid were evaluated.	↑ Relative adrenal weights in both sexes 20-hr post-exposure ↑ Adrenal ascorbic acid in females • Adrenal swelling • Controls had large variation LOEAL = 110 mg/kg (only dose tested)	Medium
Subchronic			
NCI (1978)	Osborne-Mendel rats exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/group) Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group were 0, 38, and 41 mg/kg/day for male rats and 0, 37, and 39 mg/kg/day for female rats, respectively.	High doses suspended at 17 weeks due to high mortality (male = 18; female = 20)	Medium
LOAEL = lowest-observed-adverse-effect level			

Studies in laboratory animals provide slight evidence of adrenal effects related to ethylene dibromide exposure. In a high quality subchronic inhalation study in rats, swelling and vacuolation of adrenal cortical cells of the zona fasciculata was identified at 75 ppm ([NTP, 1982](#)). Two medium quality oral rat studies revealed significant increase in relative adrenal weight in both sexes and decreased ascorbic acid levels in females receiving 110 mg/kg/day for an acute duration ([Nachtomi et al., 1968](#)) and significantly increased incidence of adrenal cortex degenerative lesions in males when exposed to 38 mg/kg/day at a chronic duration ([NCI, 1978](#)). The currently available evidence suggests, but is not sufficient to conclude, that ethylene dibromide may cause adrenal effects in humans under relevant exposure circumstances due to lack of epidemiological and mechanistic evidence. The interactive web-based evidence integration table for [adrenal](#) (accessed June 2026) effects is available in HAWC.

A.7 Cancer

The human and animal studies described below were not selected for quantitative dose-response analysis. The available epidemiological data was not considered suitable for quantitative cancer dose-response assessment due to human data were to support conclusions regarding an association between ethylene dibromide exposure and carcinogenicity ([Niehoff et al., 2019](#); [Hart et al., 2018](#); [Dow Chemical, 1992b](#); [Sobel et al., 1987](#); [Sweeney et al., 1986](#); [Ott et al., 1980](#); [Turner and Barry, 1979](#)). Animal studies identified across inhalation, oral, and dermal exposure routes were not suitable for quantitative analysis due to experimental design limitations that make it difficult to conduct dose-response analysis ([Adkins et al., 1986](#); [Wong et al., 1982](#)). In general, the animal studies discussed below only evaluated effects from a single administered dose or a single exposure concentration respective to the route of administration of interest. This lack of multiple exposure levels precluded characterization of dose-response relationships and quantitative modeling.

A.7.1 Human Evidence

All available epidemiology references that met PECO screening criteria and assessed the association between ethylene dibromide and cancer are discussed in this section regardless of the overall quality determination from data quality evaluation of these studies.

Two prospective cohort studies assessed the association between census tract level air concentrations of several chemicals, including ethylene dibromide, and breast cancer incidence in large cohorts of women from across the United States. Hart et al. ([2018](#)) assessed data from the Nurses' Health Study II and Niehoff et al. ([2019](#)) assessed data from the Sister Study. Both studies used the EPA National Air Toxics Assessment (NATA) database of census-tract level modeled air concentration data to assess exposure to ethylene dibromide.

The Nurses' Health Study II is a prospective cohort study that began in 1989 with 116,430 female nurses aged 25 to 42 years at enrollment. Time-varying Cox proportional hazards were used to assess the association between ethylene dibromide exposure quartiles and incidences of invasive breast cancer. Potential confounders were included in the models and sensitivity analyses of subgroups were performed. The overall breast cancer hazard for the second lowest ethylene dibromide exposure quartile was statistically significantly lower than the lowest ethylene dibromide exposure quartile (reference group), with a hazard ratio (HR) of 0.89 (95% CI: 0.81–0.99). There was no statistically significant difference between the two higher ethylene dibromide exposure quartiles and the reference group (quartile 3 HR 0.93 [95% CI: 0.83–1.05] and quartile 4 HR 0.91 [95% CI: 0.80–1.02]). When estrogen receptor positive and negative groups were separated out, no statistically significant difference between any ethylene dibromide exposure quartiles and the reference group was found. Strengths of this study include the prospective design, large sample size, long follow-up period, high follow-up rate, appropriate consideration of potential confounders, and appropriate statistical methods. The main limitation of this study is that measurements at the census-tract level do not fully account for exposures at the individual level, so there is some potential for exposure misclassification. This study had a high overall quality determination rating.

In the other prospective cohort study, of 49,718 women from the Sister Study cohort of women from across the United States, Niehoff et al. ([2019](#)) examined the associations between census tract air concentrations of several chemicals, including ethylene dibromide, and breast cancer (*i.e.*, breast cancer diagnosis [overall], tumor characteristics and estrogen receptor positive [ER+] invasive breast cancer). The EPA National Air Toxics Assessment (NATA) database of census-tract level modeled air concentrations data was used to assess exposure. This study was generally well-conducted, but measurements at the census-tract level do not fully account for exposures at the individual level so there

is some potential for exposure misclassification. The study did not find statistically significant associations between ethylene dibromide and breast cancer in single pollutant analyses. However, a classification tree analysis identified combinations of ethylene dibromide, age, BMI, and other chemicals related to overall breast cancer, with an association for ethylene dibromide in combination with methylene chloride and propylene dichloride in women ages 40 to 58 years. Thus, the results provide some evidence that ethylene dibromide might interact with other factors including other chemicals in the etiology of some breast cancer cases, but there is insufficient information to be conclusive or to determine a quantitative association for ethylene dibromide. EPA assigned this study a medium overall quality determination rating.

Sorbel et al. (1987) conducted a case-control study that assessed the associations between exposure to 13 chemical substances, including ethylene dibromide, and soft-tissue sarcoma among workers in a large multi-chemical manufacturing facility located in Michigan. The paper reported that the target population was 37,000 chemical workers who had worked for at least 1 year in the facility between the years of 1940 through 1979. The study included a small sample size of 14 cases who died due to soft-tissue sarcoma and 126 controls who were matched with cases on sex and race, and “with a few exceptions,” on year of birth and year of hire. One case and six controls were identified as having ethylene dibromide exposure and the association was not statistically significant (OR: 1.52 and 95%; CI: 0.18–13.09). A substantial limitation of this study is that duration of exposure and latency periods were not adequately addressed. The exposure was assessed as dichotomous ever exposed vs. never exposed in the analyses. However, the authors reported that “the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his six referents ranged from 66 days to 9.4 years.” Thus, there is some indication that longer exposure durations might pose a risk, but whether and to what extent that might be the case cannot be determined based on the available data. The small number of participants in this study with any exposure to ethylene dibromide (7 individuals) limits the potential for further quantitative assessment by exposure duration. For example, if exposure had been dichotomized using a cutoff of 10 years instead of ever/never then there would have been one case exposed for greater than 10 years compared to zero controls exposed for greater than 10 years resulting in an indeterminately high odds ratio. Ultimately, this study had limited sensitivity to adequately assess associations that might be dependent on exposure duration. EPA assigned this study a low overall quality determination rating.

Sweeney et al. (1986) in a historical cohort of 2,510 male workers at a tetraethyl lead manufacturing plant located in East Texas investigated mortality, including cancer mortality. Workers were employed for at least 1 day during the years from 1952 to 1977. In addition to tetraethyl lead, several other chemicals were produced or used at the plant including ethylene dibromide, ethylene dichloride, chloroethane, ethylene, inorganic lead, and various dyes. However, there were no quantitative measures of exposure to ethylene dibromide other than duration of work. SMRs were calculated for workers from the plant compared to males in the United States, stratified by race, 5-year age groups, and 5-year calendar time periods. There was no statistically significant increase in mortality from malignancies. Limitations of this study include the lack of ethylene dibromide-specific quantitative exposure data, the inability to separate out the exposure of interest from other co-exposures, and the potential for healthy worker effect. All-cause mortality was lower than expected in the workers, which is consistent with the healthy worker effect. Although no statistically significant elevation in cancer-related mortality was found, there were some observations of slightly increased mortality due to all malignancies and to some cancer types, but these findings were not statistically significant. EPA assigned this study a medium overall quality determination rating.

Ott et al. (1980) and Dow Chemical (1992b) evaluated mortality in 169 male employees in 2 manufacturing plants located in Texas and Michigan. Assessments were based on existing records and

discussions with workers formerly associated with the plants. For the facility in Texas there was no air sampling but there was job process documentation to assess potential exposure. For the Michigan facility, personal and area sampling measures ranged from 0 to 110 ppm. There was an increase in mortality due to cancer among employees with greater than six years of exposure to ethylene dibromide in the Michigan plant (observed: 5 deaths; expected: 2.2 deaths) but no statistical testing or confidence intervals were reported. In addition to the lack of statistical testing, limitations of this study include a lack of information on participation rates and study population characteristics, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants. EPA assigned this study a low overall quality determination rating.

Turner and Barry (1979) conducted a survey study investigating infertility and mortality (including cancer-related mortality) in 351 male workers in two ethylene dibromide manufacturing plants in Great Britain. Workers had potential exposures to ethylene dibromide for at least 4 years. Overall, no statistically significant increase in mortality from any cause, including cancer, was observed. This study had several limitations, particularly in the methods used to assess exposure and outcome. EPA assigned this study a low overall quality determination rating.

Overall, the epidemiology evidence for carcinogenicity in humans is indeterminate due to lack of sufficient data. Only a small number of epidemiology studies assessed associations between ethylene dibromide and cancer outcomes. Two studies assessed the association between ethylene dibromide exposure and breast cancer. Although these breast cancer studies were determined to be of medium or high quality, the assessment of ethylene dibromide exposure at the census-tract level rather than the individual level was a limitation. These studies were specific to breast cancer and did not assess other cancer types. One study assessed soft-tissue sarcoma, and three studies assessed cancer mortality. These studies had limitations and were determined to be of low or medium quality. There were no substantial findings of statistically significant positive or negative associations between ethylene dibromide exposure and cancer in this limited epidemiologic database.

A.7.2 Laboratory Animal Evidence

EPA identified one dermal, two oral animal studies, and two inhalation studies that evaluated the effects of ethylene dibromide on cancer outcomes. The inhalation studies were of high overall quality; however, none of the identified studies were selected for dose-response analysis due to limitations in single dose administered. Studies with high overall quality determinations are described in Section 2.4.3, whereas studies considered uninformative or of lower utility for dose response assessment are summarized below.

Inhalation Studies

In inhalation study, female A/J mice were exposed to 0, 20, or 50 ppm of ethylene dibromide for 6 months (6 hours/day, 5 days/week), with findings indicating a statistically significant increase in pulmonary adenomas. The exposure was repeated in a subsequent study evaluating ethylene dibromide alone. Comparable increases in pulmonary adenoma incidence were observed across both exposure levels, with no treatment-related mortalities reported (Adkins et al., 1986).

In another study by Wong et al. (1982), Sprague-Dawley rats were exposed to 0 or 20 ppm of ethylene dibromide vapor for 18 months (7 hours/day, 5 days/week). The study reported increased incidences of mammary gland tumors in females and noted lower body weights in treated groups compared to controls. Males had a higher mortality rate (90%) than females (70%). Histological findings included spleen atrophy, hemosiderosis, and various tumors in both sexes, with insignificant increases in tumors in the liver, kidneys, and lungs (Wong et al., 1982). Despite Wong et al. (1982) was limited to a single

dose, which prevented a dose-response analysis, this limitation did not compromise the study's validity. The study received high overall ratings for key elements and carcinogenicity interpretation, including its design, animal model suitability, and outcome assessment. Consequently, the study was deemed to be of high overall quality.

Collectively, these studies underscore the carcinogenic potential of ethylene dibromide associated with inhalation exposures, demonstrating its ability to induce a range of tumors across multiple sites in both rats and mice. A summary of cancer inhalation studies is presented in Table_Apx A-15.

8651 **Table Apx A-15. Cancer Inhalation Study Summaries**

Reference	Study Brief Description	POD	Effects at POD	Remarks (Overall Quality Determination) ^a
NTP (1982)	F344 rats (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide in whole body chamber, for 5 hours/day, 5 days/week, for 2 years B6C3F1 mice (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide, in whole body chamber, for 5 hours/day, 5 days/week for 78 weeks	10 ppm (LOAEC)	Carcinogenic effects observed include increased incidences of carcinomas, adenocarcinomas, and adenomas of the nasal cavity in both sexes; adenomatous polyps of the nasal cavity in males; alveolar/bronchiolar adenomas and carcinomas (combined) in females. Other cancers reported include fibroadenomas of the mammary gland in females, hemangiosarcoma of the circulatory system in both sexes, and mesotheliomas of the tunica vaginalis. Carcinogenic effects included alveolar/bronchiolar carcinomas and adenomas in both sexes, nasal cavity carcinomas, mammary gland adenocarcinomas, hemangiosarcoma of the circulatory system, and fibrosarcoma in the subcutaneous tissue.	Exposure Duration-rat: Male and female controls: 104-106 weeks Low-dose: 103 weeks (both sexes) High-dose: 88 weeks (males), 91 weeks (females) Exposure Duration-mice: Male controls: 79 weeks Female controls: 104-106 weeks Male low and high-dose: 78 weeks Female low-dose: 103 weeks Female high-dose: 90 weeks Limitation: Two dose groups, different exposure durations, high mortality at high-dose. OQD: High
Adkins et al. (1986)	B6C3F1 mice (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide, in whole body chamber, for 5 hours/day, 5 days/week for 78 weeks	20 ppm (LOAEC)	Increased incidence of pulmonary adenomas observed in both treatment groups across two studies.	Limitation: No NOAEL identified; only female mice exposed. OQD: High
Wong et al. (1982)		20 ppm (LOAEL)	Observed effects included mammary tumors (adenoma, fibroadenoma, carcinoma, adenocarcinoma) in females, lower body weights in both sexes, high mortality (90% in males, 77% in females), spleen atrophy, hemosiderosis, spleen hemangiosarcoma, adrenal tumors, and mesenchymal tumors. Non- significant increases in liver, kidney, and lung tumors were also noted.	Limitation: Only one concentration tested, limiting dose-response assessment, this limitation did not invalidate the study design, and outcome assessments as indicators of high quality OQD: High
POD = point of departure; LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level; OQD = overall quality determination ^a Overall quality determination (OQD) determined as described in the <i>Draft Systematic Review Protocol for Ethylene Dibromide</i> (U.S. EPA, 2026i).				

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Oral Studies

Study conducted by Stoner et al. (1986), where A/J mice (16 per sex per group) were administered ethylene dibromide via oral gavage at 0 or 840 mg/kg in a tricapylin vehicle, three times per week for eight weeks (24 doses total). No significant differences in lung tumor incidence or multiplicity were observed, nor were there liver foci or gross histopathological findings identified. The dose of 840 mg/kg was identified as the maximum tolerated dose (MTD). Although Stoner et al. (1986) had methodological limitations, including evaluation of only a single dose level, these deficiencies did not compromise the confidence in the tumor findings. The study was rated high overall because key elements critical to internal validity and interpretation of carcinogenicity outcomes, including characterization of the test substance, appropriate control groups, suitable animal model, well-described exposure conditions, and histopathological analysis. Consequently, the study was considered for carcinogenic effects, although its utility for dose response assessment is limited (Stoner et al., 1986).

Van Duuren et al. (1985) investigated the effects on female B6C3F1 mice. In this study, female B6C3F1 mice (30 per group) were dosed with 4mM (750 mg/L) ethylene dibromide in drinking water for a total of 512 days, resulting in a calculated exposure of 103 mg/kg/day as reported by the authors. The study reported a LOAEL of 103 mg/kg/day, noting tumor incidences in the forestomach, liver, and esophagus. Limitations of the study included a single dose level, 34% decrease in water consumption, and potential dehydration (Van Duuren et al., 1985).

Parallel to the study in female mice, Van Duuren et al. (1985) also examined male B6C3F1 mice under similar conditions. Male B6C3F1 mice (30 per group) were similarly dosed with 4mM (750 mg/L) ethylene dibromide in drinking water for 456 days, with a calculated exposure of 116 mg/kg/day. The LOAEL was 116 mg/kg/day, with tumors observed in the forestomach, glandular stomach, and liver. Limitations included a single dose level and a 25% decrease in water consumption, potentially contributing to dehydration (Van Duuren et al., 1985). Palatability resulted in reduced water intake, making the study's overall quality determination rating uninformative.

Van Duuren et al. (1986) conducted another study to assess the chronic effects of ethylene dibromide. In this study, B6C3F1 mice (50 per sex per group) were administered 2.0 mM ethylene dibromide in drinking water for 18 months. Actual doses were calculated to be 1.4 mg/mouse/day for males and 1.2 mg/mouse/day for females. The study reported a LOAEL of 1.4 mg/mouse/day for males and 1.2 mg/mouse/day for females, with observed papillomas and squamous carcinomas in the esophagus and forestomach. Study limitations included a single concentration and reduced water intake (36% less in males, 25% less in females), which contributed to the study's overall quality determination rating of uninformative (Van Duuren et al., 1986). A summary of cancer oral studies is presented in Table_Apx A-16.

8691 Table Apx A-16. Cancer Oral Study Summaries

Reference	Study Brief Description	POD	Effects at POD	Remarks (Overall Quality Determination) ^a
NCI (1978)	Osborne-Mendel rats (50/sex/group) were given ethylene dibromide via gavage in corn oil, 5 days/week, in a chronic cancer bioassay. Control groups received either corn oil or no treatment. Time-weighted average doses were 0, 38, and 41 mg/kg/day for males, and 0, 37, and 39 mg/kg/day for females.	38 mg/kg/d (LOAEL)	Carcinogenicity is observed with squamous cell carcinoma of the forestomach, degenerative lesions in the adrenal cortex, and testicular atrophy.	Endpoints evaluated: Mortality (daily), clinical signs of toxicity, body weight, food consumption, and palpation for tissue masses (weekly). Significant increases in forestomach squamous-cell carcinomas in both sexes. Increased hemangiosarcoma incidence in low-dose males but not high-dose males. Time-adjusted increases in hepatocellular carcinoma and cortical adenoma in high-dose females. Limitation: Inconsistent timing and dosing; high-dose- treatment was suspended at week 15 (death of 18 males, 20 and was not resumed until week 30. As a result, males were on test for 49 weeks while females remained on test for 61 weeks. Male vehicle controls were treated for 49 weeks, followed by a 14-week recovery period before sacrifice, whereas female vehicle controls were treated until week 61 with a 2-weeks recovery. Some females were sacrificed at week 59, while others were maintained until week 107. Surviving male were sacrificed at week 49, and surviving females were terminated at week 63. OQD: Medium
Van Duuren et al. (1985)	(Female Mice) 6-8 week, B6C3F1 mice (30/group) were dosed with 4mM (750 mg/L) ethylene dibromide in drinking water for 512 days. Calculated exposure was 103 mg/kg/day.	103 mg/kg/d (LOAEL)	Tumor incidence in forestomach, glandular stomach, liver, and esophagus	Additional Information: 34% decrease in water consumption and 10-20% body weight loss, likely contributing to dehydration. Median survival was 465 out of 512 days. Limitation: Single dose study Confounding variables in the test design and procedures including water consumption, which in both males and females was calculated to differ by less than 20% from controls due to plausibility issues. Consequently, the effect of long-term dehydration cannot be distinguished from the effects of the chemical of interest. OQD: Uninformative
	(Male Mice) 6-8 weeks old, B6C3F1 mice (30/group) were dosed with 4mM (750 mg/L) ethylene dibromide in drinking water for 456 days. Calculated exposure was 116 mg/kg/day.	116 mg/kg/d (LOAEL)	Tumor incidence in forestomach, glandular stomach, and liver	Additional Findings: 25% decrease in water consumption and dehydration likely contributed. Survival was 389 out of 456 days. Limitation: Single dose study. OQD: Uninformative

Reference	Study Brief Description	POD	Effects at POD	Remarks (Overall Quality Determination) ^a
Stoner et al. (1986)	A/J mice (16/sex/group) received ethylene dibromide via oral gavage at 0 or 840 mg/kg in tricapyrin vehicle, 3 times/week for 8 weeks (24 doses total).	MTD 840-Negative in a lung tumor bioassay	Lung tumor response. No significant differences in lung tumor incidence or multiplicity, no liver foci or gross findings.	Additional Information: The concentration of tricapyrin was not specified. The study handled three separate control groups with similar responses, minimizing impact on results. Limitations: Only one dose tested (MTD), no positive control, part of a screening study for multiple chemicals. OQD: High
Van Duuren et al. (1986)	B6C3F1 mice (50/sex/group) were administered 2.0 mM ethylene dibromide in drinking water for 18 months. Actual doses were 1.4 mg/mouse/day for males and 1.2mg/mouse/day for females. Male intake was 1.4 mg/mouse/day, and female intake was 1.2 mg/mouse/day.	1.4 mg/mouse/day (males), 1.2 mg/mouse/day (females) (LOAEL)	Papilloma and squamous carcinoma of the esophagus and squamous carcinoma of the forestomach.	Additional Information: Males ingested 36% less water than controls, and females ingested 25% less, confounding the data ethylene dibromide was used as a positive control in a study evaluating chlorinated humic acids. Limitations: Single concentration reduced water intake due to palatability. OQD: Uninformative
POD = point of departure; LOAEL = lowest-observed-adverse-effect level; OQD = overall quality determination ^a Overall quality determinations (OQDs) are determined as described in the <i>Draft Systematic Review Protocol for Ethylene Dibromide</i> (U.S. EPA, 2026i).				

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Dermal Study

A study conducted by Van Duuren et al. (1979) evaluated the carcinogenic potential of ethylene dibromide using chronic skin bioassay (for 440 to 594 day) and a tumor initiation/promotion skin carcinogenesis assay in female Ha:ICR Swiss mice. In the chronic bioassay, doses of 25 or 50 mg of ethylene dibromide in 0.2 mL acetone were applied to the skin of mice, with acetone vehicle and untreated control groups included, resulting in a significant increase in papillomas and lung tumors at the 50 mg/application dose. In the tumor initiator/promoter assay, 75 mg of ethylene dibromide in 0.2 mL acetone was applied to the skin of female mice as the tumor initiator, followed by application of the tumor promoter Phorbol 12-myristate 13-acetate (PMA) application. No significant increase in tumor incidence was observed compared with the PMA control group. Both studies had several limitations, including issues with test substance volatility, control inconsistencies, and limited endpoint evaluation (Van Duuren et al., 1979). The lack of variability, measures of volatility, inconsistent controls, and limited endpoints and sample size contributed to the overall study quality determination of uninformative. A summary of cancer dermal study is presented in Table_Apx A-17.

Table_Apx A-17. Cancer Dermal Study Summaries

Reference	Study Brief Description	POD	Effects at POD	Remarks (Overall Quality Determination) ^a
Van Duuren et al. (1979)	Chronic cancer bioassay: 25 or 50 mg ethylene dibromide in 0.2 mL acetone applied to 30 female Ha:ICR Swiss mice for 581 days. Positive and negative controls included.	50 mg/application (LOAEL)	Increased incidence of papillomas and lung tumors	The test material was applied dermally 3 days per week for 581 days Limitation: No measures for volatility; inconsistent controls; limited endpoints; single-sex, small group size. OQD: Uninformative
	Tumor initiator/promoter assay: 75 mg ethylene dibromide in 0.2 mL acetone applied to 30 female Ha:ICR Swiss mice. PMA applied after 14 days. Duration is not clearly specified.	75 mg/application (NOAEL)	Increased incidence of papillomas and lung tumors	No measures for volatility; unclear duration; inconsistent controls; limited endpoints.
POD = point of departure; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; OQD = overall quality determination ^a Overall quality determination (OQD) are determined as described in the <i>Draft Systematic Review Protocol for Ethylene Dibromide</i> (U.S. EPA, 2026i).				

Appendix B NON-CRITICAL NON-CANCER HUMAN HEALTH OUTCOMES

As described above in Sections 2.3 and 2.4, all studies identified through systematic review were considered for potential POD derivation and used to inform the weight of scientific evidence (Section 2.5) for the human health hazard assessment. This appendix focuses on study summaries and endpoint discussions for non-critical non-cancer health outcomes, that were not considered further for POD derivation due to various study limitations and uncertainties.

B.1 Mortality

B.1.1 Human Evidence

There have been several case reports and case series indicating that acute exposure to ethylene dibromide is associated with human fatalities ([Pahwa et al., 2013](#); [Singh et al., 2007](#); [Osterloh, 1986](#); [Saraswat et al., 1986](#); [Letz et al., 1984a, b](#)).

Two fatalities occurred after exposure to ethylene dibromide in a tank at a facility in the San Joaquin Valley, California ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)). A 31-year-old male worker “collapsed within 5 minutes after entering a 28,500 L nurse tank” ([Letz et al., 1984a](#)). Shortly after, a 46-year-old male supervisor climbed into the tank with the aim of rescuing his co-worker but also collapsed. They were pulled out of the tank by “fire department personnel wearing self-contained breathing apparatuses” after being in the tank for 20 to 45 minutes and then were washed with a fire hose ([Letz et al., 1984a](#)). An assessment of this incident was indeterminate as to whether the workers collapsing was due to inhalation of ethylene dibromide or other potential causes such as lack of oxygen. Both collapsed victims were reported to have had extensive skin contact with 7.5 cm of liquid at the bottom of the tank. Analyses conducted by Cal-OSHA indicated that this liquid contained 0.1 to 0.3% ethylene dibromide as well as high concentrations of nitrates and phosphates and traces of dichloropropene and dichloropropane. Approximately 20 hours after the incident, the mean concentration of ethylene dibromide in the air inside the tank was 28 ppm, with a range of 15 to 41 ppm, and no other airborne toxins were detected. After exposure, the first worker suffered from metabolic acidosis, CNS depression, liver damage, and ultimately cardiopulmonary arrest, resulting in death 12 hours after exposure. The day after exposure, the second worker had abnormal serum urea nitrogen, creatinine, serum uric acid, bilirubin, lactate, and serum bromide; but was alert and his main symptoms were erythema and blisters on his trunk and legs. However, by the next day he was stuporous and had metabolic acidosis and hepatic and renal failure, which ultimately lead to his death 64 hours after exposure. Although it was noted that some exposure in these cases might have occurred via inhalation or ingestion, based on the level of ethylene dibromide in the tank fluid, the extent of the men’s contact with that fluid, the lack of signs of pulmonary damage, and the skin lesions that developed in the second case, the primary route of exposure was reported as being dermal. Thus, based on generally well-documented clinical, histopathologic, toxicologic, and industrial hygiene data on the incident, the authors concluded that “a primarily dermal exposure to a 0.1% solution of ethylene dibromide for brief periods (20 to 60 minutes) was fatal for both men” ([Letz et al., 1984a](#)).

There have been several fatalities associated with ingestion of ethylene dibromide, which provide information relevant to estimating an LD50 for human exposure. In particular, a study of patients (mostly males aged 21+ years) with acute ethylene dibromide ingestion exposure in India found that 38 out of 64 (59%) patients died ([Singh et al., 2007](#)). Mortality was 20% in those who consumed a half ampule (1.5 mL) of ethylene dibromide and 46% in those who consumed one ampule ([Singh et al., 2007](#)). The time from exposure to death ranged from 12 hours to 5 days ([Singh et al., 2007](#)). Because the

mortality was 46% ($\approx 50\%$) in those who consumed one ampule, the LD50 is approximately one ampule. One 3-mL ampule of Fumigrain has been reported to contain 6,480 mg of ethylene dibromide ([Prakash et al., 1999](#)). Therefore, the human LD50 for ethylene dibromide can be estimated as 6,480 mg ethylene dibromide per 80 kg body weight equals 81 mg/kg.

Other papers reported ingestion exposure in smaller sample sizes. For example, six cases of attempted suicide via ingestion of ethylene dibromide in Udaipur, India, were reported from December 1982 to June 1984 ([Saraswat et al., 1986](#)). Each of the six people ingested one ampule of ethylene dibromide. Two of these cases died, and four were hospitalized but survived. The two who died were females, one age 17 and one age 23. The four who survived included three female friends of the 17-year-old, who were ages 16, 17, and 18, as well as a 20-year-old male ([Saraswat et al., 1986](#)). Thus, ingestion of one ampule of ethylene dibromide was fatal in 1/3 of the individuals aged between 16 and 23 in this sample.

Additionally, a study reviewed 58 cases of ethylene dibromide ingestion in India from 2007 to 2012, with the aim of assessing the effect of time of start of therapeutic plasma exchange on survival ([Pahwa et al., 2013](#)). The age range of the cases was 15 to 45 and the male to female ratio was 3:2. Five cases were lost to follow-up, and six cases were hypotensive at hospital admission. The other 47 cases received therapeutic plasma exchange at different times after ethylene dibromide exposure. Overall, of the 47 patients with acute ethylene dibromide exposure who received therapeutic plasma exchange, 39 survived, and eight died. Survival was nine times higher in those who received therapeutic plasma exchange within 24 hours compared to those who received therapeutic plasma exchange more than 24 hours after ingestion of ethylene dibromide. Thus, although therapeutic plasma exchange may increase survival, it might not always be available in sufficient time to prevent acute lethality due to ingestion of ethylene dibromide.

These acute exposure case reports and case series did not undergo data quality evaluation because they were screened as Supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)). However, these studies provide evidence of adverse mortality outcomes potentially occurring following acute exposure to ethylene dibromide.

In addition to these reports of acute lethality, EPA identified studies that evaluated disease-specific mortality from chronic ethylene dibromide exposure ([Dow Chemical, 1992b](#); [Sweeney et al., 1986](#); [Turner and Barry, 1979](#)). Sweeney et al. (1986) in a historical prospective study, investigated mortality among 2,510 male workers at a tetraethyl lead manufacturing plant located in East Texas. Workers were employed for at least one day during the years 1952 to 1977 and were exposed to tetraethyl lead, ethylene dibromide, and other chemicals. However, this study did not report quantitative measurements of exposure other than duration of work. Standardized mortality ratios (SMRs) were calculated based on cause-specific mortality for males in the U.S. stratified by race, 5-year age groups, and 5-year calendar time periods. Overall, mortality among workers was lower than expected. No statistically significant increase in mortality due to any specific cause was found. The main limitations of this study are the inability to separate out the exposure of interest from other co-exposures, the lack of ethylene dibromide-specific quantitative exposure data, and the potential for healthy worker effect. EPA assigned this study a medium overall quality determination rating.

Similarly, Ott et al. (1980) and Dow Chemical (1992b) studied mortality in 169 male employees in two manufacturing plants located in Texas and Michigan. Because both plants were not operational in 1969 and 1979, respectively, assessments were based on existing records and discussions with workers formerly associated with the plants. Although exposure estimates were lacking for the facility in Texas, exposures ranged from 0 to 110 ppm for the Michigan facility. Statistically significant increases in

influenza and pneumonia mortality in the Michigan group were reported. No statistically significant increases in emphysema, chronic bronchitis or asthma mortality were reported. However, there was limited exposure measurement, and the study lacked adequate information on how outcomes were ascertained. Additionally, it had a relatively small number of participants and cases and expected cases were calculated without a measure of variance. EPA assigned this study a low overall quality determination rating.

Turner and Barry ([1979](#)) conducted a retrospective cohort study examining mortality, including cancer mortality, among 351 male workers in two ethylene dibromide manufacturing plants in Great Britain. Ethylene dibromide had been produced at two factories during the period from 1940 to 1970. Factory A started production of ethylene dibromide in 1940 and continued until 1970; factory B started production in 1954. The process involved the extraction of bromine from sea water and its subsequent reaction with ethylene to form ethylene dibromide. The potential exposure hazard was therefore restricted to involving the extraction of bromine and ethylene dibromide production. Workers with potential exposures to ethylene dibromide were employed for at least four years, and the rates from cancer were compared with the values from the general population in the same part of the country over a similar period. No statistically significant increase in cancer mortality among workers compared to the general population was observed. There were concerns with methods for assessing exposure and outcome, and with the limited statistical analyses. EPA assigned this study a low overall quality determination rating.

B.1.2 Laboratory Animal Evidence

EPA identified two acute, five short-term, three subchronic, and five chronic animal studies that evaluate the effects of ethylene dibromide inhalation on mortality and metabolic outcomes. Additionally, 10 acute and two chronic animal gavage studies were identified; and three acute dermal studies were identified.

Acute Inhalation

Rats were exposed, whole body, to ethylene bromide vapor concentrations of 200, 400, 1,600, 5,000, or 10,000 ppm for various durations ranging from 0.02 to 16 hours; the durations differed for each group ([Rowe et al., 1952](#)). Groups of 20 rats were also exposed to 100 ppm for 8.5, 12, or 16 hours. Finally, a separate group of females only (20/group) were exposed to 50, 500, 200, or 800 ppm for 0.1, 0.7, 2.5, or 7 hours. Mortality was recorded and animals were observed for changes in behavior and body weight changes for two to three weeks, or until it was certain they had recovered from the effects of exposure. The LC50 for an approximately 7-hour exposure duration visually appears to be up to 200 and less than 250 ppm. CNS depression was observed at “higher concentrations.” Deaths at higher exposures occurred within 24 hours of exposure and were due to respiratory failure and cardiac arrest. Delayed deaths (up to 12 days after exposure) at lower concentrations were due to pneumonia that developed due to lung injury. EPA assigned this study a medium overall quality determination rating.

Guinea pigs (10–20/group, mixed sex) were exposed whole-body to ethylene dibromide vapor concentrations of 200 ppm for 7 hours or to 400 ppm for 2, 3, 5, or 7 hours ([Rowe et al., 1952](#)). No mortality occurred in the 200 ppm group, or in animals exposed to 400 ppm for 2 hours. In animals exposed to 400 ppm for 3, 5, or 7 hours, mortality occurred in 5/10, 18/20, and 20/20 animals, respectively. LC50 values were not provided in the study. From the information provided, the guinea pig 7-hour inhalation LC50 is at least 200 and less than 400 ppm. EPA assigned this study a medium overall quality determination rating.

Short-Term Inhalation

In a short-term duration exposure study, rats (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, to 7-hour exposures in 9 days (the methods indicated a frequency of 5 days/week) ([Rowe et al., 1952](#)). The studies included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Three out of 10 animals died after 1, 5, and 7 exposures. Surviving rats were thin and unkempt. The results likely represent a LOAEC of 100 ppm; however, based on reporting deficiencies and failure to use the more appropriate control, the study was considered uninformative and a reliable POD cannot be determined.

In a short-term duration exposure study, rabbits (four females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, for up to four 7-hour exposures in four days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). Animals suffered severe intoxication and two of four animals died within two days and a third died during exposure on the third day. The last animal was sacrificed following the fourth exposure. Two additional rabbits were exposed to the same concentration for 7-hours on two consecutive days and then sacrificed. These animals lost weight (data not shown). The results likely represent a LOAEC of 100 ppm; however, based on reporting deficiencies and failure to use the more appropriate control, the study was considered uninformative and a reliable POD cannot be determined.

Pregnant mice were exposed to ethylene dibromide by inhalation chamber for 23 hours/day, 10 days, starting on gestational day 6 ([Short et al., 1978](#)). Exposure groups were 0 ppm (n = 18), 20 ppm (n = 20), 38 ppm (n = 20), 80 ppm (n = 22), and 0 ppm with feed restriction (n = 18). Mice were sacrificed on gestational day 18 for fetal assessment of soft tissue and skeletal abnormalities. Significant mortality in dams was seen at 38 ppm. Significant dam body weight change was seen during exposure at 20 ppm. A LOAEC of 20 ppm was determined for metabolic endpoints, and 38 ppm for mortality. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

Pregnant rats were exposed to ethylene dibromide in an inhalation chamber for 23 hours/day, 10 days, starting on gestational day 6 ([Short et al., 1978](#)). Exposure groups were 0 ppm (n = 17), 20 ppm (n = 15), 38 ppm (n = 16), 80 ppm (n = 16) and 0 ppm with feed restriction (n = 16). Significant dam body weight change was seen during exposure at 38 ppm, where the feed-restricted control group consumed similar amounts of food. Excessive mortality was seen in the 80 ppm group. A LOAEC of 38 ppm was determined for metabolic endpoints, and 80 ppm for mortality. EPA assigned this study a high overall quality determination rating.

Female CD rats (20/group) were exposed to 0, 20, 39, or 80 ppm ethylene dibromide 7 hours/day, 7 days/week for three weeks ([Short et al., 1978](#)). The exposed females were then bred with untreated males and sacrificed mid-gestation (3 weeks post-exposure) to assess implants, viable implants, resorptions, and reproductive histopathology. Females exposed to 80 ppm consumed less food than controls, lost weight during the study, and had significant mortality (20%). A LOAEL of 80 ppm was determined for weight loss and mortality. EPA assigned this study a high overall quality determination rating.

Subchronic Inhalation

In a subchronic duration exposure study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for as many as 63 exposures in 91 days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. More than 50% of the males died due to pneumonia and infections in the upper respiratory tract. Four treated females died. Treated animals showed reduced growth, but the difference was not statistically significant. A LOAEC of 50 ppm was determined metabolic and mortality endpoints. EPA assigned this study a low overall quality determination rating.

In a chronic-duration study, guinea pigs (8/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 25 ppm, 7 hours/day, 5 days/week for a total of 145 exposures in 205 days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Half of the males and 2/8 females died due to infections of the upper respiratory tract. There were no effects on general appearance, behavior, growth, or final body weights. Based on the information provided, a chronic LOAEC of 25 ppm was identified, based on the mortality effects. EPA assigned this study to low overall quality determination rating.

Male CD rats (18-20/group) were exposed to 0, 19, 39, or 89 ppm ethylene dibromide 7 hours/day, 5 days/week for 10 weeks via inhalation chamber ([Short et al., 1979](#)). Males exposed to 89 ppm consumed less food, gained less weight, and had higher mortality (21%) than controls. Males exposed to 39 ppm gained less weight than controls. A LOAEL of 39 ppm was assigned for metabolic endpoints, and 89 ppm for mortality. EPA assigned this study a high overall quality determination rating.

Chronic Inhalation

B6C3F1 mice (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide for 78 weeks to 2 years ([NTP, 1982](#)). Throughout the study, mean body weights of high-dose mice of either sex were lower than those of the corresponding untreated controls. Survival of the low- and high-dose female and male mice was significantly shorter than that in the corresponding controls. The principal cause of early death in control and dosed male mice was ascending, suppurative urinary tract infection that resulted in necrotic, ulcerative lesions around the urethral opening, chronic or suppurative cystitis (often with urinary tract obstruction), and ascending suppurative pyelonephritis. A LOAEC of 10 ppm was identified for mortality. EPA assigned this study a high overall quality determination rating.

F344 rats (n = 50/sex/dose) were exposed by inhalation to 0, 10, or 40 ppm ethylene dibromide six hours/day, five days/week, for two years ([NTP, 1982](#)). Throughout the study, mean body weights of high-dose rats of either sex were lower than those of the corresponding untreated controls. Survival of the high-dose rats of either sex was significantly shorter than that in the corresponding controls although no evaluation was conducted to investigate the principal cause of death in this study. A 40 ppm LOAEC was identified for metabolic and mortality effects. EPA assigned this study a high overall quality determination rating.

In a chronic-duration study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 25 ppm, 7 hours/day, 5 days/week for a total of 151 exposures in 213 days ([Rowe et al., 1952](#)). The

study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Half of the male rats died due to pneumonia and infections of the upper respiratory tract. 16/20 females survived. There were no effects on general appearance, behavior, growth, or final body weights. Based on the information provided, a chronic LOAEC of 25 ppm was identified due to mortality effects. EPA assigned this study a low overall quality determination rating.

Male and female Sprague-Dawley rats (48/sex/group) were exposed to 0 or 20 ppm ethylene dibromide vapor in air 7 hours/day, 5 days/week for 18 months, either alone or in combination with disulfiram (Antabuse) through diet ([Wong et al., 1982](#)). Only results for rats exposed to ethylene dibromide alone are described here. At the end of the 18-month study, both male and female exposed rats had significantly lower body weights than controls. Significant mortality was observed, with a mortality rate of 90% in males and 77% in females. A LOAEL of 20 ppm was determined for metabolic and mortality outcomes. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

Female strain A/J mice were exposed to 0, 20, or 50 ppm ethylene dibromide for 6 hours/day, 5 days/week, for six months in whole body dynamic chambers ([Adkins et al., 1986](#)). The 6-month study with ethylene dibromide was repeated two times. Treatment related mortality was observed in the first study (30/30, 11/30 and 11/30 mice survived to planned study termination in the 0, 20, and 50 ppm groups, respectively). No treatment related mortality was observed in the second study (58/60, 57/60, and 57/60 mice survived to planned study termination in the 0, 20 and 50 ppm groups, respectively). A mortality LOAEC of 20 ppm was identified for study one, while a NOAEC of 20 ppm was identified for study two. EPA assigned this study a medium overall quality determination rating for mortality data for quality of experiment structure.

Acute Oral

In a mechanistic study evaluating the effects of exposure on microsomal responses, Male Sprague-Dawley rats (3 animals/group) were administered a dose of ethylene dibromide in mineral oil at 625 mg/kg, via gavage ([Moody et al., 1981](#)). Animals were sacrificed 1 or 18 hours after dosing. Control rats were used, but details (untreated vs. vehicle control) were not provided. Systemic endpoints were limited to mortality and body weights. No mortality or loss of body weight was observed. No toxicity values were reported by the study author. A NOEL of 625 mg/kg was determined for mortality and metabolic endpoints. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

Young adult rats (60 males and 40 females) were administered a 10% solution of ethylene dibromide in olive oil emulsified in 2 mL of a 5 to 10% acacia solution as a single dose via gavage ([Rowe et al., 1952](#)). Animals were observed for approximately 2 weeks. The specific doses tested were not reported. The reported LD50 (95% CI) for male rats was 0.146 g/kg (0.126–0.170) and for female rats was 0.117 g/kg (0.108–0.126). EPA assigned this study a low overall quality determination rating.

Twenty young adult female mice were dosed via intubation with approximately 2 mL of 1-3% solution of ethylene dibromide emulsified in olive oil ([Rowe et al., 1952](#)). The LD50 (95% CI) was 0.420 g/kg (0.353–0.500). Dosages were reported, but the specific concentration of ethylene dibromide was not reported. EPA assigned this study a low overall quality determination rating due to inadequate dosage reporting.

Fifty-five mature young adult female rabbits were dosed via intubation with a 10% solution of ethylene dibromide in olive oil emulsified in 2 mL of a 5 to 10% acacia solution as a single dose ([Rowe et al., 1952](#)). Animals were observed for approximately 2 weeks. The reported LD50 (95% CI) was 0.055 g/kg (0.044–0.069). EPA assigned this study a low overall quality determination rating due to inadequate dosage reporting.

Young adult guinea pigs (40, mixed gender) were administered a 10% solution of ethylene dibromide in olive oil emulsified in 2 mL of a 5 to 10% acacia solution as a single dose ([Rowe et al., 1952](#)). Animals were observed for approximately 2 weeks. The reported LD50 (95% CI) for guinea pigs is 0.110 g/kg (0.098–0.122). EPA assigned this study a low overall quality determination rating due to inadequate dosage reporting.

Rabbits (1/group) were exposed to ethylene dibromide by single oral gavage at 20 mg/kg, 25 mg/kg, 30 mg/kg, 50 mg/kg, 100 mg/kg, 250 mg/kg, 500 mg/kg, 1,000 mg/kg, 2,000 mg/kg, or 3,500 mg/kg ([Kettering Laboratory, 1943](#)). The minimum lethal dose was determined to be between 30 and 50 mg/kg. Muscle weakness, collapse, shallow respiration and mortality occurred within 3.5 hours after a single-dose oral gavage dose of 2,000 mg/kg. At 1,000 mg/kg, nystagmus with contracted pupils, muscle incoordination, ataxia and death occurred within 4 hours. A dose of 500 mg/kg produced muscle weakness and death within 6 hours. Rabbits given doses of 50, 100, and 250 mg/kg died at 34, 20, and 12 to 16 hours, respectively. A NOAEL of 30 mg/kg was identified for mortality. When evaluated using data quality criteria for animal toxicity, EPA assigned this study an uninformative overall quality determination rating because only one animal was utilized per group.

Male and female Fischer 344 rats (6rats/sex/dose) received 40, 80, 130 (male only), 160 or 320 mg/kg via single oral gavage ethylene dibromide ([Dow Chemical, 1992a](#)). The single dose oral LD50 for male rats was 116 mg/kg with an approximate slope of 6.8. The LD50 for female rats was 133 mg/kg, with an approximate slope of 4.5. Two weeks post-treatment signs of toxicity observation included lethargy in all sexes, palpebral closure, rapid shallow breathing (80–320 mg/kg), and unconsciousness in one female rat (320 mg). Survived rats exhibited steady body weight gain during a 2-week recovery. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a high overall quality determination rating.

In a peroral toxicity study, Sprague-Dawley rats (5/sex/group) were exposed by stomach intubation to ethylene dibromide (purity not reported) in corn oil as single doses of 50, 100, 200, 400, or 800 mg/kg and then observed for 14 days ([Withheld, 1979](#)). Animals were observed for mortality and signs of toxicity at least daily. Other endpoints included body weight and body weight gain. All test animals exposed to 400 or 800 mg/kg died within 24 hours of dosing, and no deaths occurred in the exposure groups up to 200 mg/kg. Weight gain was dose-related in the 50, 100, and 200 mg/kg groups. For both sexes combined, the author-reported 14-day LD50 (95% CI) was 283 mg/kg (245–326). EPA assigned this study a high overall quality determination rating.

In a peroral toxicity study, Sprague-Dawley rats (5/sex) were exposed by stomach intubation to a single ethylene dibromide (purity not reported) dose of 400 mg/kg and then observed for 14 days ([Withheld, 1979](#)). Animals were observed for mortality and signs of toxicity daily. Other endpoints included body weight and body weight gain. All test animals died within 24 hours of dosing. No body weights were reported because of the early termination of test animals. No author-derived toxicity values were provided. An LC₁₀₀ of 400 mg/kg was determined based on the mortality data reported. EPA assigned this study a high overall quality determination rating.

Acute percutaneous absorption was conducted on male and female New Zealand white rabbits (2/sex/group) ([Dow Chemical, 1992a](#)). Rabbits were treated with 63, 50, 130, 200 or 320 mg/kg of undiluted ethylene dibromide. The LD50 was 121 mg/kg, with an approximate slope of 3.7. Lethargy was observed in many rabbits following treatment. EPA assigned this study a high overall quality determination rating for mortality.

Chronic Oral

Osborne-Mendel rats were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/group) ([NCI, 1978](#)). Control animals were either gavaged with corn oil (20/sex) or remained untreated (20/sex). Time-weighted averaged doses achieved in each group were 0, 38, and 41 mg/kg/day for male rats and 0, 37, and 39 mg/kg/day for female rats. Exposures in the high-dose group were suspended at 17 weeks due to deaths of 18 males and 20 females; at week 30, treatments resumed in the remaining rats in high-dose group at the same dose the low-dose rats were receiving. At week 42, all treatments in rats were paused for a week then resumed for an additional four weeks. The study was discontinued at 49 weeks in male rats due to excessive deaths in both treatment groups. The study was discontinued for female rats at week 61. In the corn oil gavage vehicle group, male gavage doses were stopped at week 49 and animals were observed for an additional 14-week recovery period; female gavage doses were stopped at week 61 followed by a 2-week observation period (vehicle controls sacrificed at week 63). In the untreated control group, five males were sacrificed in week 59 and the remaining four in week 107. Endpoints evaluated included mortality, clinical signs of toxicity, body weight, and food consumption. Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included reddened ears and hunched appearance in all treated groups by week 5, and firm distended abdomens and abdominal urine stains in all treated groups by week 38 (incidence data not reported). Body weights decreased in males and females after 10 weeks of treatment; however, the study authors note that this decrease in mean weight may reflect increased mortality. A POD was not reported by study authors. A LOAEL of 37 mg/kg/day was identified for body weight and mortality endpoints. When evaluated using data quality criteria for animal toxicity, EPA assigned this study a medium overall quality determination rating.

B6C3F1 mice were exposed via gavage to ethylene dibromide in corn oil 5 days/week in a chronic cancer bioassay (50/sex/group) ([NCI, 1978](#)). 20 control animals received corn oil vehicle, and 20 control animals were untreated. TWA doses achieved in each group were 0, 62, and 107 mg/kg/day in mice of both sexes. Dose levels were adjusted at several points during the study. Both doses increased during week 11 and were then returned to normal levels at week 13. At week 40, the high-dose group was reduced to 60 mg/kg/day and all treatments were discontinued at week 54. All surviving male and females in the high-dose group were sacrificed at week 78. Low-dose females were sacrificed at week 91. Endpoints evaluated included mortality, clinical signs of toxicity, body weight, and food consumption. Accelerated mortality was significantly associated with increased dosage in males and females (Tarone test). Clinical signs observed included alopecia in treated animals at week 7; soft feces and body sores in both dose groups at week 14; thin, hunched appearance in the high-dose group and small inguinal nodules in some low-dose males at week 42 (incidence data not reported). Body weights were decreased in males and females after 10 weeks of treatment; however, the study authors note that this decrease in mean weight may reflect increased mortality. Mortality in untreated control mice was significantly higher than expected, with only 70% surviving through week 58. EPA assigned an uninformative overall quality determination rating due to large inconsistencies in dosing levels over time and unexpected control mortality.

Rabbits (1/group) were exposed to ethylene dibromide by single dermal application at 300, 430, 480, 750, 1,090, or 2,000 mg/kg ([Kettering Laboratory, 1943](#)). No immediate (local or systemic) reactions

were observed following test substance application. No description of the outcome assessment methodology for how systemic effects were evaluated was provided. Death occurred at doses of 1,090 mg/kg/day (40 hours post-exposure) and 2,000 mg/kg/day (5 hours post-exposure). A NOAEL of 750 mg/kg/day was assigned for mortality. When evaluated using data quality criteria for animal toxicity, EPA assigned this study an uninformative overall quality determination rating because only one animal was utilized per group.

Acute Dermal

In a dermal toxicity study, New Zealand white rabbits (2/sex/group) were dermally exposed to ethylene dibromide (purity not reported) doses of 109, 218, 436, or 872 mg/kg by application of undiluted ethylene dibromide to the unabraded back of each animal ([Withheld, 1979](#)). The trunk of the animal was covered with vinylite sheeting, which was removed along with residual ethylene dibromide after 24 hours. Animals were observed for mortality and signs of toxicity at least daily for 14 days. Other endpoints included body weight and body weight gain. Test animals exposed to 436 or 872 mg/kg ethylene dibromide died within 3 days of exposure. Weight gain was dose-related in the 109 and 218 mg/kg groups for female rabbits only. No signs of toxicity were observed other than skin irritation. An author-reported 14-day dermal LD50 of 308 mg/kg was reported. EPA assigned this study a high overall quality determination rating for mortality.

In an acute dermal toxicity study, ethylene dibromide was dermally applied to the skin of rabbits at doses of 0.21 (n = 15), 0.30, 0.65, and 1.1 (n = 5) g/kg for 24 hours under occlusion ([Rowe et al., 1952](#)). No further details were provided (e.g., use of vehicle). At the end of the exposure period, the impervious sleeves were removed and the area was cleansed with soap and water. The animals were observed for two weeks, or until they recovered from the effects of exposure for mortality. All animals exhibited marked depression of the CNS. A sufficient drop in body temperature caused the higher dosed animals to feel cold to the touch. Deaths occurred within 4 days in all exposure levels. Mortality occurred in 1/15, 2/5, 4/5, and 5/5 animals in the 0.21, 0.30, 0.65, and 1.1 g/kg groups, respectively. No LD50 was calculated. An acute LOAEL of 0.30 g/kg was determined for this review based on mortality. EPA assigned this study a medium overall quality determination rating.

B.1.3 Evidence Integration and Summary

Although mortality is a critical health outcome and is consistently observed in both human case reports and animal studies, the endpoints summarized in this section were not used quantitatively for POD derivation or dose-response analysis due to limitations in overall data quality or quantitative detail. For example, limitations such as lack of quantitative exposure data in human case reports, absence of appropriate control groups, and insufficient detail for dose-response modeling ([Pahwa et al., 2013](#); [Singh et al., 2007](#); [Dow Chemical, 1992b](#); [Osterloh, 1986](#); [Saraswat et al., 1986](#); [Sweeney et al., 1986](#); [Letz et al., 1984a, b](#); [Ott et al., 1980](#); [Turner and Barry, 1979](#)). In animal studies, limitations included high mortality at higher doses relative to other health outcomes, lack of sufficient dose groups, inconsistent reporting of exposure durations, and inadequate reporting of control data ([Dow Chemical, 1992a](#); [Adkins et al., 1986](#); [NTP, 1982](#); [Wong et al., 1982](#); [Moody et al., 1981](#); [Short et al., 1979](#); [Withheld, 1979](#); [NCI, 1978](#); [Short et al., 1978](#); [Rowe et al., 1952](#); [Kettering Laboratory, 1943](#)). As a result, while mortality outcomes inform the overall weight of evidence for ethylene dibromide hazard, only studies meeting higher overall quality and quantitative standards for methodological rigor and quantitative utility were carried forward for quantitative assessment.

There is moderate evidence that acute ethylene dibromide exposure is associated with mortality in humans. The quality of the database somewhat decreases the strength of the evidence. There have been several cases of deaths reported to be associated with ethylene dibromide exposure, including several

suicide attempts via ingestion of ethylene dibromide. Although case studies and case series generally are less informative for causal inference due to their lack of a control or comparison group, reported suicide attempts have similarities to intentional dosing studies with the individual serving as their own control, and in some cases the specific dose was documented. The consistency of the findings somewhat increases the strength of the evidence. Acute exposure to ethylene dibromide via ingestion consistently was associated with hospitalization and often death. In addition to evidence of lethality associated with acute ingestion exposure, there was one incident in which two individuals died after exposure to ethylene dibromide that was reported to be primarily dermal. The magnitude and precision of the association somewhat increases the strength of the evidence. In one study, mortality was 46% in those who consumed one ampule (3 mL) of ethylene dibromide, which indicates an approximate LD50 of 81 mg/kg ([Singh et al., 2007](#)). That study also provided evidence of dose-response, which increases the strength of the evidence, with 20% mortality in those who consumed a half-ampule (1.5 mL) of ethylene dibromide ([Singh et al., 2007](#)).

Meanwhile, there is *robust* evidence in laboratory animal studies that mortality is related to ethylene dibromide exposure. EPA identified 30 independent experiments with mortality endpoints, spanning acute, short-term, subchronic, and chronic durations and inhalation, oral, and dermal exposures. 18 of these experiments are high or medium quality. In acute and short-term inhalation studies, PODs for mortality start at 20 ppm ([Short et al., 1978](#)) with LC50s greater than 200 ppm but less than 250 or 400 ppm, depending on species ([Rowe et al., 1952](#)). Subchronic and chronic inhalation studies have PODs as low as 10 ppm ([NTP, 1982](#)).

Acute and short-term oral studies report LD50s as low as 116 mg/kg in animals ([Dow Chemical, 1992a](#)), although human data indicate a lower LD50 of 81 mg/kg. A chronic LOAEL of 37 mg/kg/day was identified in animals ([Dow Chemical, 1992a](#)). A single study reports a mortality NOEL of 625 mg/kg in rats that were administered test compound in corn oil, then sacrificed for analysis after 1 or 18 hours ([Moody et al., 1981](#)). Acute dermal studies report a rabbit LOAEL of 0.3 g/kg ([Withheld, 1979](#)) or an LD50 of 308 mg/kg ([Rowe et al., 1952](#)).

In cases where an animal toxicology study was rated low or uninformative quality, the rating is generally related to underreporting, causing lack of clarity of the exposure level, or due to only one animal being utilized per exposure group. Nonetheless, all low-quality and uninformative references show evidence of mortality. In some cases, a reference is rated lower quality due to excessively high mortality in subject animals, thus preventing appropriate statistical analysis for a variety of endpoints.

Cause of death is sometimes reported, with authors most commonly referencing pulmonary arrest, cardiac arrest, or respiratory infection—likely as a result of lung tissue damage as a result of exposure. LC50s are determined for a variety of animal species, and for many timepoints during acute studies. Weight loss is seen in tandem with increased mortality.

The currently available evidence indicates that ethylene dibromide likely causes mortality in humans under relevant exposure circumstances. This determination is based on robust evidence of human mortality following acute exposure and robust evidence of animal mortality following acute, short-term, subchronic, and chronic exposures to varying doses of ethylene dibromide. The interactive web-based evidence integration table for [mortality](#) (accessed June 2026) is available in HAWC.

B.2 Neurological/Behavioral Toxicity

B.2.1 Human Evidence

EPA identified one study that investigated the association between exposure to ethylene dibromide and depression ([Beard et al., 2014](#)).

This study examined the relationships between exposure to specific pesticides, including ethylene dibromide, and depression among male private pesticide applicators (n = 21,208) in the Agricultural Health Study, which is a prospective cohort study. Exposure to ethylene dibromide among the pesticide applicators was assessed based on questionnaire data. Analyses assessed individuals that had used and had not used ethylene dibromide, with cumulative lifetime days of ethylene dibromide use categorized as 0 days, 1 to 8 days, 9 to 28 days, and 28 or more days.

The outcome of depression was assessed based on “enrollment and farmer questionnaires and the follow-up interview”, which asked about doctor-diagnosed depression ([Beard et al., 2014](#)). Depression cases were divided into three groups. The “pre-enrollment enrollment only” (PRE-E) group consisted of “applicators who reported a previous diagnosis of depression at enrollment, but who did not confirm their pre-enrollment diagnosis at follow-up.” The “pre-enrollment both” (PRE-B) group consisted of participants who “reported a previous diagnosis of depression at both enrollment and follow-up” or “reported a previous diagnosis at follow-up only but with an age at diagnosis less than their age at enrollment”. The “post-enrollment” (POST) group consisted of “applicators who reported a previous diagnosis of depression at follow-up but not at enrollment, and whose reported age at diagnosis equaled or exceeded their age at enrollment” ([Beard et al., 2014](#)).

Ethylene dibromide exposure for greater than 28 days was associated with an increased odds of depression in all three case groups (described above), which was statistically significant in the PRE-E and PRE-B groups, but not the POST group, with odds ratios (ORs) and 95% confidence intervals (CIs) as follows: PRE-E (OR = 2.6; 95% CI: 1.2–5.8), PRE-B (OR = 2.7; (95% CI: 1.2–6.1), POST (OR = 1.7 (95%; CI: 0.6–4.5) ([Beard et al., 2014](#)). Across the lifetime exposure days categories, there was a positive exposure-response trend for the three case groups, which was statistically significant in the PRE-E and PRE-B, but not the POST group, with trend OR (95% CI) as follows: PRE-E trend (OR = 1.7; 95% CI: 1.1–2.5); PRE-B trend (OR = 1.7; 95% CI: 1.1–2.6); and POST (trend OR = 1.3; 95% CI: 0.8–2.2).

Because the statistically significant associations were in the PRE groups, temporality is uncertain. However, the authors noted evidence that reduces the likelihood that these findings are due to reverse causation, including that different pesticide handling practices were not inversely associated with depression in the study population. Overall, this was a medium confidence study of a large cohort. In addition to the large sample size, strengths of the study include appropriate participant selection methods, the use of directed acyclic graphs to identify relevant potential confounders, and appropriate statistical modeling with adjustment for relevant confounders and inverse probability weighting for missing data. The main limitation of the study is that exposure and outcome were self-reported, so there is some potential for exposure misclassification and outcome misclassification. However, the Discussion section of the paper cited studies indicating that this self-reporting is unlikely to have resulted in substantial risk of bias ([Beard et al., 2014](#)). EPA assigned this study a medium overall quality determination rating during systematic review.

B.2.2 Laboratory Animal Evidence

EPA identified one developmental, one acute, one subchronic, and one chronic study that evaluated the effects of ethylene dibromide via inhalation on neurological/behavioral outcomes. Two additional acute (1 oral and 1 dermal) and one subchronic (oral) animal studies were identified.

Developmental Inhalation

Male (n = 40) and female (n = 20) Fisher-344 (F-344) rats were exposed to 0, 3, 10, or 40 ppm ethylene dibromide, 6 hours/day, 5 days/week for 13 weeks via inhalation ([Dow Chemical, 1980](#)). Serial sacrifices of 10 males/treatment group were conducted after 1, 6 and 13 weeks (5, 29, and 67 exposure days respectively). An additional group of rats were held for an 89-day recovery period following the 13-week exposure. No change in absolute brain weight was found at any dose level in either males or females. Statistically significant increases in relative brain weight in males (but not females) exposed to 40 ppm ethylene dibromide for 6 or 13 weeks or 10 ppm ethylene dibromide for 6 weeks were considered secondary reflections of the lower body weights of these groups. No major limitations were identified in this study that impacts its quality. EPA assigned this study a high overall quality determination rating during systematic review. In a developmental neurotoxicity study ([Smith and Goldman, 1983](#)) pregnant Long-Evans female rats (n = 4/treatment group) were exposed to ethylene dibromide via inhalation at concentrations of 0, 0.43, 6.67, or 66.67 ppm for 4 hours/day, 3 day/week, from GDs 3 to 20. No maternal toxicity or neurological/behavioral effects in offspring were observed at the lowest dose (0.43 ppm). At 6.67 ppm, dams exhibited mild signs of stress—including increased defecation and slightly reduced gestational weight gain and their offspring exhibited enhanced motor coordination (measured by rotorod performance) and learning (brightness discrimination in a T-maze). Following exposure to the highest dose (66.67 ppm), maternal stress responses were more pronounced, with increased defecation and greater reduction in maternal body weight gains and statistically significant improvements in rotorod performance and acquisition of learned brightness discrimination compared to controls. The study authors suggest that the enhanced behavioral outcomes observed in the pups may be secondary to maternal stress rather than direct neurotoxic effects of ethylene dibromide on fetal neurodevelopment. The NOEL is 0.43 ppm for this study and no major study quality limitations were identified. EPA assigned this study a high overall quality determination rating during systematic review.

Acute Inhalation

In an acute study, rats were exposed to a single, whole-body dose of ethylene bromide vapor concentrations (200, 400, 1,600, 5,000, or 10,000 ppm) for various durations ranging from 0.02 to 16 hours; the durations differed for each group ([Rowe et al., 1952](#)). Groups of 20 rats were also exposed to 100 ppm for 8.5, 12, or 16 hours. Mortality was recorded and animals were observed for changes in behavior and body weight changes for 2 to 3 weeks, or until it was certain they had recovered from the effects of exposure. Data were plotted showing vapor concentration (ppm) vs. duration of exposure (hours). For each concentration, the durations producing 0.01, 50, and 99% mortality are shown. Based on the graph, the LC50 for an approximately 7-hour exposure duration visually appears to exceed 200 and less than 250 ppm. CNS depression, measured by touch as decreased body temperature, was observed at higher concentrations. Deaths at higher exposures occurred within 24 hours of exposure and were due to respiratory failure and cardiac arrest. CNS depression in this context may be considered a part of a constellation of effects related to mortality. Delayed deaths (up to 12 days after exposure) at lower concentrations were due to pneumonia that developed due to lung injury. Prior to death, animals showed evidence of weight loss, rough and unkempt fur, irritability, and blood-tinged fluid from the nose. This study is considered uninformative for neurological/behavioral effects due to lack of clarity in reporting.

Subchronic Inhalation

In a subchronic, dose-range finding study ([NTP, 1982](#)) to inform chronic study doses F344 rats (4–5 male; 5–6 female) and B6C3F1 mice (10 male/10 female) were exposed to 0, 3, 15 or 75 ppm ethylene dibromide for 6 hours/day, 5 days/week for 13 weeks. Animals were observed twice daily for mortality and for signs of toxicity or abnormal behavior. No qualitative or quantitative behavioral findings were reported. EPA assigned this study a high overall quality determination rating during systematic review.

Chronic Inhalation

F344 rats (n = 50/sex/dose) were exposed via inhalation to 0, 10, or 40 ppm ethylene dibromide, 6 hours/day for 5 days/week, in a primarily 2-year cancer study ([NTP, 1982](#)). The authors reported observing behavior during clinical observations and performing gross pathology of the brain (among other organs). Throughout the study, mean body weights of high-dose male and female rats were lower than those of the corresponding untreated controls. However, absolute/relative brain weights were not reported either quantitatively or qualitatively for either males or females at any dose. Beginning at week 52, an increasing number of high-dose (40 ppm) animals exhibited weakness of the limbs or body. These data are not reported quantitatively or by sex. The authors state in the methods section that they collected brains to conduct gross pathological examinations, but the findings were not reported quantitatively or qualitatively. A LOAEC is not defined for neurological/behavioral effects. Noted limitations including only two dose levels were tested and that these groups were exposed for different durations. The low-dose was considered too high and the authors reported high mortality in the high-dose group. EPA assigned this study a high overall quality determination rating during systematic review.

Acute Oral

In an acute oral study, rabbits (1/group, not clearly stated) were exposed to ethylene dibromide by single gavage delivery of 20, 25, 30, 50, 100, 250, 500, 1,000, 2,000, or 3,500 mg/kg body weight ([Kettering Laboratory, 1943](#)). The minimum lethal dose was determined to be between 30 and 50 mg/kg. Muscle weakness, collapse, shallow respiration and mortality occurred within 3.5 hours after a single-dose oral gavage dose of 2,000 mg/kg/day. At 1,000 mg/kg/day, nystagmus with contracted pupils, muscle incoordination, ataxia and death occurred within 4 hours. A dose of 500 mg/kg/day produced muscle weakness and death within 6 hours. Rabbits given doses of 50, 100, and 250 mg/kg/day died at 34, 20, and 12 to 16 hours, respectively. No clinical signs were observed in these rabbits. Pathological effects that occurred in animals that died include irritation of the gastrointestinal tract, congestion in organs (not specified), focal degeneration in cells of the liver and kidney and pulmonary edema. Limitations included the use of a single rabbit (n = 1) for each dose. Methods were not adequately described. No information was provided on the vehicle used, gavage volume, timing of observations and necropsy, follow up time, or tissues examined at necropsy. Histopathology findings were not described in detail and were not associated with dose. EPA assigned this study a medium overall quality determination rating during systematic review.

Subchronic Oral

In a subchronic oral study, male rats were fed ethylene dibromide for 90 days from weanling stage at 0, 100, and 500 ppm (5 rats from each group) and mated with unexposed females ([Shivanandappa et al., 1987](#)). This was primarily a male reproductive study that also evaluated organ weight and conducted histopathological examination of the brain. Food intake and growth of ethylene dibromide fed rats were not affected throughout the experimental period. Relative weights of the brain did not show any changes. Histopathological examination of the organs did not show any significant pathological changes in ethylene dibromide fed rats at any dosage. The study reports test substance was provided with the diet and water *ad libitum*. But as reported above, the study authors did not make any adjustment in the actual

administered doses based on the estimated ethylene dibromide loss due to evaporation, nor did they measure potential ethylene dibromide loss from the diet fed to test animals *ad libitum*. Therefore, the actual administered dose is estimated to be much lower than reported and is essentially unknown, making the study unusable. EPA assigned this study an uninformative overall quality determination rating during systematic review.

Acute Dermal

In an acute dermal toxicity study, the test material was dermally applied to the skin of rabbits at doses of 0.21 (n = 15), 0.30, 0.65, and 1.1 (n = 5) g/kg for 24 hours under occlusion ([Rowe et al., 1952](#)). No further details were provided (e.g., use of vehicle). At the end of the exposure period, the impervious sleeves were removed and the area was cleansed with soap and water. The animals were observed for 2 weeks, or until they had recovered from the effects of exposure for mortality, and signs of irritation on the skin. This resulted in moderate to severe erythema, edema, and necrosis “in all cases.” Healing occurred with scar formation. All animals exhibited marked depression of the CNS. A sufficient drop in body temperature caused the higher dosage animals to feel cold to the touch. Deaths occurred within 4 days in all exposure levels. Mortality occurred in 1/15, 2/5, 4/5, and 5/5 animals in the 0.21, 0.30, 0.65, and 1.1 g/kg groups, respectively. No LD50 was calculated. An acute LOAEL of 0.30 g/kg (the lowest dose) was determined for this review based on CNS effects. CNS depression in this context may be considered a part of a constellation of effects related to mortality. This study is considered uninformative for neurological/behavioral effects due to lack of clarity in reporting.

B.2.3 Mechanistic Evidence

EPA identified several *in vivo* and *in vitro* experimental studies that report mechanistic evidence consistent with neurotoxicity following exposure to ethylene dibromide. Experimental evidence indicates that ethylene dibromide produces neurotoxic effects, including disruptions in early neural development, reductions in somite formation in rat fetal liver GST-catalyzed bioactivation on growth parameters in cultured rat embryos ([Mitra et al., 1992b](#)). A similar study by the same research group ([Mitra et al., 1992a](#)) using GST derived from human fetal liver also resulted in significant structural alterations in the developing fore-, mid-, and hind-brain; the olfactory and optic system in a similar cultured rat embryonic system. Another study reported changes in neurotransmitter related enzyme activities such as choline acetyltransferase, acetylcholine esterase and glutamic acid decarboxylase levels across several regions including the cerebellum, corpus striatum, hippocampus, hypothalamus, frontal cortex, with some effects persisting to postnatal (PND 21) ([Hsu et al., 1985](#)). These findings provide mechanistic support for ethylene dibromide induced neurotoxicity.

B.2.4 Evidence Integration and Summary

Although neurological and behavioral toxicity is recognized as a potential health outcome for ethylene dibromide, the endpoints summarized in this section were not used quantitatively for POD derivation or dose-response analysis due to limitations in overall data quality or quantitative detail. For example, limitations such as lack of quantitative exposure data in human studies, reliance on self-reported outcomes, small sample sizes, and potential confounding by co-exposures ([Beard et al., 2014](#)). In animal studies, limitations included insufficient dose-response information, absence of NOAELs, lack of sufficient dose groups, and inconsistent or incomplete reporting of critical endpoints ([Shivanandappa et al., 1987](#); [NTP, 1982](#); [Dow Chemical, 1980](#); [Rowe et al., 1952](#); [Kettering Laboratory, 1943](#)). As a result, while these endpoints inform the overall weight of evidence for neurological and behavioral toxicity, only studies meeting higher overall quality and quantitative standards for methodological rigor and quantitative utility were carried forward for quantitative assessment.

The evidence for neurological toxicity in humans is slight. There is some indication of a potential association between ethylene dibromide exposure and the mental health outcome of depression. However, only one epidemiological study of the association between ethylene dibromide exposure and this outcome was identified ([Beard et al., 2014](#)). Although the study was medium quality and found a positive association between ethylene dibromide exposure and depression, the lack of additional studies assessing this association substantially decreases the strength of the evidence. Other studies have found associations between non-specific exposure to any pesticides and depression, which somewhat increases the strength of the evidence. However, consistency between study findings cannot be determined because only one epidemiologic study was identified that specifically assessed the association between ethylene dibromide exposure and depression. The magnitude and precision of the observed associations in the study were neither extremely large nor extremely small. The study found a positive exposure-response trend, which somewhat increases the strength of the evidence. Because this study assessed human data, the relevance to humans increases the strength of the evidence.

Laboratory animal studies provide slight evidence of neurological effects in relation to ethylene dibromide inhalation, oral, or dermal exposure at high levels. Chronic inhalation exposure to 40 ppm ethylene dibromide is associated with muscle weakness, while subchronic studies showed no similar effects ([NTP, 1982](#)). Acute inhalation, dermal, or oral exposure to higher levels of ethylene dibromide is associated with central nervous system depression, including decreased body temperature and respiratory failure ([Rowe et al., 1952](#); [Kettering Laboratory, 1943](#)). Additional studies stated no change in brain organ weight when investigated at short-term and subchronic exposure ([Shivanandappa et al., 1987](#); [NTP, 1982](#); [Dow Chemical, 1980](#)).

Evidence on neurological outcomes based on mechanistic data showed effects in neurodevelopment resulting in altered growth parameter bioactivation ([Mitra et al., 1992b](#)) and development and function of the brain and sensory systems ([Mitra et al., 1992a](#)). Evidence was considered slight for neurological outcomes.

Overall, evidence suggests neurological/behavioral effects may occur due to ethylene dibromide exposure at high levels. The interactive web-based evidence integration table for [neurological/behavioral](#) (accessed June 2026) effects is available in HAWC.

B.3 Immune/Hematological Toxicity

B.3.1 Human Evidence

EPA identified two studies that investigated relationships between ethylene dibromide exposure and immune-mediated disease outcomes ([Hoppin et al., 2009](#); [Dow Chemical, 1992b](#); [Ott et al., 1980](#)). Additionally, two studies were identified that evaluated the associations between ethylene dibromide exposure and immune/hematological biomarkers of effect ([Parks et al., 2019](#); [Lebailly et al., 1998](#)).

A cross-sectional study evaluated the associations between lifetime use of pesticides, including ethylene dibromide, and prevalent adult-onset asthma in male farm workers in the Agricultural Health Study ([Hoppin et al., 2009](#)). Exposure was assessed using self-reported questionnaire data on lifetime use of pesticides including ever-use, frequency of use, number of years used and decade of first use of specific pesticides including ethylene dibromide. Additionally, participants reported if they ever experienced pesticide poisoning (self-report/doctor diagnosis) or high pesticide exposure events (based on response to the questionnaire question “Have you ever had an incident or experience while using any type of pesticide which caused you unusually high personal exposure?”). The study also compared an unexposed referent group plus two exposure levels defined based on the median of intensity-adjusted

lifetime days of use (adjusted for application methods, mixing habits, repairs, and use of PPE). Compared to never use, ever use of ethylene dibromide was statistically significantly associated with allergic asthma (OR = 2.07; 95% CI: 1.02–4.20). A significant trend in the exposure-response model was also observed ($p < 0.05$). No statistically significant relationship was observed for non-allergic asthma (OR = 1.25; 95% CI: 0.73–2.15) ([Hoppin et al., 2009](#)). The finding of an association between ethylene dibromide and allergic (but not non-allergic) asthma provides an indication of potential immune modulation. However, the cross-sectional study design precludes determination of temporality. Although the study was generally well-conducted, another limitation is that exposure was based on self-reported data rather than direct measurements. EPA assigned this study a medium overall quality determination rating during systematic review.

An occupational retrospective cohort study in Michigan and Texas ([Dow Chemical, 1992b](#); [Ott et al., 1980](#)) found that ethylene dibromide exposure was statistically significantly associated with influenza and pneumonia mortality but was not significantly associated with increased mortality due to other causes. The number of observed and expected deaths were calculated by employment status (exposed/unexposed), and by employment length (3 levels) as well as stratifying by interval since first exposure (3 levels). Concerns about this study include a lack of information on participation rates and study population characteristics, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants. Although the results should be interpreted with caution, they provide some indication of a potential association between ethylene dibromide exposure and infectious disease mortality, which potentially could be due to immune modulation. EPA assigned this study a low overall quality determination rating during systematic review.

In addition to these studies of disease outcomes, two studies assessed biomarker outcomes. One study assessed blood cell counts in a cross-sectional group of farmers ($n = 29$) in Calvados, France, during different periods of the growing season ([Lebailly et al., 1998](#)). Exposure was assessed using interviews with farmers and expressed as acreage and hours spent spraying pesticides. The specific pesticides used by the farmers were not stated. Although ethylene dibromide was mentioned in the paper, ethylene dibromide-specific exposure information for the farmers in this study could not be determined from the author-reported information. There was a difference that was borderline significant ($p = 0.08$) between groups of farmers regarding lymphocyte and eosinophil counts. No statistically significant associations were observed for leukocyte, neutrophil, monocyte, basophil, red blood cell, or platelet counts. This study does not provide sufficient information for determining the potential immune hazard of ethylene dibromide exposure because a substantial limitation of this study is that it is not clear whether or to what extent the farmers in this study were exposed to ethylene dibromide. EPA assigned this study an uninformative overall quality determination rating during systematic review.

Another study assessed the association between the use of 46 individual pesticides and autoantibody biomarkers ([Parks et al., 2019](#)). A statistically significant association was found between lifetime use of ethylene dibromide and detection of extractable nuclear autoantibodies (ENA) or anti-dsDNA autoantibodies, with an age-adjusted odds ratio of 5.07 (95% CI: 1.10–23.4; $p = 0.038$). Lifetime use of ethylene dibromide was not statistically significantly associated with the detection of antinuclear antibodies (ANA). This study was generally well-conducted and provides some indication that ethylene dibromide might be associated with autoimmune outcomes. However, there is some potential for exposure misclassification due to self-reporting. Additionally, some models did not adjust for covariates or correlated pesticides due to small numbers of participants with ENA or anti-dsDNA autoantibodies. This study did not undergo data quality evaluation because it was screened as supplemental based on the PECO screening criteria described in the *Draft Systematic Review Protocol for Ethylene Dibromide* ([U.S. EPA, 2026i](#)).

B.3.2 Laboratory Animal Evidence

EPA identified eight animal studies (2 short-term, 5 subchronic, and 1 chronic) that evaluate the effects of ethylene dibromide via inhalation on immune/hematological outcomes.

Short-Term Inhalation

In a short-term duration exposure study, rats (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm, to seven 7-hour exposures in 9 days (the methods indicated a frequency of 5 days a week) ([Rowe et al., 1952](#)). The studies included two groups of controls, one unexposed and one air-exposed control (numbers not specified). Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Hematological examinations were conducted periodically in representative rats. Animals were necropsied at the time of sacrifice. Lungs, heart, liver, kidneys, spleens, and testes were weighed and microscopically examined along with the adrenal glands and pancreas. In many cases blood was collected for determination of BUN levels and plasma-prothrombin-clotting time was determined (only in animals exposed to 100 ppm). Three out of 10 animals died after 1, 5, and 7 exposures. Surviving rats were thin and unkempt. Lung, liver, and kidney weights were purportedly significantly increased, however the data table only shows the unexposed controls (n = 4). Histopathology showed thickening of the alveolar walls with slight leucocytic infiltration of the lungs, cloudy swelling in the liver, and congestion and hemosiderosis of the spleen (incidence data not reported). The results are likely to represent a LOAEC of 100 ppm; however, based on reporting deficiencies and failure to use the more appropriate control, a reliable POD cannot be determined. EPA assigned this study a low overall study quality determination rating during systematic review.

Four groups of CDF (F344) rats (9 weeks old), consisting of 40 male and 20 female rats in each group, were used for this study ([Nitschke et al., 1981](#)). Animals were exposed via inhalation to 0, 3, 10, or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 1 week (10 males/group). Males in the 10-ppm group had hyperplasia of the nasal respiratory epithelium. One of these rats also had focal epithelial cell necrosis of the nasal respiratory epithelium. Males in the 40-ppm group had scattered to diffuse hyperplasia of the respiratory epithelium. A LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia. EPA assigned this study a high overall quality determination rating during systematic review.

Subchronic Inhalation

In a subchronic duration exposure study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day for 5 days/week for as many as 63 exposures in 91 days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, and body weights were recorded twice per week. Hematological examinations were conducted periodically in representative rats. Animals were necropsied at the time of sacrifice. Lungs, heart, liver, kidneys, spleens, and testes were weighed and microscopically examined along with the adrenal glands and pancreas. More than 50% of the males died due to pneumonia and infections in the upper respiratory tract. Four treated females died. Absolute organ weights changes included increased lung, liver, and kidney weights and decreased testes weights in males and increased liver and kidney weights in females. Female spleen weights were decreased. These changes were significant compared with the unexposed controls. No effects were observed in any other endpoints evaluated including no associated clinical chemistry or histopathological changes in the organs noted above. A LOAEC of 50 ppm is determined for significant organ weight changes (liver, kidney, lung, spleen, and testes) in male and/or female rats. EPA assigned this study a medium overall quality determination rating during systematic review.

Four groups of CDF rats (9 weeks old), consisting of 40 male and 20 female rats in each group, were used for this study. Animals were exposed via inhalation to 0, 3, 10, or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 13 weeks (10/sex/group), or for 13 weeks plus an 88 to 89-day recovery to evaluate lesion reversibility (10/sex/group) ([Nitschke et al., 1981](#)). Females had a slight but significant decrease in packed cell volume and hemoglobin concentration. No language is provided to determine if this persists through the recovery period. Relative liver weights in males exposed to 40 ppm were significantly elevated, persisting into the recovery period. Liver weights in females exposed to 10 ppm (absolute) or 40 ppm (absolute and relative) were also significantly different than control prior to the recovery period, where weights then returned to that of controls. Males exposed to 40 ppm had increased relative kidney weights, but this change did not persist after the recovery time. Brain, heart, thymus, and testes weights were not affected. Males and females exposed to 10 ppm had isolated to multifocal hyperplasia of the nasal respiratory epithelium. One female also had epithelial cell necrosis of the nasal respiratory epithelium. However, animals that underwent the recovery period following a 13-week exposure to 10 ppm showed no nasal epithelium changes. Males and females exposed to 40 ppm had diffuse or focal nonkeratinizing squamous metaplasia, hyperplasia of the respiratory epithelium, and focal necrosis of the respiratory epithelium. Only one female 40 ppm rat that underwent the recovery period had histological abnormalities: an isolated focus of epithelial hyperplasia in the respiratory epithelium of the nasal turbinates. EPA assigned this study a high overall quality determination rating during systematic review.

In this study, male and female CDF (F-344) rats were exposed to 0, 3, 10, or 40 ppm ethylene dibromide, 6 hours/day, 5 days/week for 13 weeks, and an additional group of rats were held for an 88- to 89-day recovery period following the 13-week exposure period ([Nitschke et al., 1981](#)). Female rats exposed to 40 ppm ethylene dibromide for 13 weeks had a statistical decrease in hematocrit and hemoglobin. The statistical increase in hematocrit of males exposed to 3 ppm ethylene dibromide for 13 weeks and the statistical decrease in total white blood cell counts of males exposed to 3 or 10 ppm ethylene dibromide for six weeks were of no toxicologic significance due to a lack of a dose response and the expected variability in this parameter. EPA assigned this study a high overall quality determination rating during systematic review.

Four groups of CDF (F344) rats (9 weeks old), consisting of 40 male and 20 female rats in each group, were used for this study ([Nitschke et al., 1981](#)). Animals were exposed via inhalation to 0, 3, 10, or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 6 weeks (10 males/group). Males in the 10-ppm group had isolated diffuse hyperplasia of the nasal respiratory epithelium. Males in the 40-ppm group had multifocal to diffuse hyperplasia and multifocal cell necrosis in the respiratory epithelium. A LOAEL of 10 ppm was assigned for nasal respiratory hyperplasia. EPA assigned this study a high overall quality determination rating during systematic review.

Four groups of CDF (F344) rats (9 weeks old), consisting of 40 male and 20 female rats in each group, were used for this study ([Nitschke et al., 1981](#)). Animals were exposed via inhalation to 0, 3, 10, or 40 ppm ethylene dibromide 6 hours/day, 5 days/week for 13 weeks (10/sex/group), or for 13 weeks plus an 88-89 day recovery to evaluate lesion reversibility (10/sex/group). Males and females exposed to 10 ppm had isolated to multifocal hyperplasia of the nasal respiratory epithelium. One female also had epithelial cell necrosis of the nasal respiratory epithelium. However, animals that underwent the recovery period following 13-week exposure to 10 ppm showed no nasal epithelium changes. Males and females exposed to 40 ppm had diffuse or focal nonkeratinizing squamous metaplasia, hyperplasia of the respiratory epithelium, and focal necrosis of the respiratory epithelium. Only one female 40 ppm rat that underwent the recovery period had histological abnormalities—an isolated focus of epithelial hyperplasia in the respiratory epithelium of the nasal turbinates. A LOAEL of 10 ppm was assigned for

nasal respiratory hyperplasia in animals that did not undergo the recovery period. EPA assigned this study a high overall quality determination rating during systematic review.

Chronic Inhalation

Male and female Sprague-Dawley rats (48/sex/group) were exposed to 0 or 20 ppm ethylene dibromide vapor in air 7 hours/day, 5 days/week for 18 months (Wong et al., 1982). Significant mortality was observed, with a mortality rate of 90% in males and 77% in females. Spleen atrophy and hemosiderosis was observed in males. EPA assigned this study a high overall quality determination rating during systematic review.

B.3.3 Mechanistic Evidence

EPA considered available mechanistic evidence that may contribute to the weight of scientific evidence for immune/hematological effects. The Agency identified four mechanistic studies that investigated ethylene dibromide ability to induce immune/hematological effects in human lymphoblasts and lymphocytes (Channarayappa and Nath, 1992; Crespi et al., 1985; Tucker et al., 1984; Perocco and Prodi, 1981).

Tucker et al. (1984) examined changes in frequency of sister-chromatid exchanges in lymphocytes exposed to ethylene dibromide *in vitro*. Human peripheral lymphocyte cultures were stimulated with phytohemagglutinin to proliferate and exposed with ethylene dibromide in the presence or absence of air for up to 8 hours. Cells were then harvested 75 hours after culture initiation, and second-division. Overall, SCE frequency was approximately doubled in cultures treated with ethylene dibromide. Also, Channarayappa and Nath (1992) evaluated micronuclei kinetics and persistence in mononucleated cells and binucleated human peripheral lymphocytes following 4 hours and continuous (until harvest) exposure to ethylene dibromide. Compared to the controls, a statistically significant higher incidence of micronuclei was observed in binucleated cells. In continuously exposed mononucleated cells, there was a higher frequency of micronuclei

Crespi et al. (1985) tested ethylene dibromide for its ability to induce gene mutations in two human lymphoblastoid cell lines, designated as AHH-1 and TK6. AHH-1 and TK6 human lymphoblasts were exposed with several doses of ethylene dibromide *in vitro*. In AHH-1 cells, statistically significant mutagenic responses were observed at or above 5 µg/mL of ethylene dibromide compared to controls. Additionally, statistically significant increases in gene mutations in TK6 cells were observed at or above 20 µg/mL of ethylene dibromide compared to controls. In addition to these results, Perocco and Prodi (1981) evaluated effects of ethylene dibromide on the inhibition of scheduled (cell division) and unscheduled (DNA repair) DNA syntheses observed as tritiated thymidine uptake in human lymphocytes. Lymphocytes were collected from healthy blood donors and cultured for a 4 hour period in the presence 10 mM hydroxyurea and three doses of ethylene dibromide (2.5, 5, and 10 µL/mL) in the presence or absence of S-9 mix metabolizing system. Compared to controls, ethylene dibromide elicits significant DNA damage by inhibiting scheduled and unscheduled DNA synthesis. These findings provide mechanistic support for ethylene dibromide induced immune/hematological toxicity.

Kaphalia et al. (1992) determined covalent binding of radiolabeled ethylene dibromide to albumin under *in vitro* and *in vivo* conditions in rats. For the *in vivo* covalent binding, 25 mg/kg body weight of ethylene dibromide was given daily to male rats for 12 consecutive days and the animals were sacrificed at 24 hours following the last dose. A major radioactive peak eluted at an elution volume corresponding to 65,000 Dalton molecular mass was found to be associated to albumin at a level of 0.14 nmol equivalent ethylene dibromide/mg protein. For the *in vitro* covalent binding, human plasma or purified albumin was incubated with radiolabeled ethylene dibromide in the presence of phenobarbital-treated rat

liver microsomes and NADPH-generating system. Approximately 0.28 nmol equivalent ethylene dibromide/mg protein was found to be associated to albumin (about 2-fold higher than the *in vivo* binding). Binding of ¹⁴C-label to albumin under *in vivo* and *in vitro* conditions was further supported by the affinity chromatography of albumin fraction isolated by SE-HPLC. Reversed-phase HPLC analysis of pronase digest of the albumin obtained from *in vitro* studies indicated formation of several amino acid adducts of ethylene dibromide and/or its metabolites.

B.3.4 Evidence Integration and Summary

Although immune and hematological toxicity is recognized as a potential health outcome for ethylene dibromide, the endpoints summarized in this section were not used quantitatively for POD derivation or dose-response analysis due to limitations in overall data quality or quantitative detail. For example, limitations such as lack of quantitative exposure data in human studies, reliance on self-reported exposures and outcomes, small sample sizes, and potential confounding factors like co-exposures ([Parks et al., 2019](#); [Hoppin et al., 2009](#); [Lebailly et al., 1998](#); [Dow Chemical, 1992b](#); [Ott et al., 1980](#)). In animal studies, limitations included insufficient dose-response information, absence of NOAELs, lack of sufficient dose groups, and inconsistent or incomplete reporting of critical endpoints ([Wong et al., 1982](#); [Nitschke et al., 1981](#); [Rowe et al., 1952](#)). As a result, while these endpoints inform the overall weight of evidence for immune and hematological toxicity, only studies meeting higher overall quality and quantitative standards for methodological rigor and quantitative utility were carried forward for quantitative assessment.

The evidence for immune/hematological toxicity in humans is slight. There is some indication of a potential association between ethylene dibromide exposure and immune-related outcomes including allergic asthma, antibodies, and infectious disease mortality. However, the quality of the database substantially decreases the strength of the evidence. Only four relevant studies were available, two of which had substantial limitations. Consistency between study findings cannot be fully determined due to the small number of studies, but no substantial inconsistencies were identified. The magnitude and precision of the observed associations are neither extremely large nor extremely small. There was limited availability of data to assess dose-response, but the asthma study found a statistically significant trend in exposure-response models, which somewhat increases the strength of the evidence. Because these studies assessed human data, the relevance to humans increases the strength of the evidence.

The evidence for immune/hematological toxicity in animals is slight. Inflammation, hyperplasia, and necrosis are seen across many organ systems following test animal exposure to ethylene dibromide. In short-term and subchronic exposures, this includes lungs, liver, and spleen ([Nitschke et al., 1981](#); [Rowe et al., 1952](#)). Chronic studies show evidence of splenic atrophy and hemosiderosis ([Wong et al., 1982](#)). There is some evidence of additional immune effects in blood, but data availability for these types of endpoints is low. A significant increase or decrease in serum hemocrit and hemoglobin is sometimes seen, as well as a decrease in white blood cell counts ([Nitschke et al., 1981](#)).

Evidence on immune/hematological outcomes based on mechanistic data showed changes in frequency of sister-chromatid exchanges ([Channarayappa and Nath, 1992](#); [Tucker et al., 1984](#)), and increases in mutagenic responses and damage to DNA by the inhibition of DNA synthesis in cells resulting from ethylene dibromide exposure *in vitro* might be associated with adverse immune/hematological outcomes ([Crespi et al., 1985](#); [Perocco and Prodi, 1981](#)). However, the exact mechanism by which this occurs is not known. Thus, evidence was considered slight for immune/hematological outcomes. Overall, evidence suggests immune/hematological effects can occur due to ethylene dibromide exposure. The interactive web-based evidence integration table for [immune/hematological](#) (accessed June 2026) effects is available in HAWC.

B.4 Diabetes Outcomes

B.4.1 Human Evidence

EPA identified one study that evaluated the association between exposure to ethylene dibromide and diabetes outcomes ([Wang et al., 2024](#)).

Wang et al. ([2024](#)) conducted a cross-sectional study that examined the associations between exposure to VOCs (including ethylene dibromide) and diabetes and diabetes retinopathy among U.S. adults using NHANES data (n = 2,932). Average levels of ethylene dibromide in whole blood were reported as 10.60, 11.00, and 11.00 ng/L for subjects without diabetes, and diabetes with non-diabetic retinopathy and diabetes with diabetic retinopathy, respectively. Reported levels of ethylene dibromide were significantly associated with the odds of diabetes (OR = 7.85; 95% CI: 6.59–9.37) and diabetes retinopathy (OR = 2.91; 95% CI: 2.25–3.70). However, there were substantial concerns about methods for addressing non-detects in the exposure assessment. All of the values for ethylene dibromide were non-detectable in the NHANES data. The paper used the imputed estimates from NHANES, which were the same for all of the individuals in each group. The differences in reported ethylene dibromide levels between groups were due to differences in rounding in the NHANES dataset. Due to these substantial flaws, EPA assigned this study an uninformative overall quality determination rating during systematic review.

B.4.2 Evidence Integration and Summary

The evidence for diabetes outcomes in animals is *indeterminate* due to lack of reported data.

The evidence for diabetes outcomes in humans is *indeterminate*. Only one epidemiological study of the association between ethylene dibromide exposure and this outcome was identified ([Wang et al., 2024](#)). The study had substantial flaws, which made the findings uninformative.

Overall, evidence is *inadequate* to determine whether ethylene dibromide might be associated with potential diabetes hazard. The interactive web-based evidence integration table for [diabetes](#) (accessed June 2026) outcomes is available in HAWC.

B.5 Renal Toxicity

B.5.1 Human Evidence

Several case reports and case series have reported associations between acute exposure to ethylene dibromide and renal toxicity ([Singh et al., 2007](#); [Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Prakash et al., 1999](#); [Osterloh, 1986](#); [Saraswat et al., 1986](#); [Letz et al., 1984a, b](#)).

In a case series describing 64 cases of acute exposure to ethylene dibromide, nephrotoxicity was reported in 32 (50%) of the cases ([Singh et al., 2007](#)).

Renal toxicity has been documented in several cases of acute ingestion exposure, including in cases who died ([Saraswat et al., 1986](#)), as well as several cases who were hospitalized but survived ([Mehrotra et al., 2001](#); [Singh et al., 2000](#); [Prakash et al., 1999](#)).

Six cases of attempted suicide via ingestion of ethylene dibromide in Udaipur, India, were reported from December 1982 to June 1984 ([Saraswat et al., 1986](#)). Each of the six people ingested one ampule of ethylene dibromide. Two of these cases died; four were hospitalized but survived. Autopsies were

performed on the two persons who died. In one case, the kidneys were reported to have normal glomeruli but cloudy swelling of the tubules and “occasional tubular necrosis.” The autopsy of the other case found kidney congestion ([Saraswat et al., 1986](#)).

A case report described a 20-year-old weighing 56 kg who consumed a 3-mL ampule of Fumigrain containing 6,480 mg of ethylene dibromide ([Prakash et al., 1999](#)). This person was reported to have acute renal failure and other issues that were treated such that he survived ([Prakash et al., 1999](#)).

Similarly, a case report of a 16-year-old male who ingested one ampule (3 mL) of ethylene dibromide reported that the individual developed acute renal failure as well as other issues ([Singh et al., 2000](#)). This person was hospitalized for 20 days, received hemodialysis and an anti-hepatic coma regime, and survived this acute exposure to ethylene dibromide ([Singh et al., 2000](#)).

Another paper reported that two men, ages 29 and 20 years, who each ingested 3 mL of ethylene dibromide and were hospitalized but survived after this acute exposure to ethylene dibromide ([Mehrotra et al., 2001](#)). One of the cases developed renal failure within 48 hours after exposure, which was treated with peritoneal dialysis ([Mehrotra et al., 2001](#)).

In addition to acute ingestion, other routes of acute exposure have been associated with adverse renal outcomes. Two workers who died after collapsing in a tank of ethylene dibromide had extensive acute dermal exposure ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)). Both cases had metabolic acidosis. An autopsy of the first case indicated liver damage as well as several other issues. The second case had renal failure and other issues ([Osterloh, 1986](#); [Letz et al., 1984a, b](#)).

These studies provide evidence that acute exposure to ethylene dibromide, via oral ingestion and potentially other exposure routes, is associated with renal toxicity, which may be severe and might contribute to fatalities. These studies did not undergo data quality evaluation because they were screened as Supplemental based on the PECO screening criteria described in the 2021 Draft Systematic Review Protocol ([U.S. EPA, 2021](#)). However, these studies provide evidence of adverse renal outcomes potentially occurring following acute exposure to ethylene dibromide.

B.5.2 Laboratory Animal Evidence

EPA identified one acute, one short-term, and four subchronic animal studies that evaluate the effects of inhalation exposure to ethylene dibromide on renal outcomes. Additionally, two oral acute studies were identified.

Acute Inhalation

Rats were exposed, whole body, to ethylene dibromide vapor concentrations of 200, 400, 1,600, 5,000, or 10,000 ppm for various durations ranging from 0.02 to 16 hours; the durations differed for each group ([Rowe et al., 1952](#)). Groups of 20 rats were also exposed to 100 ppm for 8.5, 12, or 16 hours. Finally, a separate group of females only (20/group) were exposed to 50, 500, 200, or 800 ppm for 0.1, 0.7, 2.5, or 7 hours. Animals were observed for changes in behavior and body weight changes for 2 to 3 weeks, or until it was certain they had recovered from the effects of exposure. Data were plotted showing vapor concentration (ppm) vs. duration of exposure (hours). For each concentration, the durations producing 0.01, 50, and 99% mortality were calculated. A subset of animals killed 16 to 24 hours after exposure showed increased kidney weights and histopathological changes including slight interstitial congestion, edema, and slight cloudy swelling of the tubular epithelium. Due to reporting deficiencies, these histological findings cannot be matched to particular exposure levels and a POD cannot be reliably identified. This reference is considered uninformative for renal endpoints.

Short-Term Inhalation

In a short-term duration exposure study, rats (10 females) were exposed to ethylene dibromide vapor concentrations of 0 and 100 ppm to seven 7-hr exposures in nine days (the methods indicated a frequency of 5 days/week) ([Rowe et al., 1952](#)). The studies included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Kidneys were weighed and microscopically examined. In “some cases” frozen sections of kidney were stained with Oil Red O. Three out of 10 animals died after 1, 5, and 7 exposures. Surviving rats were thin and unkempt. Kidney weights were purportedly significantly increased; however, the data table only shows the unexposed controls (n = 4). Air-only control responses were not reported, which would have been the more appropriate comparator. Based on reporting deficiencies and failure to use the more appropriate control, the study was considered uninformative, and a reliable POD cannot be determined.

Subchronic Inhalation

In a subchronic duration exposure study, rats (20/sex) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm 7 hours/day, 5 days/week for as many as 63 exposures in 91 days ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Kidneys were weighed and microscopically examined. In “some cases” frozen sections of kidney were stained with Oil Red O. More than 50% of the males died due to pneumonia and infections in the upper respiratory tract. Four treated females died. Treated animals showed reduced growth but the difference was not statistically significant. Absolute kidney weights increased in males and females. A LOAEC of 50 ppm is determined for significant kidney weight changes. EPA assigned this study a low overall quality determination rating during systematic review due to lack of clarity in reporting.

In a subchronic duration exposure study, guinea pigs (8/group – unclear whether 8/sex or 8 total) were exposed to ethylene dibromide vapor concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for 80 days (57 exposures total) ([Rowe et al., 1952](#)). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Kidneys were weighed and microscopically examined. In “some cases” frozen sections of liver were stained with Oil Red O. Both male and female final body weights were significantly decreased compared to the unexposed controls (reductions of 26% in males and 24% in females). No comparisons were made to the air-only control group, but these data were not provided. The increases in absolute kidney weights observed likely reflect the decreased body weights observed. There was slight interstitial congestion and edema with slight parenchymatous degeneration of the tubular epithelium in 8/14 kidneys. Control incidences and statistical significance were not reported. A tentative LOAEL of 50 ppm was determined based on kidney histopathology; however, there are reporting deficiencies, and the study did not use the most appropriate control group as a comparator. EPA assigned this study a low overall quality determination rating during systematic review.

Young adult rabbits (1 female and 3 males) were exposed whole body to ethylene dichloride vapors at concentrations of 0 and 50 ppm for 7 hours/day, 5 days/week for 84 days (totaling 59 exposures) (Rowe et al., 1952). The study included two groups of controls, one unexposed and one air-exposed control (numbers not specified). This reference reported multiple experiments, and it is not clear which endpoints were definitively assessed in each separate experiment. Generally, animals that received repeat exposures were monitored for mortality and changes to appearance and behavior, with body weights recorded twice per week. Animals were necropsied at the time of sacrifice. Kidneys were weighed and microscopically examined. In “some cases,” frozen sections of kidney were stained with Oil Red O. No significant effects were observed in any of the endpoints examined except for a “slight increase in...kidney weights” (data and significance were not reported). Because the data were not provided and the statement about significance is unclear, a reliable POD cannot be determined. EPA assigned this study a low overall quality determination rating during systematic review.

Four groups of CDF (F344) rats (9 weeks old), consisting of 40 male and 20 female rats in each group, were used for this study (Nitschke et al., 1981). Animals were exposed via inhalation to 0, 3, 10, or 40 ppm ethylene dibromide for 6 hours/day, 5 days/week for 13 weeks (10/sex/group), or for 13 weeks plus an 88- to 89-day recovery period to evaluate lesion reversibility (10/sex/group). In animals that were exposed for 13 weeks without the recovery period, significantly decreased body weights were observed in male rats at 40 ppm. By the end of the recovery period, weights returned to control levels. In females exposed to 40 ppm without the recovery period, the specific gravity of urine was significantly decreased. The specific gravity of urine returned to control levels following the recovery period. A renal LOAEL of 40 ppm in female animals was identified for changes in urine specific gravity. EPA assigned this study a high overall quality determination rating during systematic review.

Acute Oral

Rabbits (1/group – not clearly stated) were exposed to ethylene dibromide by single oral gavage at 20, 25, 30, 50, 250, 500, 1,000, 2,000, or 3,500 mg/kg (Kettering Laboratory, 1943). The minimum lethal dose was determined to be between 30 and 50 mg/kg. Pathological effects that occurred in animals that died across all dose groups include focal degeneration in cells of the kidney. EPA assigned an uninformative overall quality determination rating to the study as there was only one animal per test dose.

Groups of four or five male Wistar rats received a single gavage dose of 0 or 10 mg/100 g bodyweight (100 mg/kg) and sacrificed at various time points (up to 48 hours after dosing) for assessment of cell proliferation (3H-thymidine incorporation), mitotic activity, and histopathology in the kidney (Ledda-Columbano et al., 1987). There were no deaths and no body weight differences compared to the control group. Significant increases in cell proliferation were observed at 20, 30, 36, and 48 hours after dosing. Numbers of mitoses per 1,000 cells scored were significantly increased at 30 and 36 hours after dosing but not at earlier or later timepoints. Histopathology performed on animals sacrificed between 8 and 48 hours after dosing showed no necrosis; no other details of histopathology findings were reported. The 100 mg/kg dose group, the only dose tested, was identified as a mechanistic LOAEL. EPA assigned this study a medium overall quality determination rating during systematic review.

B.5.3 Evidence Integration and Summary

Although renal toxicity is recognized as a potential health outcome for ethylene dibromide, the endpoints summarized in this section were not used quantitatively for POD derivation or dose-response analysis due to limitations in overall data quality or quantitative detail. For example, limitations such as lack of quantitative exposure data and control groups in human case reports (Singh et al., 2007; Mehrotra et al., 2001; Singh et al., 2000; Prakash et al., 1999; Osterloh, 1986; Saraswat et al., 1986; Letz

et al., 1984a, b) and insufficient dose-response information, lack of sufficient dose groups, or incomplete reporting of critical endpoints in animal studies (Ledda-Columbano et al., 1987; Nitschke et al., 1981; Rowe et al., 1952; Kettering Laboratory, 1943). As a result, while these studies inform the overall weight of evidence for renal toxicity, only studies meeting higher overall quality and quantitative standards for methodological rigor and quantitative utility were carried forward for quantitative risk assessment.

Epidemiology studies provide slight evidence that acute ethylene dibromide exposure is associated with adverse renal outcomes. The quality of the database somewhat decreases the strength of the evidence. The available studies were case studies and case series, which generally are less informative for causal inference due to their lack of a control or comparison group. However, several of the cases were reported suicide attempts, which have similarities to intentional dosing studies with the individual serving as their own control. The consistency of the findings somewhat increases the strength of the evidence, as adverse renal outcomes were found in some, but not all, of the cases. The lack of precision of the findings somewhat decreases the strength of the evidence. The data were not adequate to evaluate a dose-response pattern, which neither increases nor decreases the strength of the evidence. Because the cases occurred in humans, the relevance to humans increases the strength of the evidence. This moderate epidemiologic evidence of renal toxicity is specific to acute exposure, as epidemiologic data were not available to assess renal outcomes potentially associated with chronic exposure.

There is slight evidence of renal effects of ethylene dibromide in laboratory animal studies. Acute inhalation in rats resulted in increased kidney weight and slight interstitial congestion, edema, and slight cloudy swelling of the tubular epithelium of the kidney (Rowe et al., 1952). Organ weight increase was also observed following short-term (Rowe et al., 1952) and subchronic (Nitschke et al., 1981) inhalation exposure in rats, while the histopathological findings are supported by subchronic inhalation exposure in guinea pigs (Rowe et al., 1952). An oral gavage study in rabbits supports this focal degradation of kidney tissue (Kettering Laboratory, 1943), while oral exposure in rats resulted in kidney cell proliferation (Ledda-Columbano et al., 1987).

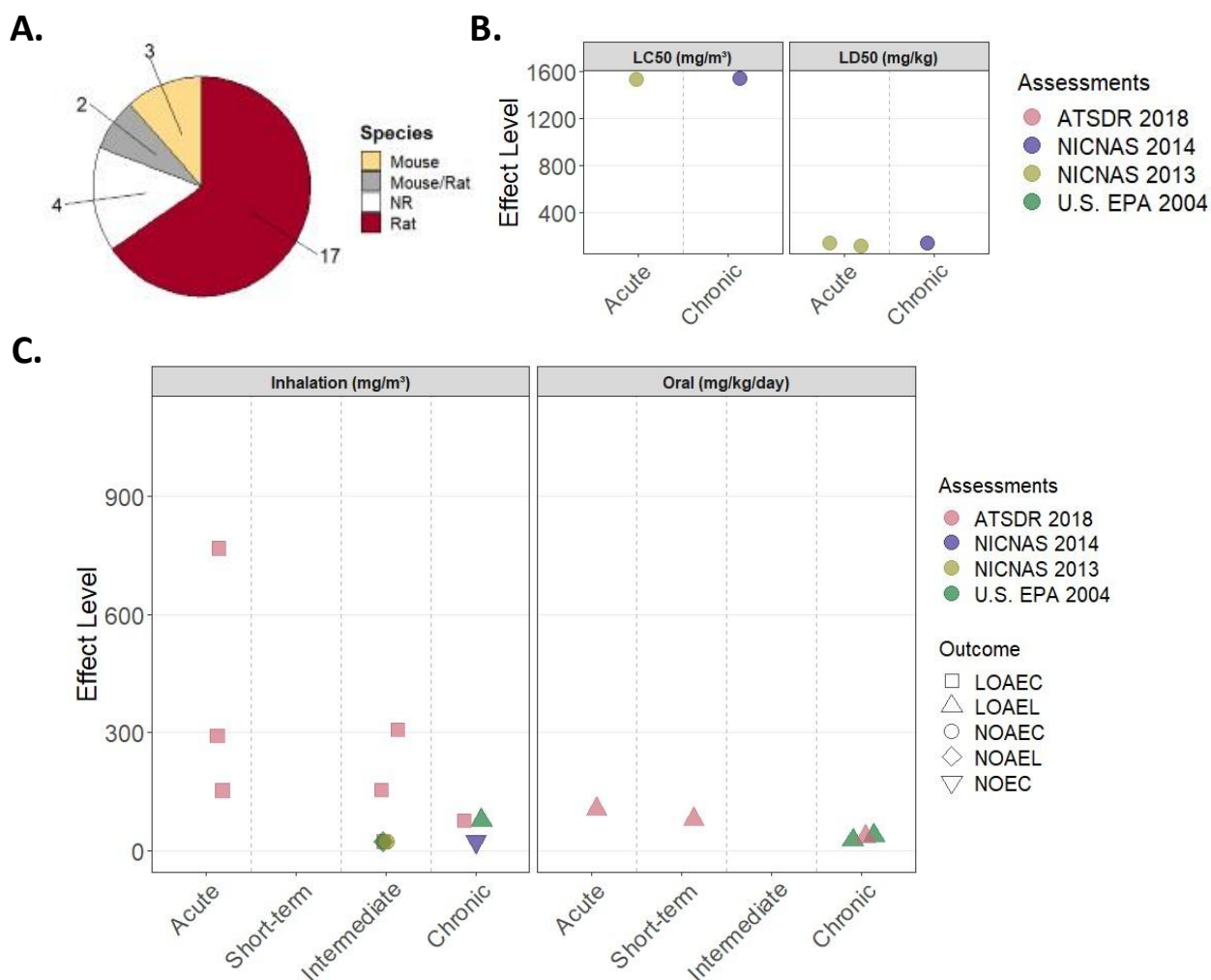
The currently available evidence suggests, but is insufficient to conclude, that ethylene dibromide may cause adverse renal outcomes in humans under relevant exposure circumstances, based on moderate human evidence of adverse renal outcomes following acute exposure and slight animal toxicology evidence of adverse renal outcomes following acute, short-term, and subchronic exposure. The interactive web-based evidence integration table for renal (accessed June 18, 2026) effects is available in HAWC.

Appendix C PREVIOUS HUMAN HEALTH ASSESSMENTS AND OVERALL SUMMARY OF HUMAN HEALTH OUTCOMES EXTRACTED FROM SYSTEMATIC REVIEW

EPA utilized systematic review to gather reasonably available information for human health related outcomes resulting from exposure to ethylene dibromide. When compared to previous assessments, the Agency's approach considered a broader range of exposure routes, exposure durations, and exposed species demonstrating the breadth of information considered. To better visualize the data available in these previous assessments and the information reviewed and extracted, see Figure_Apx C-1 and Figure_Apx C-2, respectively. The effect level values are represented as either mg/m^3 for inhalation exposures or $\text{mg}/\text{kg}/\text{day}$ for oral exposures. When assessments reported inhalation data in ppm, the effect level value was converted using Equation_Apx C-1, which accounted for the molecular weight (MW) of ethylene dibromide, atmospheric pressure (atm), gas constant ($0.08206 \text{ L} \cdot \text{atm} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$), and temperature in Kelvin (K). A standard atmospheric pressure (1 atm) and temperature (25°C or 298.15 K) were assumed. In the following sections, EPA compared the data considered in previous assessments (Figure_Apx C-1) to reasonably available human health hazard information identified and extracted via systematic review (Figure_Apx C-2) when relevant. The Agency next categorized hazard data by exposure durations, where hazard data resulting from acute and short-term exposure durations were grouped together (acute/short-term; <30 days), and subchronic/chronic human health hazard data (chronic; >30 days) were grouped together.

Equation_Apx C-1. Conversion of Inhalation Units from ppm to mg/m^3

$$\frac{\text{mg}}{\text{m}^3} = \frac{(\text{ppm}) \times MW \left(\frac{\text{g}}{\text{mol}} \right) \times (\text{atm})}{\text{gas constant} \left(\frac{\text{L} \cdot \text{atm}}{\text{mol} \cdot \text{K}} \right) \times \text{temperature} (\text{K})} = \frac{(\text{ppm}) \times (187.86 \frac{\text{g}}{\text{mol}}) \times (1 \text{ atm})}{0.08206 \left(\frac{\text{L} \cdot \text{atm}}{\text{mol} \cdot \text{K}} \right) \times 298.15 \text{ K}}$$



Figure_Apx C-1. Summary of Limited Health-Related Outcomes from Previous Ethylene Dibromide Assessments

Reported health-related outcomes from previous assessments of ethylene dibromide show the limited information currently available. The data, visualized above, shows (A) the species utilized for PODs, (B) toxicity values, and (C) effect level outcomes. Colors in (B) and (C) represent data from each associated assessment listed in the legend (right), described in more detail in the text below.

Given the relatively small set of studies identified in systematic review and the different approaches in the previous assessments, EPA opted to consider the full set of studies with relevant routes of exposure identified through systematic review (Figure_Apx C-2) rather than narrowing the scope of the draft risk evaluation based on the previous assessments (Figure_Apx C-1). This allowed EPA to consider a wider range of studies using various species other than rodents (*i.e.*, guinea pigs, hens, monkeys, rabbits), as noted in A (Figure_Apx C-2), with the numbers representing the occurrences of the listed species in the reviewed assessments/studies. Previous ethylene dibromide assessments primarily relied on rodent data (A, within Figure_Apx C-2). In plots B and C within Figure_Apx C-2, each color represents a single value from a given reference in our systematic review workflow that reported health-related outcome metrics. Previous assessments listed in Figure_Apx C-2 are represented in the figure legend. However, given the number of studies from our systematic review workflow, we do not depict these references in the legend. Rather, they are available in more detail in EPA's *Draft Data Extraction Information for*

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Human Health Hazard Animal Toxicology and Epidemiology for Ethylene Dibromide ([U.S. EPA, 2026c](#)) and on the following [HAWC webpage](#) (accessed June 18, 2026).

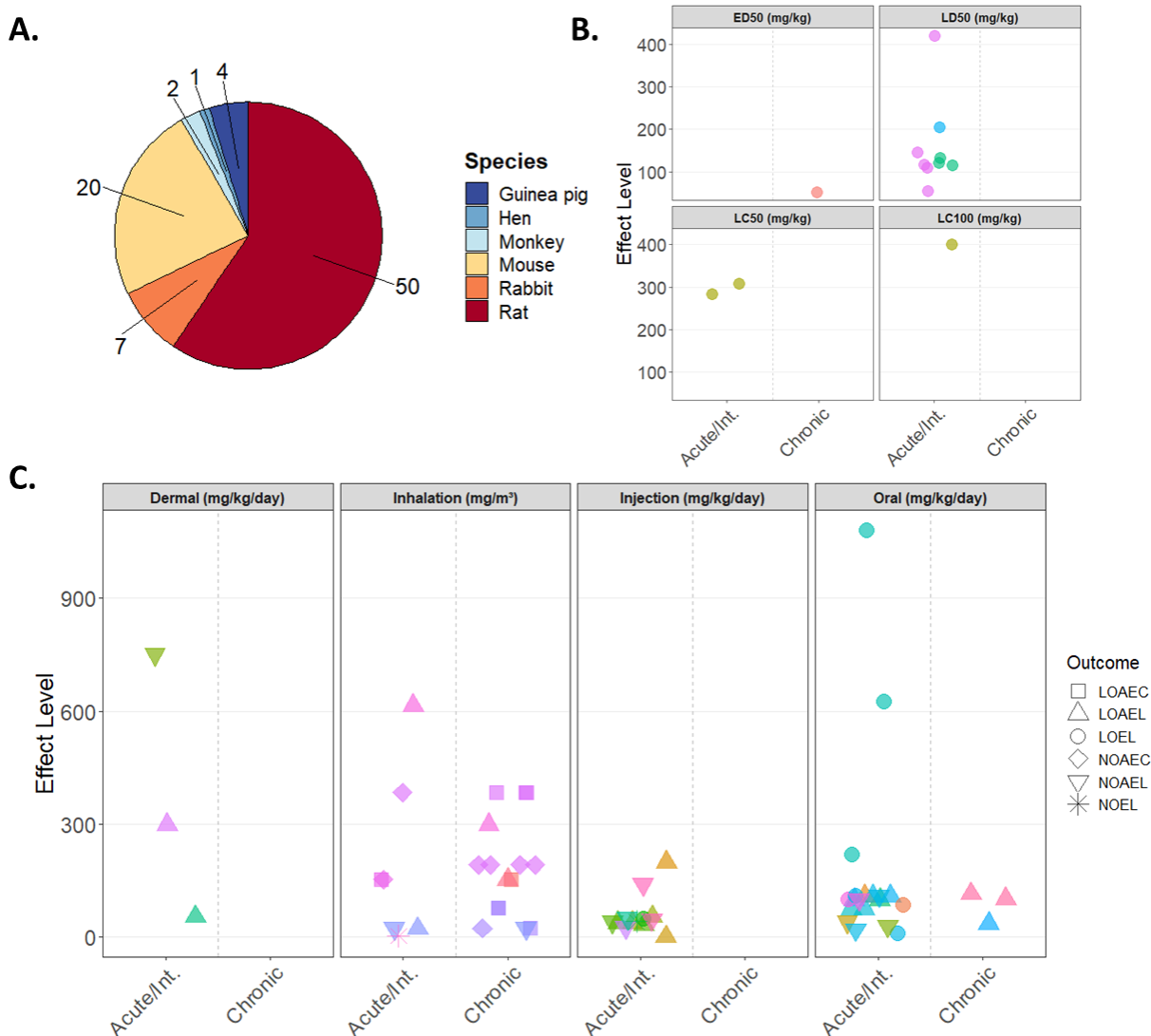
Table_Apx C-1. EPA Considered Hazard Values for Ethylene Dibromide Compared to Previous Assessments

Exposure Route	Exposure Duration	Previous Assessments (Range/Type)	EPA (Range/Type)
Effect Levels			
Dermal	–	Not reported	NOAEL: 750 mg/kg/day
			LOAEL: 55–300 mg/kg/day
Inhalation	Acute	LOAEC: 153.7–768.3 mg/m ³	LOAEC: 153.7 mg/m ³
	Intermediate	LOAEC: 23.1–307.3 mg/m ³	LOAEL: 23–384.2 mg/m ³
		NOAEC: 23.1 mg/m ³	NOAEC: 153.7–384.2 mg/m ³
		NOAEL: 23.1 mg/m ³	NOAEL: 23.1 mg/m ³
		NOEC: 23.1 mg/m ³	NOEL: 3.3 mg/m ³
	Chronic	LOAEL: 76.8 mg/m ³	LOAEL: 153.7–299.7 mg/m ³
		LOAEC: 76.8 mg/m ³	LOAEC: 76.8–153.7 mg/m ³
		NOEC: 23 mg/m ³	NOAEC: 23–192.1 mg/m ³
		Not reported	NOAEL: 23.1 mg/m ³
Oral	Acute	LOAEL: 107 mg/kg/day	LOAEL: 75–110 mg/kg/day
	Short-term	LOAEL: 80 mg/kg/day	LOEL: 10–1080 mg/kg/day
	Chronic	Not reported	NOAEL: 20–110 mg/kg/day
		LOAEL: 27–38 mg/kg/day	LOAEL: 37–116 mg/kg/day
Injection	Acute	Not reported	NOAEL: 25–141 mg/kg
		Not reported	NOEL: 42 mg/kg
		Not reported	LOAEL: 1.25–200 mg/kg
		Not reported	LOEL: 50 mg/kg
LOAEC = lowest-observed-adverse-effect concentration; NOAEC = no-observed-adverse-effect concentration; NOAEL = no-observed-adverse-effect level; NOEC = no-observed-effect concentration; LOAEL = lowest-observed-adverse-effect level; LOEL = lowest-observed-effect level			

Overall, while not all previously reported values are consistent with EPA's considered POD values (i.e., lethal dose values), the effect levels noted from previous assessments are within an order of magnitude of those in EPA's systematic review workflow (Table_Apx C-1). Earlier assessments reported relatively high lethal dose values for both inhalation (LC50) and oral (LD50) exposures. However, EPA's systematic review identified substantially lower LC50 estimates and a wider, lower-range set of LD50 values. The systematic workflow was also able to also collect and consider different exposure routes (i.e., dermal, injection) and a larger number of acute/chronic studies for similar exposure routes (i.e., inhalation, oral). EPA found that although other agencies did not provide dermal effect level data, several assessments identified effects from short-term and intermediate exposures. Previous evaluations also used inhalation values for short-term, intermediate, and long-term exposures that were generally consistent with EPA's findings. The Agency's systematic review identified additional inhalation studies covering short-term, intermediate, and long-term exposure periods, with results aligning with earlier assessments. For oral exposures, earlier assessments established values for short-term, intermediate, and

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long-term effects that were largely in agreement with those considered by EPA. The Agency also notes that multiple studies used injection exposures to determine effect levels. More details on the specific studies, and how they were utilized in EPA's draft risk evaluation for ethylene dibromide, are in the preceding sections.



Figure_Apx C-2. Summary of Health-Related Outcomes from EPA's Data Extractions of Ethylene Dibromide

Reported health-related outcomes from previous studies of ethylene dibromide showing (A) the species utilized for PODs, (B) toxicity values, and (C) effect level outcomes. Given the number of assessments considered, another graph copy with the assessment key is available on the following [HAWC webpage](#) (accessed June 2026).

Previous assessments have identified sufficient evidence across multiple evidence streams (human, animal, and mechanistic data) to support a quantitative cancer and non-cancer risk assessment, and inform cancer hazard designations (*e.g.*, likely, probable) that are generally consistent. ([U.S. EPA, 2004b](#)) and ([CalEPA, 2001](#)) calculated hazard values for chronic cancer and non-cancer, which are characterized in ([ATSDR, 2018](#)). Although they did not calculate hazard values, their review for this draft risk assessment showed agreement with PODs selected by ([U.S. EPA, 2004b](#)) for identification of multisite tumor formation across species and exposure routes supported by robust mutagenicity as the

key evidence supporting cancer classifications. While these assessments were published years apart, the evidence relied upon establishing cancer and non-cancer PODs remain consistent. In this draft risk assessment/TSD, EPA selected ([NCI, 1978](#)) as cancer oral and chronic non-cancer oral PODs as well as ([NTP, 1982](#)) as cancer inhalation and chronic non-cancer inhalation PODs. ([U.S. EPA, 2004b](#)) also utilized ([NCI, 1978](#)) and ([NTP, 1982](#)) for cancer and non-cancer chronic hazard value determinations, with details provided in Table_Apx C-1 below. ([CalEPA, 2001](#)) also based on an inhalation cancer hazard value on ([NTP, 1982](#)), but utilized a different study than was selected by EPA for chronic non-cancer inhalation hazard evaluation ([Ratcliffe et al., 1987](#)).

Previous assessments have identified sufficient evidence across multiple evidence streams (human, animal, and mechanistic data) to support a quantitative cancer and non-cancer risk assessment, and inform cancer hazard designations (*e.g.*, likely, probable) that are generally consistent. ([U.S. EPA, 2004b](#)) and ([CalEPA, 2001](#)) calculated hazard values for chronic cancer and non-cancer, which are characterized in Table_Apx C-1. Although ([ATSDR, 2018](#)) did not calculate hazard values, its review in this draft assessment showed agreement with PODs selected earlier by ([U.S. EPA, 2004b](#)) for identification of multisite tumor formation across species, with the exposure routes supported by robust mutagenicity as the key evidence supporting cancer classifications. Again while these assessments were published years apart, the evidence relied upon establishing cancer and non-cancer PODs remain consistent. In this draft assessment and risk evaluation, EPA selected ([NCI, 1978](#)) as cancer oral and chronic non-cancer oral PODs, and ([NTP, 1982](#)) as cancer inhalation and chronic non-cancer inhalation PODs. ([U.S. EPA, 2004b](#)) also utilized ([NCI, 1978](#)) and ([NTP, 1982](#)) for cancer and non-cancer chronic hazard value determinations, with details listed in Table_Apx C-2 below. Also, ([CalEPA, 2001](#)) based an inhalation cancer hazard value on ([NTP, 1982](#)), but utilized a different study than was selected by EPA for chronic non-cancer inhalation hazard evaluation ([Ratcliffe et al., 1987](#)).

10000

Table Apx C-2. Summary of Previous Assessments of Ethylene Dibromide Hazard

Previous Assessments of Ethylene Dibromide Human Hazard	Hazard Value ^a (Exposure Range), Exposure Type and Duration	Basis for Hazard Value	Uncertainty Factors
U.S. Environmental Protection Agency IRIS Program, <i>Toxicological review of 1,2-dibromoethane (CAS no. 106-93-4)</i> U.S. EPA (2004b)	<u>Oral chronic non-cancer:</u> 27 mg/kg-day (LOAEL) RfD: 9E-03 mg/kg/day Gavage in corn oil, 5 days/week, for 49-61 weeks, initial doses were 40 and 80 mg/kg/day, adjustment for intermittent exposure (from 5-7 days/week) resulted in a daily dose of 27 mg/kg/day for the low-dose group	LOAEL for testicular atrophy, liver peliosis, and adrenal cortical degeneration NCI (1978)	3,000 UF _A : 10 UF _H : 10 UF _L : 10 UF _D : 10 Total UF reduced to the recommended maximum of 3, 000
	<u>Inhalation chronic non-cancer:</u> BMCL ₁₀ (HEC) 2.8 mg/m ³ RfC: 9E-03 mg/m ³ 10 ppm (77 mg/m ³) (0, 10, 40 ppm; 0, 77, or 307 mg/m ³) Whole body, 6 hours/day, 5 days/week, for 88 weeks (male) and 91 weeks (female)	BMCL ₁₀ for nasal inflammation NTP (1982) ; Nitschke et al. (1981)	300 UF _A : 3 UF _H : 10 UF _D : 10
	<u>Oral cancer:</u> Gavage in corn oil, 5 days/week, for 49-61 weeks, initial doses were 40 and 80 mg/kg/day Oral slope factor (95% upper bound) 2 (mg/kg-day) ⁻¹ Oral slope factor (central tendency) 1 (mg/kg-day) ⁻¹ The terms “upper bound” and “central tendency” in this context describes how the slope factors for the three tumor types (forestomach tumors, hemangiosarcomas, and thyroid follicular cell adenomas or carcinomas) were statistically combined to give an overall slope factor estimate	Tumor type(s): Forestomach tumors, hemangiosarcomas, thyroid follicular cell adenomas or carcinomas NCI (1978).	N/A Cancer endpoint
	<u>Inhalation cancer:</u> 10 ppm (77 mg/m ³) (0, 10, 40 ppm; 0, 77, or 307 mg/m ³) Whole body, 6 hours/day, 5 days/week, for 88 weeks (male) and 91 weeks (female) Inhalation unit risk (95% upper bound)	Tumor type(s): Nasal cavity (includes adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma), hemangiosarcomas, mesotheliomas NTP (1982)	N/A Cancer endpoint

Previous Assessments of Ethylene Dibromide Human Hazard	Hazard Value ^a (Exposure Range), Exposure Type and Duration	Basis for Hazard Value	Uncertainty Factors
U.S. Environmental Protection Agency IRIS Program, <i>Toxicological review of 1,2-dibromoethane (CAS no. 106-93-4)</i> U.S. EPA (2004b)	6E-04 (µg/m ³) ⁻¹ Inhalation unit risk (central tendency) 6E-04 (µg/m ³) ⁻¹ The terms “upper bound” and “central tendency” in this context describes how the slope factors for the three tumor types (nasal cavity tumors, hemangiosarcomas, and mesotheliomas) were statistically combined to give an overall slope factor estimate		
California OEHHA/ARB CalEPA (2001)	<u>Inhalation chronic non-cancer:</u> RfC 8.0E-04 mg/m ³ Epidemiological study 88 ppb (geometric mean 8-hour time-weighted average (TWA) exposure with peak exposures up to 262 ppb) Inhalation 8 hours per day 5 days per week Average 4.9 years (standard deviation of 3.6 years)	Chronic inhalation effects. Decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities in human males Ratcliffe et al. (1987)	300 UF _A : 10 UF _H : 1 UF _L : 10 UF _S : 3
	<u>Inhalation cancer:</u> 10 ppm (77 mg/m ³) (0, 10, 40 ppm; 0, 77, or 307 mg/m ³) Whole body, 6 hours/day, 5 days/week, for 88 weeks (male) and 91 weeks (female) Inhalation unit risk (95% upper bound) 7.1E-05 (µg/m ³) ⁻¹ Inhalation slope factor 2.5E-01 (mg/kg-day) ⁻¹ The inhalation slope factor also used as an oral slope factor	Tumor type(s): Nasal cavity (includes adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma) in male rats NTP (1982)	N/A Cancer endpoint
BMCL ₁₀ = benchmark concentration lower 95% confidence limit with a benchmark response of 10% extra risk; HEC = human equivalent concentration LOAEC = lowest-observed-adverse-effect concentration; LOAEL = lowest-observed-adverse-effect level, RfC = reference concentration; RfD = reference dose ^a All tested dose levels are indicated in parentheses, expressed in either ppm or mg/kg/day.			

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Appendix D BENCHMARK DOSE MODELING RESULTS FOR CRITICAL ENDPOINTS

D.1 Introduction

This benchmark dose (BMD) modeling appendix is in support of the *Draft Risk Evaluation for Ethylene Dibromide* ([U.S. EPA, 2026h](#)).

The NCI cancer bioassay of ethylene dibromide by the oral route (gavage administration) in Osborne-Mendel rats and B6C3F₁ mice ([NCI, 1978](#)), which is pre-GLP (Good Laboratory Practices) and is equivalent to OECD test guideline 451, supports a LOAEL of 37 mg/kg/day in rats and 62 mg/kg/day in mice based on multiple adverse effects at the lowest dose tested, including malignant tumors. The magnitude and statistical significance of adverse effects varied by sex, species, and dose but the magnitude of at least one effect reached at least 22% incidence and statistical significance ($p < 0.05$) for all sex and species combinations at the low dose.

The NCI cancer bioassay of ethylene dibromide by the inhalation route in F344 rats and B6C3F₁ mice ([NTP, 1982](#)), which is also pre-GLP and is equivalent to OECD test guideline 451, supports a LOAEC of 10 ppm based on multiple adverse effects at the lowest dose tested, including malignant tumors. The magnitude and statistical significance of adverse effects varied by sex, species, and dose but the magnitude of at least one effect reached at least 38% incidence and statistical significance ($p < 0.05$) for all sex and species combinations at the low dose.

A specialized NTP study of ethylene dibromide by the oral route (gavage administration) in F344 rats ([Ghanayem et al., 1986](#)), which is non-GLP and not equivalent to an OECD test guideline, supports a LOAEL of 40 mg/kg/day. Both forestomach epithelial cell proliferation and hyperkeratosis were observed in the study, with hyperkeratosis seen at lower doses and at higher incidences than proliferation.

A specialized study was sponsored by the EPA's Office of Toxic Substances (OTS; now known as OPPT) by the inhalation route in Charles River CD rats and CD-1 mice ([Short et al., 1978 62578](#)), which is pre-GLP and is equivalent to OECD test guideline 414, supports a LOAEC of 20 ppm based on developmental toxicity. The percentage of fetuses with specific skeletal anomalies at the low-dose reached 49.7% in rats and 28.5% in mice.

EPA conducted BMD modeling of dose-response data to refine the LOAELs/LOAECs. The Short et al. ([1978](#)) study proved to be not amenable to benchmark dose modeling due to the high degree of total litter loss at the high-dose. As a result, this study retained its LOAEC while the other studies were used to derive a BMDL/BMCL. The two cancer bioassays (oral and inhalation routes) were also analyzed to derive CSFs via multistage modeling in the BMD software.

BMD modeling was conducted with EPA's 2024 web-based version of BMD software (BMDS version 2024.1). All standard BMDS 2024.1 continuous models that use maximum likelihood (MLE) optimization and profile likelihood-based confidence intervals were used in this analysis. Standard forms of these models (defined below) were run so that auto-generated model selection recommendations accurately reflect current EPA model selection procedures in EPA's Benchmark Dose Technical Guidance ([U.S. EPA, 2012b](#)). BMDS 2024.1 models that use Bayesian fitting procedures and Bayesian model averaging were not applied in this work.

Standard BMDS 2024.1 models applied to continuous endpoints in this supplemental file include the following:

- Exponential 3-restricted (exp3-r);
- Exponential 5-restricted (exp5-r);
- Hill-restricted (hil-r);
- Polynomial Degree 3-restricted (ply3-r);
- Polynomial Degree 2-restricted (ply2-r);
- Power-restricted (pow-r); and
- Linear-unrestricted (lin-ur).

Consistent with EPA's *Benchmark Dose Technical Guidance* ([U.S. EPA, 2012b](#)), the Agency evaluated benchmark response (BMR) levels of 1 control standard deviation (1 SD) for continuous endpoints and 10% extra risk for dichotomous endpoints. Model fit was judged consistent with EPA's *Benchmark Dose Technical Guidance* ([U.S. EPA, 2012b](#)). An adequate fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination 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 [note: this is a change from previous versions of BMDS, which required variance p-value > 0.10 for adequate fit]), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (*i.e.*, $p < 0.05$), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (*i.e.*, Test 3; $p < 0.05$), the dataset was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different adequately fitting models varied greater than 3-fold; otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) was selected.

D.2 Intermediate Inhalation, Non-Cancer

D.2.1 Fetal Skeletal Malformations

D.2.1.1 Option Set 1 (Distribution and Variance = Normal and Constant)

Maximum Likelihood Approach Model Results

Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes	Show
Restricted Models									
Exponential 3	10.794	12.226	14.043	0.149	253.028	-1.829	0.528	Questionable	
Exponential 5	11.944	12.778	13.759	-	253.221	-0.003	1.47e-7	Questionable	
Hill	14.988	17.69	18.332	-	253.221	-5.70e-8	2.74e-8	Questionable	
Polynomial 2	9.443	10.355	11.505	< 0.0001	274.001	2.314	-3.115	Questionable	
Power	11.371	12.766	13.728	-	251.221	1.82e-7	1.64e-8	Questionable	
Unrestricted Models									
Linear	6.583	8.236	10.907	0	338.086	1.835	1.835	Questionable	

D.2.1.2 Option Set 2 (Distribution and Variance = Normal and Non-Constant)

Maximum Likelihood Approach Model Results

Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes	Show
Restricted Models									
Exponential 3	-	9.5	-	0	-639.778	-5.4	-5.4	Unusable	
Exponential 5	-	2.375	-	-	-550.989	-3.857	-3.857	Unusable	
Hill	7.34e-8	7.64e-8	8.00e-8	-	-2,810.783	-4.229	-4.229	Questionable	
Polynomial 2	-	19	-	-	-	-	-	Unusable	
Power	2.01e-57	2.44e-57	2.63e-57	-	-9,352.751	-4.397	-4.397	Questionable	
Unrestricted Models									
Linear	-	19	-	-	-	-	-	Unusable	

D.2.1.3 Option Set 3 (Distribution and Variance = Lognormal)

Maximum Likelihood Approach Model Results

Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes	Show
Restricted Models									
Exponential 3	-	19	-	-	-	0	25.176	Unusable	
Exponential 5	-	19	-	-	-	0	25.176	Unusable	

D.2.2 Resorptions

D.2.2.1 Option Set 1 (Distribution and Variance = Normal and Constant)

Maximum Likelihood Approach Model Results

Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes	Show
Restricted Models									
Exponential 3	26.779	33.251	37.556	1.00	453.025	7.56e-8	-9.23e-9	Questionable	
Exponential 5	20.519	30.573	32.057	-	455.025	1.07e-7	7.48e-9	Questionable	
Hill	23.889	31.322	37.247	-	455.025	4.45e-7	-2.80e-8	Questionable	
Polynomial 2	21.854	26.1	32.328	0.147	453.127	0.817	-1.1	Questionable	
Power	30.568	31.777	33.211	-	453.025	1.86e-7	-5.59e-8	Questionable	
Unrestricted Models									
Linear	16.102	22.826	39.056	0.00260	460.094	1.053	-2.163	Questionable	

D.2.2.2 Option Set 2 (Distribution and Variance = Normal and Non-Constant)

Maximum Likelihood Approach Model Results

Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes Show
Restricted Models								
Exponential 3	23.32	29.198	33.431	-	390.553	-0.564	-0.05	Questionable
Exponential 5	20.666	27.017	34.409	-	392.553	-0.564	0.583	Questionable
Hill	22.231	26.881	35.685	-	392.553	-0.564	0.583	Questionable
Polynomial 2	-	58.452	-	0.0559	403.025	-0.605	2.55	Unusable
Power	22.487	27.336	30.916	-	390.553	-0.564	0.583	Questionable
Unrestricted Models								
Linear	-	330.943	-	< 0.0001	420.921	1.231	3.165	Unusable

D.2.2.3 Option Set 3 (Distribution and Variance = Lognormal)

Maximum Likelihood Approach Model Results

Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes Show
Restricted Models								
Exponential 3*	14.952	21.335	28.541	1.00	326.23	2.533	-0.206	Recommended - Lowest AIC
Exponential 5	16.261	20.914	26.634	-	328.23	2.533	-0.206	Questionable

(Note: Flag on Exponential 3 shows the result is unusable because the residual at control > 2.0)

D.3 Intermediate Oral, Non-Cancer

Dataset

Dose (mg/kg/day)	0	9.2	18.4
Affected / Total (%)	0.0/16.0 (0.0%)	1.0/8.0 (12.5%)	6.0/8.0 (75.0%)

Settings

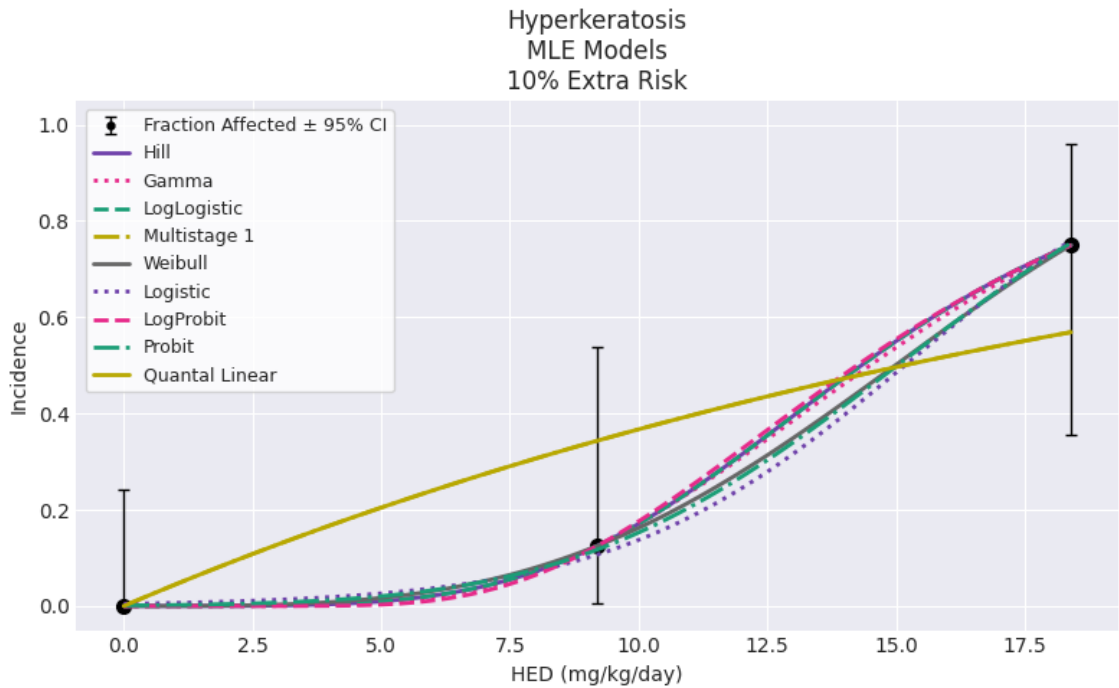
Setting	Value
BMR	10% Extra Risk
Confidence Level (1-sided)	0.95
Maximum Multistage Degree	1

Maximum Likelihood Approach

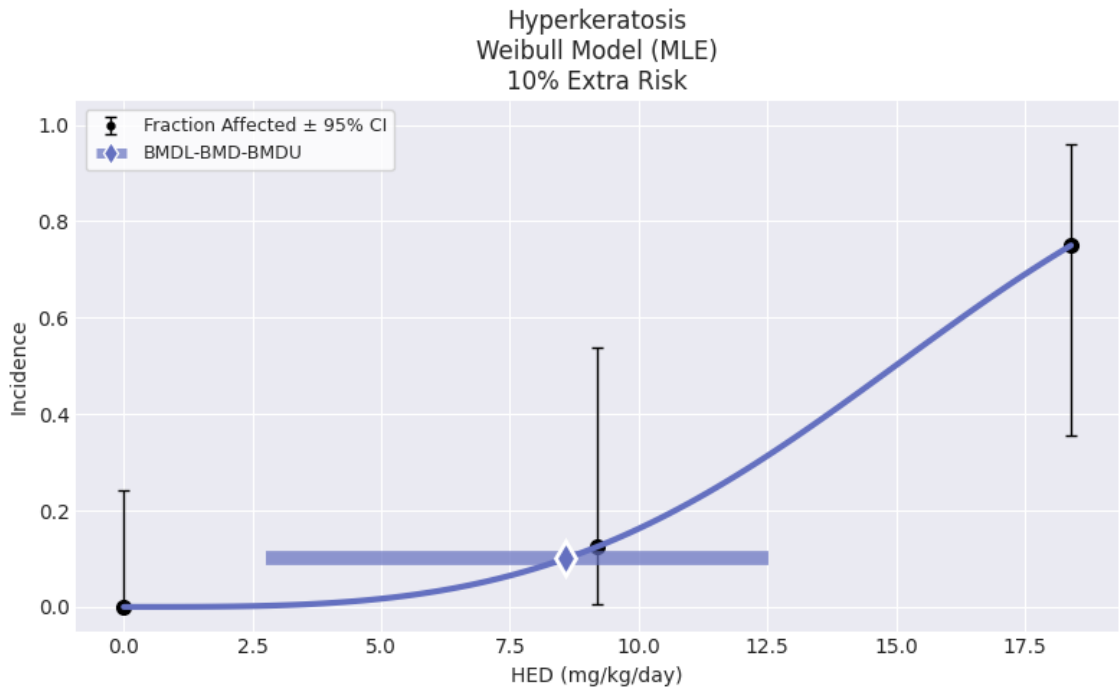
Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Hill	3.439	8.688	12.121	-	21.026	-0.	-0.	Questionable Zero degrees of freedom; saturated model
Gamma	2.879	8.697	12.59	1.	19.026	-0.	<0.001	Viable lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
LogLogistic	3.439	8.688	12.121	1.	19.026	-0.	-0.	Viable
Multistage 1 ^{a b}	1.285	2.303	4.669	0.251	20.162	-0.	-0.	Recommended - Lowest BMDL lowest dose/BMDL ratio > 3.0 lowest dose/BMD ratio > 3.0
Weibull	2.75	8.576	12.527	1.	19.026	-0.	0	Viable lowest dose/BMDL ratio > 3.0 BMD/BMDL ratio > 3.0
Logistic	5.22	9.116	12.971	0.747	19.201	-0.27	0.166	Viable
LogProbit	3.752	8.753	11.594	1.	19.026	-0.	<0.001	Viable
Probit	4.833	8.771	12.291	0.88	19.066	-0.132	0.067	Viable
Quantal Linear	1.285	2.303	4.668	0.251	20.162	-0.	-0.	Viable lowest dose/BMDL ratio > 3.0 lowest dose/BMD ratio > 3.0

^a BMDS recommended best fitting model

^b User selected best fitting model



Figure_Apx D-1. Maximum Likelihood Estimate (MLE) Models, 10% Extra Risk, Hyperkeratosis



Figure_Apx D-2. Selected Model: Weibull. Intermediate Oral Non-Cancer

Weibull Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	8.57642
BMDL	2.74996
BMDU	12.5268
AIC	19.0257
Log-Likelihood	-7.51284
P-Value	0.999606
Overall d.f.	1
Chi ²	2.4368e-07

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
a	3.37598	no	1.57814
b	7.44478e-05	no	0.612261

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

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	16	0	2.4368e-07	1.523e-08	-0.000493639
9.2	8	1	1	0.125	-5.66982e-09
18.4	8	6	6	0.75	4.73757e-09

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-7.51284	3	-	-	-
Fitted model	-7.51284	2	4.87359e-07	1	0.999443
Reduced model	-16.8103	1	18.5949	2	9.16586e-05

D.4 Chronic Inhalation, Non-Cancer

Dataset

Dose (mg/m3)	0	13.8	55.2
Affected / Total (%)	1.0/50.0 (2.0%)	5.0/50.0 (10.0%)	13.0/50.0 (26.0%)

Settings

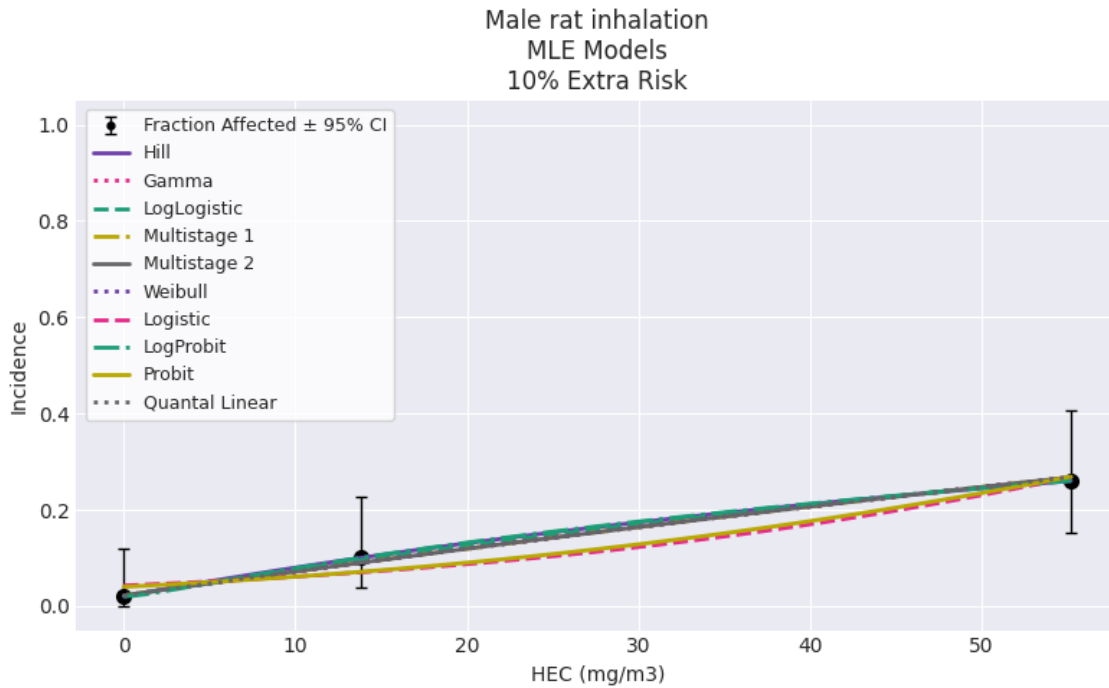
Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Multistage Degree	2

Maximum Likelihood Approach

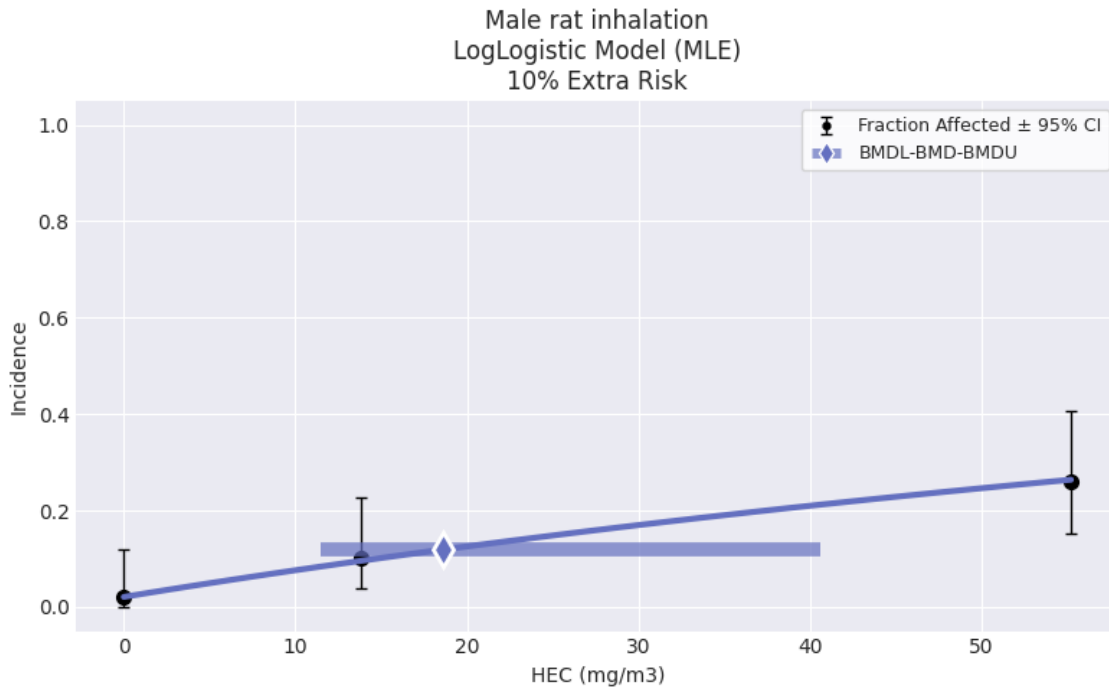
Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Hill	4.514	17.392	40.433	-	107.618	<0.001	<0.001	Questionable lowest dose/BMDL ratio > 3.0 Zero degrees of freedom; saturated model BMD/BMDL ratio > 3.0
Gamma	13.194	20.116	40.506	0.774	103.699	-0.088	0.247	Viable
LogLogistic ^{a b}	11.471	18.563	40.591	0.895	103.635	-0.034	0.11	Recommended - Lowest AIC
Multistage 1	13.193	20.116	36.581	0.774	103.699	-0.088	0.247	Viable
Multistage 2	13.193	20.116	40.972	0.774	103.699	-0.088	0.247	Viable
Weibull	13.194	20.116	41.751	0.774	103.699	-0.088	0.247	Viable
Logistic	26.598	33.653	46.848	0.249	105.02	-0.79	0.833	Viable
LogProbit	1.319	17.229	38.108	-	105.618	<0.001	-0.	Questionable lowest dose/BMDL ratio > 3.0 lowest dose/BMDL ratio > 10.0 Zero degrees of freedom; saturated model BMD/BMDL ratio > 3.0
Probit	24.719	31.74	45.573	0.279	104.835	-0.719	0.797	Viable
Quantal Linear	13.194	20.116	36.58	0.774	103.699	-0.088	0.247	Viable

^a BMDS recommended best fitting model

^b User selected best fitting model



Figure_Apx D-3. Maximum likelihood Estimate (MLE) Models, 10% Extra Risk, Centrilobular Necrosis of the Liver



Figure_Apx D-4. Selected Model: Log-Logistic. Chronic Inhalation Non-Cancer

LogLogistic Model

Version: pybmds 25.1 (bmdscore 25.1)

June 2026

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	18.5631
BMDL	11.4714
BMDU	40.5905
AIC	103.635
Log-Likelihood	-49.8175
P-Value	0.89537
Overall d.f.	1
Chi ²	0.0172955

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0206896	no	0.0608375
a	-5.1184	no	0.323409
b	1	yes	Not Reported

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

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	50	1	1.03448	0.0206896	-0.0342551
13.8	50	5	4.77049	0.0954099	0.110481
55.2	50	13	13.195	0.263901	-0.0625784

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-49.809	3	-	-	-
Fitted model	-49.8175	2	0.0171501	1	0.895808
Reduced model	-57.0001	1	14.3823	2	0.000753219

D.5 Chronic Oral, Non-Cancer

Dataset

Dose	0	11.02	11.89
(mg/kg/day)			
Affected /	0.0/40.0	11.0/50.0	12.0/50.0
Total (%)	(0.0%)	(22.0%)	(24.0%)

Settings

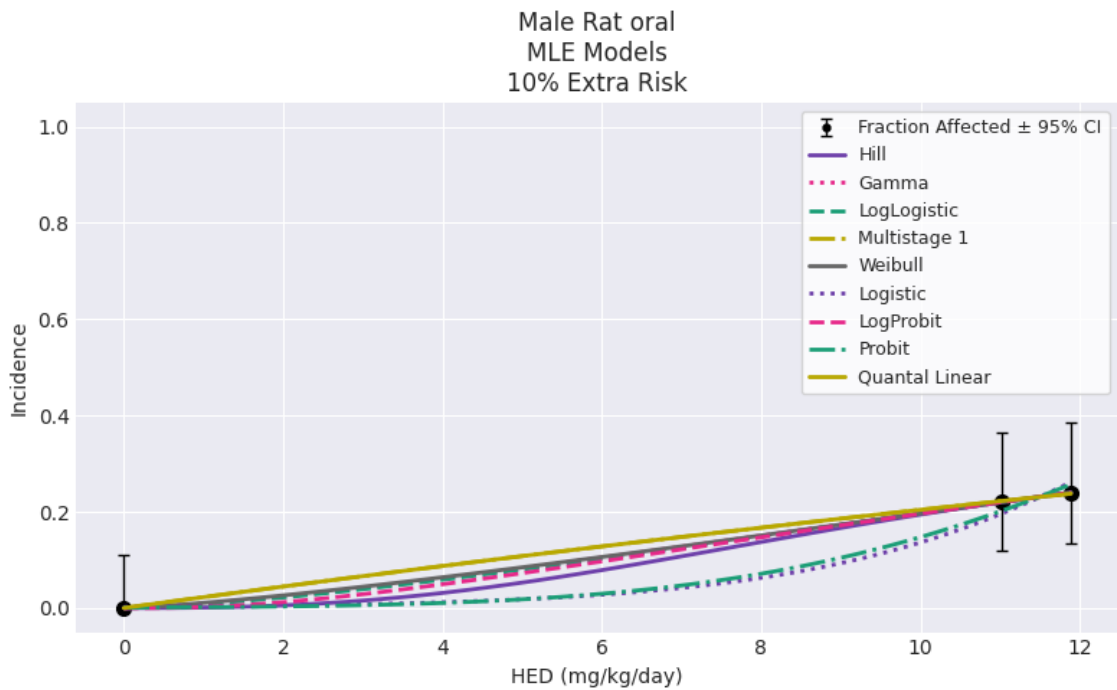
Setting	Value
BMR	10% Extra Risk
Confidence Level (one sided)	0.95
Maximum Multistage Degree	1

Maximum Likelihood Approach

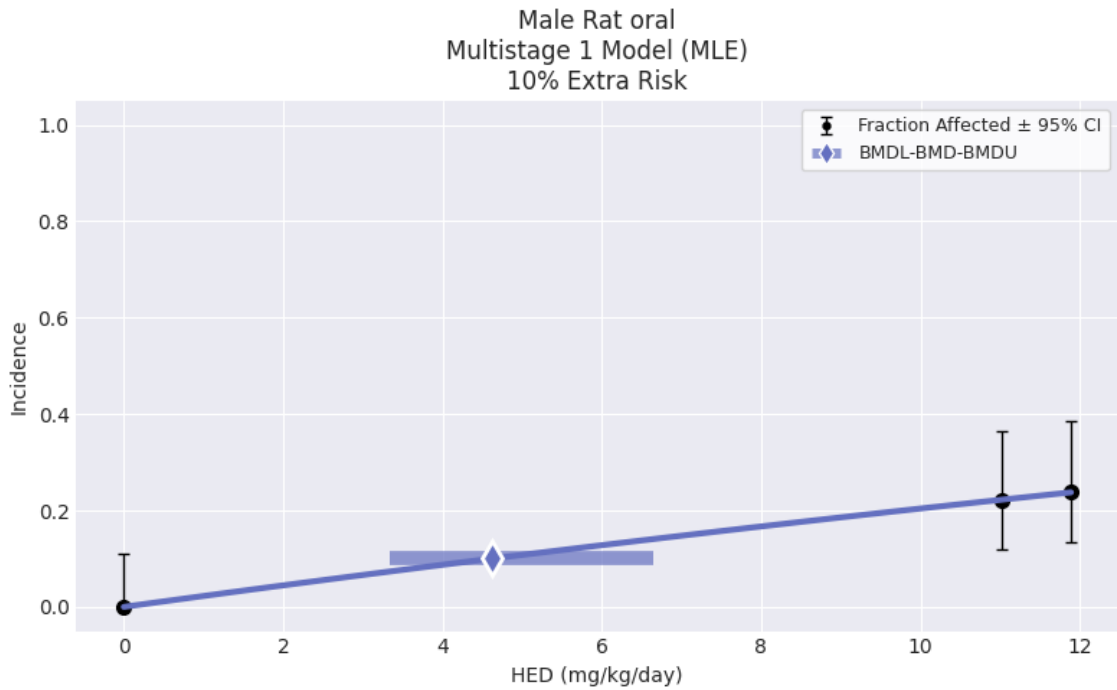
Model	BMDL	BMD	BMDU	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD	Recommendation and Notes
Hill	0	6.748	-	-	113.799	-0.001	0	Unusable Zero degrees of freedom; saturated model BMDL does not exist
Gamma	3.334	5.789	10.487	0.999	111.799	-0.001	-0.	Viable lowest dose/BMDL ratio > 3.0
LogLogistic	2.919	5.89	10.663	0.999	111.799	-0.001	-0.	Viable lowest dose/BMDL ratio > 3.0
Multistage 1 ^{a b}	3.333	4.617	6.647	0.998	109.802	-0.001	-0.001	Recommended - Lowest AIC lowest dose/BMDL ratio > 3.0
Weibull	3.334	5.721	10.643	0.999	111.799	-0.001	<0.001	Viable lowest dose/BMDL ratio > 3.0
Logistic	7.187	9.232	10.713	0.533	112.27	-0.294	0.421	Viable
LogProbit	0	6.125	10.692	0.999	111.799	-0.001	-0.	Unusable BMDL does not exist
Probit	6.753	8.905	10.704	0.646	112.042	-0.183	0.316	Viable
Quantal Linear	3.334	4.617	6.648	0.998	109.802	-0.001	-0.001	Viable lowest dose/BMDL ratio > 3.0

^a BMDS recommended best fitting model

^b User selected best fitting model



Figure_Apx D-5. Maximum Likelihood Estimate (MLE) Models, 10% Extra Risk, Focal Necrosis and Peliosis Hepatis of the Liver



Figure_Apx D-6. Selected Model: Multistage 1. Chronic Oral Non-Cancer

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	4.61658
BMDL	3.33298
BMDU	6.64749
AIC	109.802
Log-Likelihood	-53.901
P-Value	0.998432
Overall d.f.	2
Chi ²	0.0031384

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	1.523e-08	yes	Not Reported
b1	0.0228222	no	0.0567433

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

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	40	0	6.09199e-07	1.523e-08	-0.000780512
11.02	50	11	11.1184	0.222367	-0.0402537
11.89	50	12	11.8828	0.237655	0.0389543

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-53.8994	3	-	-	-
Fitted model	-53.901	1	0.00313973	2	0.998431
Reduced model	-62.5392	1	17.2797	2	0.000176917

D.6 Inhalation, Cancer

Dataset

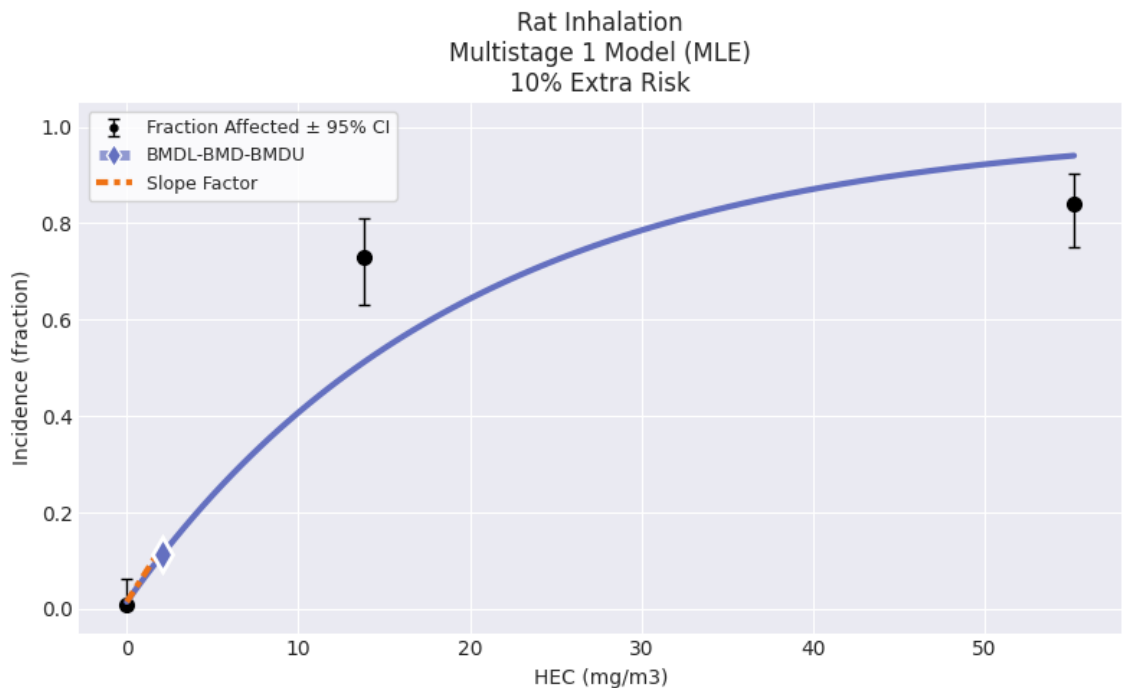
Dose (mg/m3)	0	13.8	55.2
Affected / Total (%) (fraction)	1.0/100.0 (1.0%)	73.0/100.0 (73.0%)	84.0/100.0 (84.0%)

Settings

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

Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Rat Inhalation: Multistage 1	1.775	2.073	2.434	0.056	1.02e-9	252.529	-0.392	-0.392
Rat Inhalation: Multistage 2	1.775	2.073	2.434	0.056	1.02e-9	252.529	-0.392	-0.392



Figure_Apx D-7. Selected Model: Multistage 1. Inhalation Cancer

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	2.07256
BMDL	1.7753
BMDU	2.43412
Slope Factor	0.0563284
AIC	252.529
Log-Likelihood	-124.265
P-Value	1.02161e-09
Overall d.f.	1
Chi ²	37.2832

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.0147153	no	0.0627419
b1	0.050836	no	0.266608

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	100	1	1.47153	0.0147153	-0.391604
13.8	100	73	51.1473	0.511473	4.37168
55.2	100	84	94.0452	0.940452	-4.24479

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-107.893	3	-	-	-
Fitted model	-124.265	2	32.743	1	1.05185e-08
Reduced model	-207.517	1	199.249	2	0

D.7 Oral, Cancer

Dataset

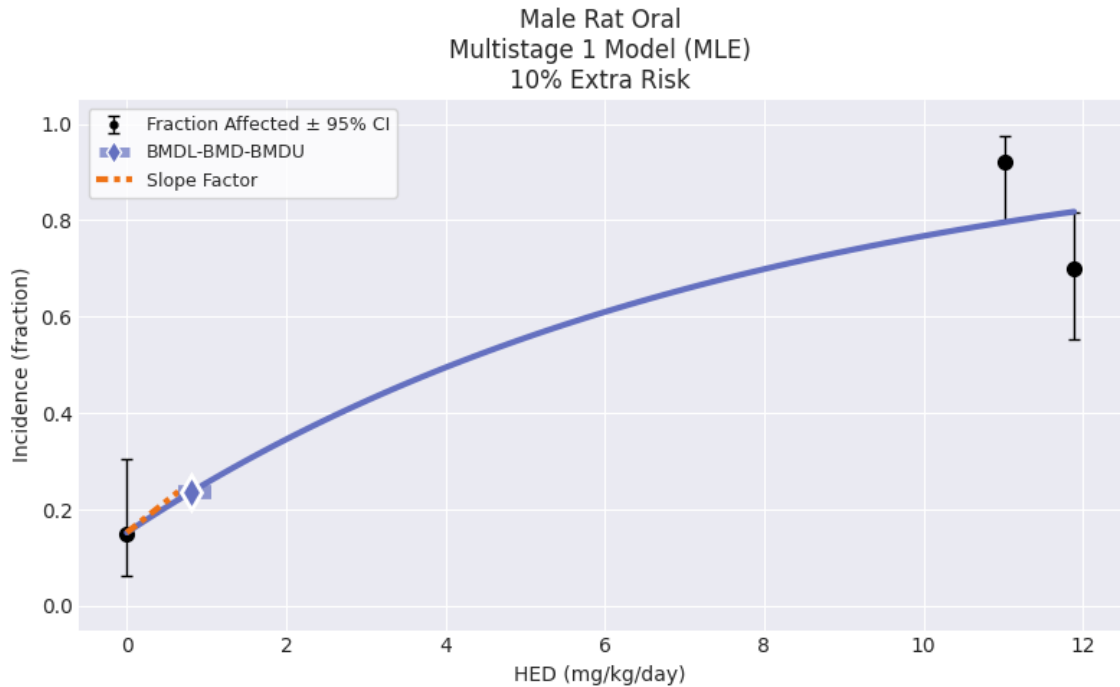
Dose	0	11.02	11.89
(mg/kg/day)			
Affected /	6.0/40.0	46.0/50.0	35.0/50.0
Total (%)	(15.0%)	(92.0%)	(70.0%)
(fraction)			

Settings

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

Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Male Rat Oral: Multistage 1	0.649	0.815	1.052	0.154	0.002	136.677	-0.038	-0.038
Male Rat Oral: Multistage 2	0.649	0.815	3.31	0.154	0.002	136.677	-0.038	-0.038



Figure_Apx D-8. Selected Model: Multistage 1. Oral Cancer

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	0.814511
BMDL	0.648558
BMDU	1.05204
Slope Factor	0.154188
AIC	136.677
Log-Likelihood	-66.3384
P-Value	0.00218249
Overall d.f.	1
Chi ²	9.38936

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.152164	no	0.0273903
b1	0.129354	no	0.214663

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	40	6	6.08657	0.152164	-0.0381092
11.02	50	46	39.8093	0.796187	2.17334
11.89	50	35	40.894	0.81788	-2.15974

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-61.39	3	-	-	-
Fitted model	-66.3384	2	9.89674	1	0.00165572
Reduced model	-92.8705	1	62.9608	2	2.13163e-14

D.8 Oral, Cancer – Bounding Exercise

Dataset

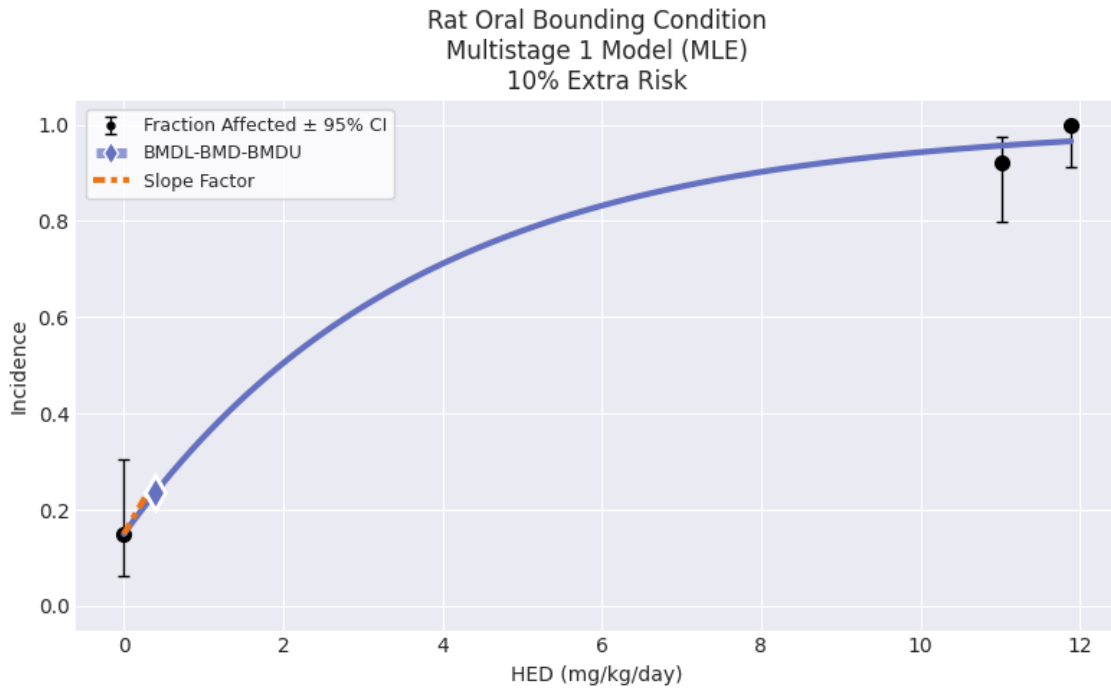
Dose (mg/kg/day)	0	11.02	11.89
Affected / Total (%)	6.0/40.0 (15.0%)	46.0/50.0 (92.0%)	50.0/50.0 (100.0%)

Settings

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

Maximum Likelihood Approach

Dataset: Model	BMDL	BMD	BMDU	CSF	P-Value	AIC	Scaled Residual at Control	Scaled Residual near BMD
Rat Oral Bounding: Multistage 1	0.297	0.39	0.51	0.337	0.065	70.489	0.009	0.009
Rat Oral Bounding: Multistage 2	0.311	2.1	2.403	0.322	0.098	69.672	0.016	0.016



Figure_Apx D-9. Alternate Model (Not Selected): Multistage 1. Oral Cancer (Bounding Condition)

Multistage 1 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	0.390106
BMDL	0.297173
BMDU	0.509607
Slope Factor	0.336504
AIC	70.4889
Log-Likelihood	-33.2444
P-Value	0.065469
Overall d.f.	1
Chi²	3.39312

Model Parameters:

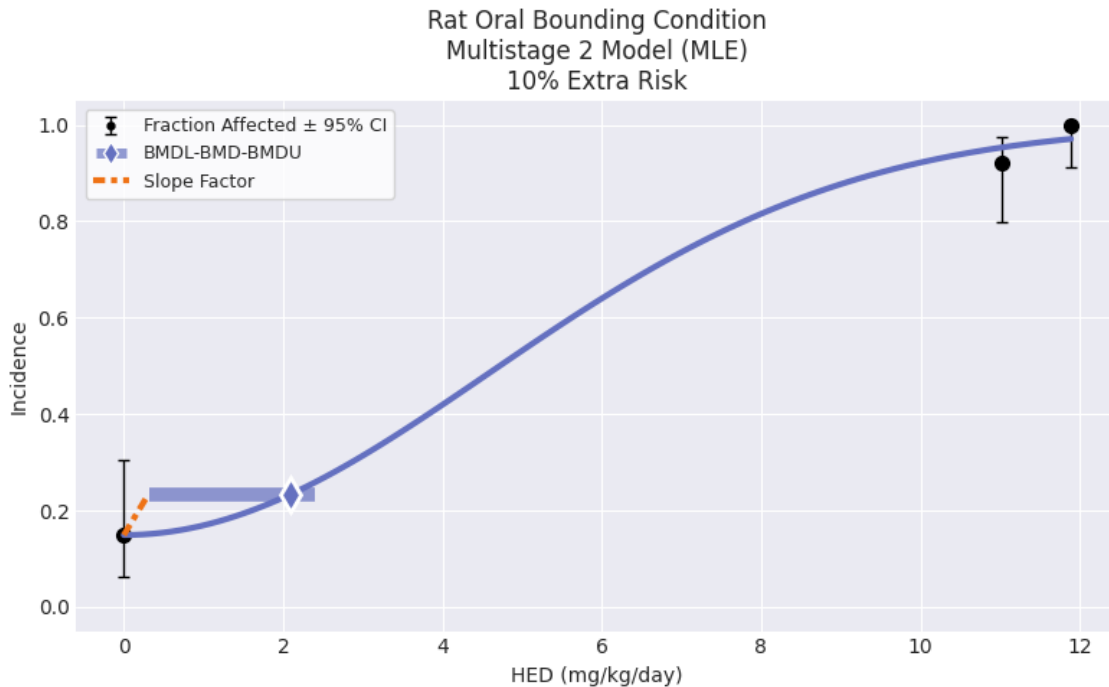
Variable	Estimate	On Bound	Std Error
g	0.149476	no	0.0273581
b1	0.270082	no	0.520122

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	40	6	5.97905	0.149476	0.00928801
11.02	50	46	47.832	0.956639	-1.27207
11.89	50	50	48.286	0.965719	1.33225

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-30.8468	3	-	-	-
Fitted model	-33.2444	2	4.79523	1	0.0285387
Reduced model	-81.8544	1	102.015	2	0



Figure_Apx D-10. Selected Model: Multistage 2. Oral Cancer (Bounding Condition)

Multistage 2 Model

Version: pybmds 25.1 (bmdscore 25.1)

Input Summary:

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

Parameter Settings:

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

Modeling Summary:

BMD	2.10022
BMDL	0.31098
BMDU	2.40264
Slope Factor	0.321564
AIC	69.6721
Log-Likelihood	-32.836
P-Value	0.0982417
Overall d.f.	1
Chi ²	2.73386

Model Parameters:

Variable	Estimate	On Bound	Std Error
g	0.149084	no	0.0273524
b1	9.94335e-18	yes	Not Reported
b2	0.0238863	no	0.555632

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

Goodness of Fit:

Dose	Size	Observed	Expected	Est Prob	Scaled Residual
0	40	6	5.96338	0.149084	0.0162571
11.02	50	46	47.6608	0.953215	-1.11218
11.89	50	50	48.5469	0.970937	1.22337

Analysis of Deviance:

Model	Log-Likelihood	# Params	Deviance	Test d.f.	P-Value
Full model	-30.8468	3	-	-	-
Fitted model	-32.836	2	3.97841	1	0.046087
Reduced model	-81.8544	1	102.015	2	0

Appendix E SPECIES SENSITIVITY DISTRIBUTION

The [SSD Toolbox](#) (v1.1; accessed June 18, 2026) is a resource that can fit SSDs to environmental hazard data ([Etterson, 2020a](#)). It runs on Matlab 2023b (23.2) for Windows 64 bit. When LC50s are available for a minimum of eight species, Web-ICE can be used to supplement the empirical data. The use of this probabilistic approach increases confidence in the hazard threshold identification as it is a more data-driven way of accounting for uncertainty.

The Web-ICE application was developed by EPA and collaborators to provide interspecies extrapolation models for acute toxicity ([Raimondo et al., 2010](#)). These models estimate the acute toxicity (LC/LD50) 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. The model returns median effect (*i.e.*, immobility) or lethal toxicity concentrations for species (EC50/LC50). Separate acute toxicity databases are maintained for aquatic animals (vertebrates and invertebrates), aquatic plants (algae), and terrestrial wildlife (birds and mammals), with 4,721 models for aquatic taxa, 102 models for algae, and 852 models for terrestrial birds and mammals in [Web-ICE](#) (v4.0; accessed June 2026) ([Raimondo et al., 2024](#); [Brill et al., 2016](#); [Raimondo et al., 2007](#)). 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. The aquatic animal database within Web-ICE is composed of 48- or 96-hour LC/EC50 values based on death or immobility. This database is described in detail in the Aquatic Database Documentation found on the [Download Model Data](#) page of Web-ICE (accessed June 2026) 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 ASTM International ([ASTM, 2014](#)) and EPA OCSPP (*e.g.*, ([U.S. EPA, 2016](#))).

E.1 Aquatic Species Sensitivity Distribution

Because LC50s were available for eight species (Table_Apx E-1), which is the minimum for SSD analysis, Web-ICE was used to supplement the empirical data. For the acute SSDs, acute exposure hazard data for aquatic vertebrates and invertebrates were curated to prioritize study quality and to assure comparability between toxicity values. For example, the empirical dataset included only LC50s for high- and medium-quality acute duration assays that measured mortality for aquatic vertebrates and invertebrates. EPA used empirical ethylene dibromide data from the fathead minnow, sheepshead minnow, medaka, and water fleas (*i.e.*, *D. magna* and *C. dubia*) as surrogate species to predict LC50 toxicity values using the Web-ICE application ([U.S. EPA, 2024b](#)). The Web-ICE Model estimated toxicity values for 128 species. For model validation, the model results are then screened by the following quality standards to ensure confidence in the model predictions. If a prediction did not meet all the quality criteria below, the prediction was eliminated from the dataset ([Willming et al., 2016](#)). Modeled data for 81 species met the following quality criteria (Table_Apx E-2):

- High R^2 (≥ 0.6)
 - The proportion of the data variance is explained by the model. The closer the R^2 value is to one, 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.
- Robust slope (0.6–1.4; 0.66–1.33 when concentration input is beyond model domain)
 - 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.

- Narrow 95% confidence intervals
- Two orders of magnitude or less between lower and upper limit.

The empirical data and modeled data that met the quality criteria were used to calculate the distribution of species sensitivity through the SSD Toolbox ([Etterson, 2020a](#)). The Toolbox's output contained several methods for choosing an appropriate distribution and fitting method, including goodness-of-fit, standard error, and sample-size corrected Bayesian Information Criterion (BIC_c) ([Burnham and Anderson, 2002](#)). For this draft ethylene dibromide assessment/TSD, EPA created two SSDs with the Toolbox to evaluate acute aquatic vertebrate and invertebrate toxicity separately. The Agency was unable to obtain a good model fit when vertebrates and vertebrates were included in the same distribution but was able to get good fits when they were separated (

Table_Apx E-3, and Table_Apx E-5). The p-value should be close to 0.5, and EPA does not use models with p-values below 0.025 or above 0.975 due to a lack of fit. The distribution and model with the lowest BIC_c value, and therefore the best fit for the data was the Gumbel distribution for the vertebrate data and the logistic distribution for the invertebrate data. Because numerical methods may lack statistical power for small sample sizes, a visual inspection of the data were also used to assess goodness-of-fit using Q-Q plots (Figure_Apx E-1 and Figure_Apx E-2).

For the Q-Q plot, the horizontal axis gives the empirical quantiles while the vertical axis gives the predicted quantiles (from the fitted distribution). The Q-Q plot demonstrates a good model fit with the data points in close proximity to the line across the data distribution. Q-Q plots were visually used to assess the goodness-of-fit for the distributions with the Gumbel distribution demonstrating the best fit near the low end of the vertebrate distribution, which is the region from which the HC05 is derived. The Gumbel distribution also carried the majority of the BIC_c weight (92%); therefore, EPA used the hazard concentration from the model with the best statistical fit. The results for this model (Figure 3-2) predicted 5% of the species (HC05) to have their LC50s exceeded at 0.81 mg/L ethylene dibromide (0.55–1.1 mg/L 95% CI). The logistic distribution demonstrated the best fit near the low end of the invertebrate distribution and carried most of the BIC_c weight (100%); therefore, EPA used the hazard concentration from the model with the best statistical fit. The results for this model (Figure 3-3) predicted 5% of the species (HC05) to have their LC50s exceeded at 0.40 mg/L ethylene dibromide (0.19–0.75 mg/L 95% CI).

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

Species	Description	Acute Toxicity Value LC50 (mg/L)	Reference
<i>Cyprinodon variegatus</i> ^a	Vertebrate	4.8	Landau and Tucker (1984)
<i>Centropomus undecimalis</i>	Vertebrate	6.2	Landau and Tucker (1984)
<i>Pimephales promelas</i> ^a	Vertebrate	4.3	Kszos et al. (2003)
<i>Oryzias latipes</i> ^a	Vertebrate	32.1	Holcombe et al. (1995)
<i>Ceriodaphnia dubia</i> ^a	Invertebrate	3.61	Kszos et al. (2003)
<i>Daphnia magna</i> ^a	Invertebrate	6.5	Kszos et al. (2003)
<i>Hydra oligactis</i>	Invertebrate	50	Herring (1988)
<i>Arbacia punctulata</i>	Invertebrate	83 ^b	Kennedy (1994)
<i>Arbacia punctulata</i>	Invertebrate	81 ^b	Kennedy (1994)
LC50 = lethal concentration (concentration that is lethal to 50% of test organisms)			
^a Species used as surrogate species to predict LC50 values using Web-ICE.			
^b SSD Toolbox calculates the geometric mean when >1 toxicity value is available for a given species. The geometric mean calculated for this species was 81.9939.			

Table_Apx E-2. SSD Model Input for Ethylene Dibromide Acute Exposure Toxicity in Aquatic Vertebrates and Invertebrates – Web-ICE Data That Met Quality Standards

Species	Description	Surrogate	Acute Toxicity Value LC/EC50 (mg/L) ^a	Geometric Mean LC50 (mg/L)
<i>Acipenser brevirostrum</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.22825	N/A
<i>Ameiurus melas</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	6.16965	N/A
<i>Carassius auratus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	5.4971	5.9411
<i>Carassius auratus</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	6.42095	
<i>Catostomus commersonii</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	6.37964	N/A
<i>Chelon macrolepis</i>	Vertebrate	Daphnid (<i>Daphnia magna</i>)	358.95838	N/A
<i>Cirrhinus mrigala</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.73696	N/A
<i>Cyprinus carpio</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	4.57111	3.7550
<i>Cyprinus carpio</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	3.08459	

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Species	Description	Surrogate	Acute Toxicity Value LC/EC50 (mg/L) ^a	Geometric Mean LC50 (mg/L)
<i>Danio rerio</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	4.1392	7.5738
<i>Danio rerio</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	4.00296	
<i>Danio rerio</i>	Vertebrate	Daphnid (<i>Daphnia magna</i>)	14.39445	
<i>Danio rerio</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	5.79982	
<i>Danio rerio</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	8.03832	
<i>Danio rerio</i>	Vertebrate	Daphnid (<i>Daphnia magna</i>)	16.97538	
<i>Etheostoma lepidum</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.02322	N/A
<i>Gambusia affinis</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.87294	N/A
<i>Gibelion catla</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	4.11007	N/A
<i>Gila elegans</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.97575	N/A
<i>Ictalurus punctatus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	4.09241	N/A
<i>Jordanella floridae</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.5405	N/A
<i>Labeo rohita</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	7.69146	N/A
<i>Lepidocephalichthys guntea</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	3.61154	N/A
<i>Lepomis cyanellus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.47391	N/A
<i>Lepomis macrochirus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.44743	3.8132
<i>Lepomis macrochirus</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	2.81252	
<i>Lepomis macrochirus</i>	Vertebrate	Daphnid (<i>Daphnia magna</i>)	8.05525	
<i>Lithobates catesbeianus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	4.7613	N/A
<i>Menidia beryllina</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.79766	N/A
<i>Oncorhynchus clarkii</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.41987	N/A
<i>Oncorhynchus kisutch</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.21915	N/A

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Species	Description	Surrogate	Acute Toxicity Value LC/EC50 (mg/L) ^a	Geometric Mean LC50 (mg/L)
<i>Oncorhynchus mykiss</i>	Vertebrate	Japanese medaka (<i>Oryzias latipes</i>)	17.21938	4.5693
<i>Oncorhynchus mykiss</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.10033	
<i>Oncorhynchus mykiss</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	2.1303	
<i>Oncorhynchus mykiss</i>	Vertebrate	Daphnid (<i>Daphnia magna</i>)	5.65807	
<i>Oncorhynchus tshawytscha</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.00194	N/A
<i>Oreochromis mossambicus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	3.14097	N/A
<i>Perca flavescens</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.06456	N/A
<i>Poecilia reticulata</i>	Vertebrate	Japanese medaka (<i>Oryzias latipes</i>)	26.70754	7.8386
<i>Poecilia reticulata</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.7709	
<i>Poecilia reticulata</i>	Vertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	6.50814	
<i>Ptychocheilus lucius</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.03511	N/A
<i>Salmo salar</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.36642	N/A
<i>Salvelinus fontinalis</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.08244	N/A
<i>Salvelinus namaycush</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.69198	N/A
<i>Xenopus laevis</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	3.42618	N/A
<i>Xyrauchen texanus</i>	Vertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.6242	N/A
<i>Acartia clausi</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.66385	2.2240
<i>Acartia clausi</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	7.45041	
<i>Allorchestes compressa</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.69697	N/A
<i>Amblema plicata</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.08619	0.6388
<i>Amblema plicata</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	1.54537	
<i>Amblema plicata</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	1.95741	
<i>Americamysis bahia</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	1.93991	2.8088
<i>Americamysis bahia</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	4.06691	
<i>Americamysis bigelowi</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.51643	N/A

Species	Description	Surrogate	Acute Toxicity Value LC/EC50 (mg/L) ^a	Geometric Mean LC50 (mg/L)
<i>Asellus aquaticus</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	10.80134	38.9453
<i>Asellus aquaticus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	140.42137	
<i>Branchinecta lynchi</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	5.16088	5.7941
<i>Branchinecta lynchi</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	6.50509	
<i>Caecidotea brevicauda</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.5259	N/A
<i>Ceriodaphnia reticulata</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	1.45167	N/A
<i>Chironomus tentans</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	29.80054	N/A
<i>Chydorus sphaericus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	2.63467	N/A
<i>Cloeon dipterum</i>	Invertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	0.00255	N/A
<i>Crangon crangon</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	3.23252	N/A
<i>Crangonyx pseudogracilis</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	54.56684	N/A
<i>Crassostrea virginica</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.70807	N/A
<i>Daphnia galeata</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	5.85327	N/A
<i>Daphnia longispina</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	11.65972	N/A
<i>Daphnia pulex</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	4.91152	6.1026
<i>Daphnia pulex</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	7.58243	
<i>Daphnia pulicaria</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	5.4748	N/A
<i>Eurytemora affinis</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	2.39745	N/A
<i>Gammarus fasciatus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	3.64505	N/A
<i>Gammarus minus</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	14.0568	N/A
<i>Gammarus pseudolimnaeus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	5.45928	6.3395
<i>Gammarus pseudolimnaeus</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	7.36167	
<i>Lampsilis rafinesqueana</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	4.37012	3.7654
<i>Lampsilis rafinesqueana</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	3.24438	
<i>Lampsilis siliquoidea</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.0304	3.0809
<i>Lampsilis siliquoidea</i>	Invertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	5.58578	

Species	Description	Surrogate	Acute Toxicity Value LC/EC50 (mg/L) ^a	Geometric Mean LC50 (mg/L)
<i>Lampsilis siliquoidea</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	4.81254	
<i>Lampsilis siliquoidea</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	3.2527	
<i>Lasmigona subviridis</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	3.05139	N/A
<i>Limnodrilus hoffmeisteri</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	29.55878	N/A
<i>Lumbriculus variegatus</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	5.0102	N/A
<i>Lymnaea stagnalis</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.74929	3.3627
<i>Lymnaea stagnalis</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	6.26881	
<i>Lymnaea stagnalis</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	8.0955	
<i>Macrobrachium nipponense</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	3.42409	N/A
<i>Margaritifera falcata</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	4.23048	4.6728
<i>Margaritifera falcata</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	5.16138	
<i>Megaloniaias nervosa</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.30967	1.4559
<i>Megaloniaias nervosa</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	2.77722	
<i>Megaloniaias nervosa</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	3.58834	
<i>Moina macrocopa</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	6.98447	N/A
<i>Ortmanniana pectorosa</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	4.63434	4.2869
<i>Ortmanniana pectorosa</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	3.96544	
<i>Palaemonetes kadiakensis</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	2.27151	4.9641
<i>Palaemonetes kadiakensis</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	10.84829	
<i>Paratanytarsus dissimilis</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	12.50868	N/A
<i>Paratanytarsus parthenogeneticus</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	14.40305	16.3983
<i>Paratanytarsus parthenogeneticus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	18.66989	
<i>Pectinatella magnifica</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	28.13474	N/A
<i>Physella gyrina</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.69828	3.0371
<i>Physella gyrina</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	5.99804	
<i>Physella gyrina</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	6.68838	
<i>Pseudodiptomus coronatus</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	1.14499	N/A

Species	Description	Surrogate	Acute Toxicity Value LC/EC50 (mg/L) ^a	Geometric Mean LC50 (mg/L)
<i>Pseudosida ramosa</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	3.12051	1.8571
<i>Pseudosida ramosa</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	1.10517	
<i>Simocephalus serrulatus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	3.58971	N/A
<i>Simocephalus vetulus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	2.96824	N/A
<i>Thamnocephalus platyurus</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	5.02224	5.3925
<i>Thamnocephalus platyurus</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	5.79003	
<i>Tigriopus japonicus</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	12.46558	N/A
<i>Trypaea australiensis</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	1,076.19071	N/A
<i>Tubifex tubifex</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	4.65963	28.2399
<i>Tubifex tubifex</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	59.49232	
<i>Tubifex tubifex</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	81.24167	
<i>Utterbackia imbecillis</i>	Invertebrate	Fathead minnow (<i>Pimephales promelas</i>)	0.95218	3.5142
<i>Utterbackia imbecillis</i>	Invertebrate	Sheepshead minnow (<i>Cyprinodon variegatus</i>)	8.0644	
<i>Utterbackia imbecillis</i>	Invertebrate	Daphnid (<i>Daphnia magna</i>)	4.60253	
<i>Utterbackia imbecillis</i>	Invertebrate	Daphnid (<i>Ceriodaphnia dubia</i>)	4.31519	
EC50 = effective concentration (concentration which induces a biological response to 50% of test organisms); LC50 = lethal concentration (concentration which is lethal to 50% of test organisms) N/A = not applicable; only 1 toxicity value available for species. ^a LC50 values as reported by Web-ICE				

Table_Apx E-3. SSD Model Predictions for Acute Ethylene Dibromide Exposure Toxicity to Aquatic Organisms

Distribution ^a	Fitting Method	HC05 (mg/L) ^b	P-Value
Normal	Metropolis-Hastings	0.3315	0.9996 ^c
Logistic	Metropolis-Hastings	0.4537	0.9918 ^c
Triangular	Metropolis-Hastings	0.0188	1 ^c
Gumbel	Metropolis-Hastings	0.1700	0.9922 ^c
Weibull	Metropolis-Hastings	0.0467	0.9840 ^c
HC05 = hazard concentration (protective of 95% of the species in the sensitivity distribution) ^a SSD was generated using SSD Toolbox v1.1 ^b Unrounded HC05 as reported by SSD Toolbox ^c Unacceptable p-value			

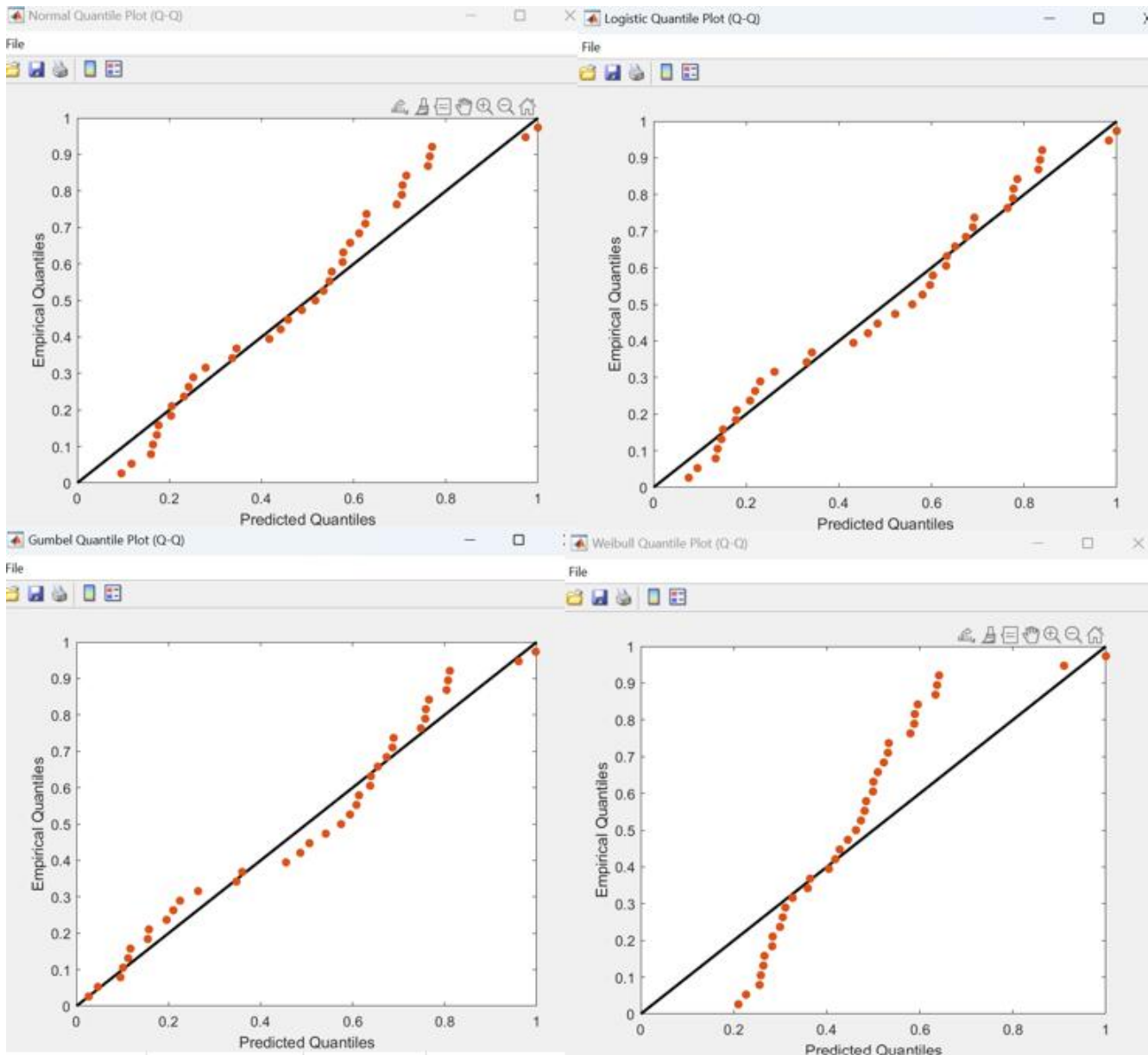
June 2026

Table_Apx E-4. SSD Model Predictions for Acute Ethylene Dibromide Exposure Toxicity to Aquatic Vertebrates

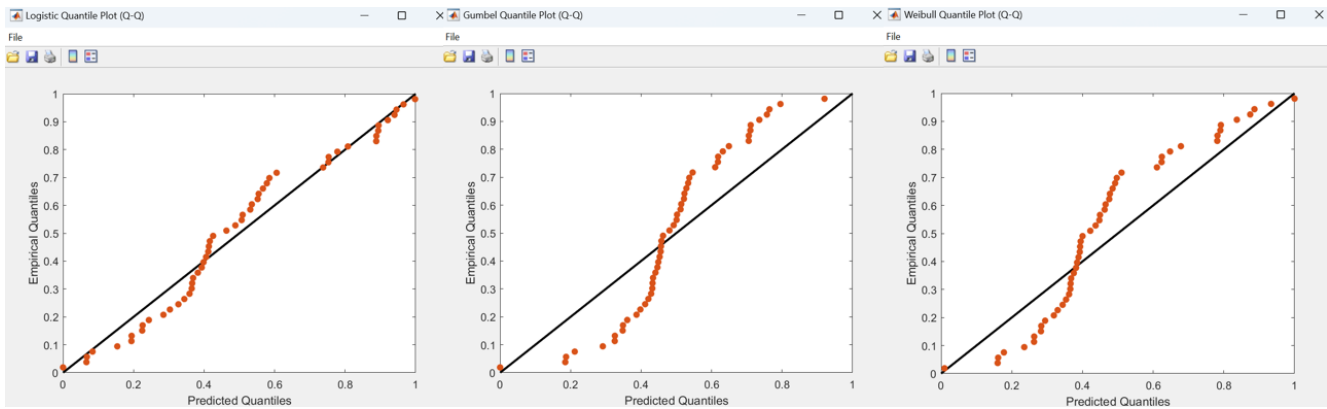
Distribution ^a	Fitting Method	HC05 (mg/L) ^b	Bayesian Information Criterion ^c	BICc Model Weight	P-Value
Normal	Metropolis-Hastings	0.4629	208.7059	0.0016	0.9582
Logistic	Metropolis-Hastings	0.5332	200.9158	0.0787	0.922
Triangular	Metropolis-Hastings	0.2296	227.603	N/A	0.9978 ^d
Gumbel	Metropolis-Hastings	0.8143	196.1172	0.9197	0.7996
Weibull	Metropolis-Hastings	0.0559	235.974	2.09E-09	0.9404
HC05 = hazard concentration (protective of 95% of the species in the sensitivity distribution) ^a SSD was generated using SSD Toolbox v1.1 ^b Unrounded HC05 as reported by SSD Toolbox ^c The model with the lowest BICc value, and therefore the best distribution fit, is bolded in this table ^d Unacceptable p-value					

Table_Apx E-5. SSD Model Predictions for Acute Ethylene Dibromide Exposure Toxicity to Aquatic Invertebrates

Distribution ^a	Fitting Method	HC05 (mg/L) ^b	Bayesian Information Criterion ^c	BICc Model Weight	P-Value
Normal	Metropolis-Hastings	0.2634	377.9471	N/A	0.9866 ^d
Logistic	Metropolis-Hastings	0.4002	365.3228	1.0000	0.9672
Triangular	Metropolis-Hastings	0.0173	406.308	N/A	0.9992 ^d
Gumbel	Metropolis-Hastings	0.1205	411.4905	9.77E-11	0.9712
Weibull	Metropolis-Hastings	0.054	389.0141	6.81E-06	0.9046
HC05 = hazard concentration (protective of 95% of the species in the sensitivity distribution) ^a SSD was generated using SSD Toolbox v1.1 ^b Unrounded HC05 as reported by SSD Toolbox ^c The model with the lowest BICc value, and therefore the best distribution fit, is bolded in this table ^d Unacceptable p-value					



Figure_Apx E-1. Q-Q plots of Species Sensitivity Distribution Model Fits with Acceptable P-Values for Aquatic Vertebrates



Figure_Apx E-2. Q-Q Plots of Species Sensitivity Distribution Model Fits with Acceptable P-Values for Aquatic Invertebrates

E.2 Terrestrial Species Sensitivity Distribution

Because LD50 or LC50 hazard values were available for eight species (Table_Apx E-6), thereby meeting the criteria for SSD analysis, empirical data were used to generate an SSD. For the acute SSD, acute exposure hazard data for terrestrial invertebrates were curated to prioritize study quality and to assure comparability between toxicity values. For example, the empirical dataset included only LD/LC50s for high and medium quality acute duration assays that measured mortality for terrestrial invertebrates. For terrestrial invertebrate species exposed to ethylene dibromide via fumigation, acute durations were defined as approximately less than 10% of organism lifespan. Because the terrestrial database available in Web-ICE only exists for birds and mammals, terrestrial invertebrate species are not available models in Web-ICE version 4.0, therefore, Web-ICE was not used to supplement empirical data.

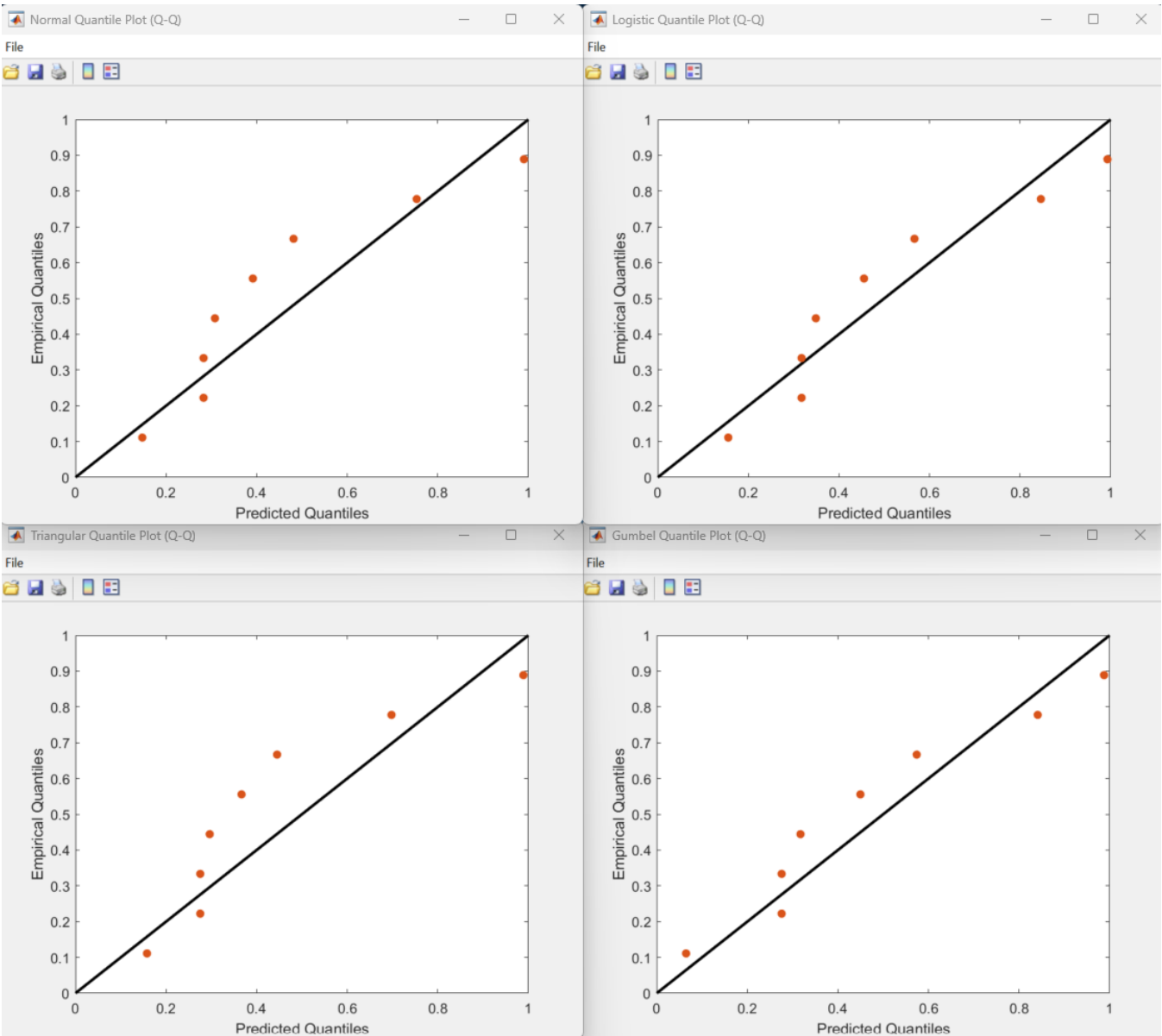
The empirical data that met quality criteria were used to calculate the distribution of species sensitivity through the SSD Toolbox (Etterson, 2020a). The SSD Toolbox's output contained several methods for choosing an appropriate distribution and fitting method, including goodness-of-fit, standard error, and sample-size corrected AIC_c (Table_Apx E-7) (Burnham and Anderson, 2002). The p-value should exceed 0.05, and EPA does not use models with p-values below 0.05 due to a lack of fit. The distribution and model with the lowest AIC_c value, and therefore the best fit for the data was the Gumbel distribution for the terrestrial invertebrate data. Because numerical methods may lack statistical power for small sample sizes, a visual inspection of the data were also used to assess goodness-of-fit using Q-Q plots (Figure_Apx E-3). For the Q-Q plot, the horizontal axis gives the empirical quantiles while the vertical axis gives the predicted quantiles (from the fitted distribution). The Q-Q plot demonstrates a good model fit with the data points in close proximity to the line across the data distribution. Q-Q plots were visually used to assess the goodness-of-fit for the distributions, and the Gumbel, Logistic, Normal and Triangular distributions all appeared to fit the low end of the curve equally. Although the Gumbel distribution is the best statistical model, the AIC_c weight of 0.64 indicates there is information in the other models that is not captured by this model. A model average prediction helps address some of the uncertainties of a single model by calculating a weighted mean across the models that had acceptable p-values (Burnham et al., 2011). Because the AIC_c weight of the Gumbel distribution was 0.64, EPA selected to use the modeled average to account for the uncertainties among these distributions. The results for this model average (Figure 3-4, produced using SSD Toolbox v1.5) predicted 5% of the species (HC05) to have their LC50s exceeded at 0.07 mg/L ethylene dibromide (0.03–0.4 mg/L 95% CI).

Table_Apx E-6. SSD Model Input for Ethylene Dibromide Acute Exposure Toxicity in Terrestrial Invertebrates – Empirical Data

Species	Acute Toxicity Value LC50 (mg/L)	Geometric Mean LC50 (mg/L)	Reference(s)
<i>Callosobruchus chinensis</i>	5.649	0.9203	Adu and Muthu (1985)
<i>Callosobruchus chinensis</i>	0.243		Adu and Muthu (1985)
<i>Callosobruchus chinensis</i>	0.499		Adu and Muthu (1985)
<i>Callosobruchus chinensis</i>	1.047		Adu and Muthu (1985)
<i>Tribolium castaneum</i>	0.476	0.5665	Rajendran and Muthu (1989)
<i>Tribolium castaneum</i>	0.519		Rajendran and Muthu (1989)
<i>Tribolium castaneum</i>	0.736		Rajendran and Muthu (1989)
<i>Cryptolestes ferrugineus</i>	0.245	0.3499	Barker (1976)
<i>Cryptolestes ferrugineus</i>	0.472		Barker (1976)
<i>Cryptolestes ferrugineus</i>	0.273		Barker (1976)
<i>Cryptolestes ferrugineus</i>	0.475		Barker (1976)
<i>Sitophilus granarius</i>	3.17	4.3503	Ellis (1972a)
<i>Sitophilus granarius</i>	5.97		Ellis (1972a)
<i>Anastrepha suspensa</i>	0.11	N/A	Brueck and Burditt (1977)
<i>Tyrophagus putrescentiae</i>	0.3	N/A	Muthu et al. (1970)
<i>Caloglyphus krameri</i>	0.3	N/A	Muthu et al. (1970)
<i>Trogoderma granarium</i>	143.9	N/A	Bains et al. (1976)
LC50 = lethal concentration (concentration which is lethal to 50% of test organisms); N/A = not applicable; only 1 toxicity value available for species			

Table_Apx E-7. SSD Model Predictions for Acute Ethylene Dibromide Exposure Toxicity to Terrestrial Invertebrates

Distribution ^a	Fitting Method	HC05 (mg/L) ^c	Akaike Information Criterion ^d	AICc Weight	P-Value
Normal ^b	Maximum-Likelihood	0.0309	41.3935	0.1080	0.0942
Logistic ^b	Maximum-Likelihood	0.0283	40.6338	0.1579	0.2649
Triangular ^b	Maximum-Likelihood	0.0280	41.7219	0.0916	0.1062
Gumbel ^b	Maximum-Likelihood	0.0975	37.8271	0.6425	0.4217
Weibull	Maximum-Likelihood	0.0016	45.1670	N/A	0.0280 ^e
Modeled Average	Maximum-Likelihood	0.0732	N/A	N/A	N/A
HC05 = hazard concentration (protective of 95% of the species in the sensitivity distribution) ^a SSD generated using SSD Toolbox v1.1. ^b Distribution included in the modeled average. ^c Unrounded HC05 as reported by SSD Toolbox. ^d The model with the lowest AICc value, and therefore the best distribution fit, is bolded in this table. ^e Unacceptable p-value.					



Figure_Apx E-3. Q-Q Plots of Species Sensitivity Distribution Model Fits with Acceptable P-Values for Terrestrial Invertebrates

Appendix F RUBRIC FOR WEIGHT OF SCIENTIFIC EVIDENCE FOR ENVIRONMENTAL HAZARD

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

The evidence considerations and criteria detailed within U.S. EPA (2021) guides the application of strength-of-evidence judgments for environmental hazard effect within a given evidence stream and were adapted from Table 7-10 of the 2021 Draft Systematic Review 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 rating for environmental hazard. Confidence levels of robust, moderate, slight, or indeterminant 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 overall quality determination rating (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 the study is to ecologically relevant endpoints). Additionally, because of the importance of the studies used for deriving hazard thresholds, the Quality of the Database consideration may have greater weight than the other individual considerations. The high, medium, and low systematic review overall quality determination ratings correspond to the evidence table ranks of robust, moderate, or slight, respectively. The evidence considerations are weighted based on professional judgment to obtain the overall confidence for each hazard threshold. In other words, the weights of each evidence property relative to the other properties are dependent on the specifics of the weight of scientific evidence and uncertainties that are described in the narrative and may or may not be equal. Therefore, the overall score is not necessarily a mean or defaulted to the lowest score. The confidence levels and uncertainty type examples are described below.

F.1 Confidence Levels

- Robust confidence suggests thorough understanding of the scientific evidence and uncertainties. The supporting weight of scientific evidence outweighs the uncertainties to the point where it is unlikely that the uncertainties could have a significant effect on the exposure or hazard estimate.
- Moderate confidence suggests some understanding of the scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize exposure or hazard estimates.
- Slight confidence is assigned when the weight of scientific evidence may not be adequate to characterize the scenario, and when the assessor is making the best scientific assessment possible in the absence of complete information. There are additional uncertainties that may need to be considered.
- Indeterminant corresponds to entries in evidence tables where information is not available within a specific evidence consideration.

F.2 Types of Uncertainties

The following uncertainties may be relevant to one or more of the weight of scientific evidence

considerations listed above and will be integrated into that property's rank in the evidence table:

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

Table_Apx F-1 and Table_Apx F-2 summarize the weight of scientific evidence and uncertainties, while increasing transparency on how EPA arrived at the overall confidence level for each exposure hazard threshold.

Table_Apx F-1. Ethylene Dibromide Evidence Table Summarizing the Overall Confidence Derived from Hazard Thresholds

Types of Evidence	Quality of Database	Consistency	Strength and Precision	Biological Gradient/ Dose-Response	Relevance ^a	Hazard Confidence
Aquatic						
Acute aquatic vertebrate assessment	Robust ^b	Robust	Robust	Robust	Robust	Robust (see Section 3.2.1.2)
Acute aquatic invertebrate assessment	Robust	Robust	Robust	Robust	Robust	Robust (see Section 3.2.2.2)
Chronic aquatic vertebrate assessment	Slight ^c	Slight	Moderate ^d	Moderate	Slight	Slight (see Section 3.2.3.3)
Chronic aquatic invertebrate assessment	Slight	Slight	Slight	Slight	Slight	Slight (see Section 3.2.4.2)
Terrestrial						
Acute mammalian assessment	Robust	Robust	Moderate	Robust	Moderate	Robust (see Section 3.3.1.3)
Chronic mammalian assessment	Robust	Robust	Moderate	Robust	Moderate	Robust (see Section 3.3.1.3)
Acute avian assessment	Slight	Moderate	Moderate	Moderate	Slight	Moderate (see Section 3.3.1.3)
Acute terrestrial invertebrate assessment	Robust	Robust	Robust	Robust	Robust	Robust (see Section 3.3.2.2)
^a Relevance includes biological, physical/chemical, and environmental relevance. ^b Robust confidence suggests thorough understanding of 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. ^c Slight confidence suggests the weight of scientific evidence may not be adequate to characterize the scenario, and the assessor is making the best scientific assessment possible in the absence of complete information. ^d Moderate confidence suggests some understanding of scientific evidence and uncertainties. The supporting scientific evidence weighed against the uncertainties is reasonably adequate to characterize hazard estimates.						

Table_Apx F-2. Considerations That Inform Evaluations of the Strength of the Evidence Within an Evidence Stream (*i.e.*, Apical Endpoints, Mechanistic, or Field Studies)

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

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

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Appendix G MAMMALIAN LC50 DERIVATION

Based on data published in Table 3 in Rowe et al. (1952), author reported exposure concentrations and durations were used to extrapolate an LC50 hazard value for exposure of rats to ethylene dibromide via inhalation. This was done in accordance with OECD Test No. 403, Acute Inhalation Toxicity, which gives guidance for a $C \times t$ protocol as an alternative to traditional protocols to assess inhalation toxicity. In this approach, multiple concentrations and durations can be utilized for toxicity exposures. This approach is generally taken to reduce the number of animals needed for toxicity assessment and to obtain lethality data. In accordance with OECD guidance on inhalation toxicity studies, median lethal concentration values can be estimated from multiple exposure durations by combining exposure concentration (C), exposure time (t), and the toxic load exponent (n). The toxicological relationship between concentration and duration is described by Haber's law, which states that for the concentration of a poisonous gas, $C \times t = k$, where C is the concentration of the gas, t depicts the time necessary to inhale the gas, and k is a constant dependant on both the gas and effect (Haber, 1924). Haber's law assumes the relationship between C and t are linear in a log-log plot. In cases where the relationship is not linear (e.g., concentration has a greater impact than duration), $C^n \times t = k$ may be used where n depicts a chemical-specific constant that typically ranges from 0.8 to 3.5. Cases where $n > 1$ indicates concentration has a greater impact on toxicity than duration.

Rowe et al. (1952) reported mortality in rats ($n = 711$) exposed to ethylene dibromide via inhalation across multiple concentrations and durations (shown below in Table_Apx G-1). Using the author-reported data, EPA estimated an LC50 hazard value for exposure of rats to ethylene dibromide via inhalation. This estimation was calculated by multiplying the nominal vapor concentrations (C), given in mg/L, by the durations (t), reported in hours, to obtain Ct values. Ct values, in addition to the total number of rats used for each trial, and the total number of deaths from each trial were then used in a dose-response model, specifically a binomial generalized nonlinear regression model, using the drc R package (Ritz et al., 2015).

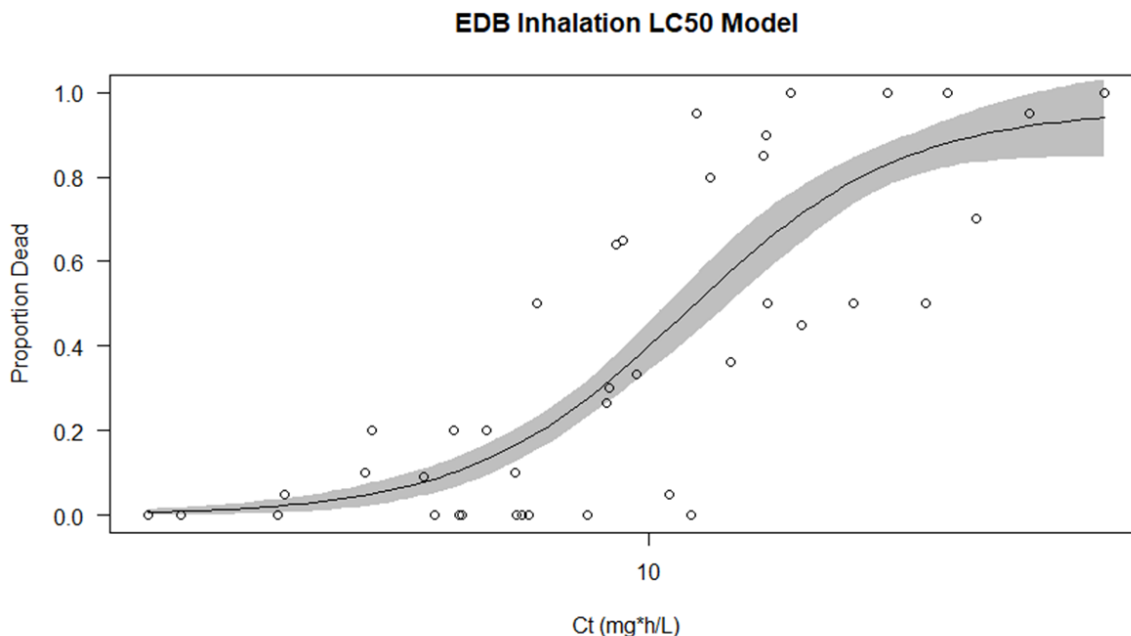
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Table_Apx G-1. Toxicity Data from Rats Exposed to Ethylene Dibromide via Inhalation

Concentration (mg/L)	Duration (Hours)	Ct	Total	Deaths
0.77	8.5	6.545	20	0
0.77	12	9.24	20	0
0.77	16	12.32	20	0
1.54	1.4	2.156	20	0
1.54	2	3.08	5	0
1.54	3	4.62	11	1
1.54	4	6.16	5	0
1.54	5	7.7	10	3
1.54	7	10.78	11	4
1.54	8.5	13.09	20	9
1.54	12	18.48	20	10
1.54	16	24.64	20	19
3.08	0.6	1.848	20	0
3.08	0.8	2.464	20	1
3.08	1	3.08	20	2
3.08	1.4	4.312	25	5
3.08	2	6.16	25	16
3.08	2.5	7.7	20	19
3.08	3	9.24	20	17
3.08	5	15.4	20	20
6.16	0.4	2.464	20	4
6.16	0.5	3.08	20	4
6.16	0.63	3.8808	20	10
6.16	0.8	4.928	20	13
12.3	0.2	2.46	30	0
12.3	0.3	3.69	15	4
12.3	0.4	4.92	15	12
12.3	0.5	6.15	20	20
23.1	0.1	2.31	20	0
23.1	0.2	4.62	10	5
38.5	0.04	1.54	20	0
38.5	0.05	1.925	30	3
38.5	0.07	2.695	15	5
38.5	0.1	3.85	10	9
38.5	0.14	5.39	20	20
77	0.02	1.54	20	0
77	0.03	2.31	20	1
77	0.05	3.85	4	2
77	0.07	5.39	10	7
77	0.1	7.7	20	20

From the data shown above, EPA estimated a 4-hour LC50 of 2.12 (1.90–2.34) mg/L. Ct values were used in a log-logistic regression, three-parameter model using the drc R package for dose-response models. The three-parameter log-logistic model was chosen in part by examining the deviance residuals and best fit of the curve. In this case, when $n = 1.35$, the deviance residuals look more symmetrical which indicates a better fit. For additional information about log-logistic regression and fit options using the drc R package, please see the Package ‘drc’ – Version 3.0-1 guide ([2025](#)).



Figure_Apx G-1. Drc R Package Log-Logistic Regression

Appendix H SCREENING TOOL FOR ESTIMATING ENVIRONMENTAL RISK VIA INHALATION

Screening Tool for Inhalation Risk (STIR) is a tool used and developed by Office of Pesticide Programs as a screening tool for ecological risk assessment ([U.S. EPA, 2010](#)). STIR can be used to predict inhalation hazard for avian species based on pesticide-specific information when empirical data are not available. STIR utilizes allometric scaling to relate inhalation rate to body weight in order to derive an estimated inhalation dose for a 0.020 kg bird and a 0.015 kg mammal ([Mineau et al., 1996](#)). Due to the potential exposure of birds to ethylene dibromide via inhalation, STIR provides a way to model potential risk. Physical chemical properties, including molecular weight and vapor pressure, are used to estimate vapor phase exposure. Spray droplet exposure estimates and rate are also accounted for by the tool. These exposure estimates can then be used to compare to avian and mammalian toxicity data. STIR uses mammalian-oral, mammalian-inhalation, and avian-oral empirical toxicity values as inputs to model avian-inhalation toxicity values. Additionally, an adjustment factor is utilized that accounts for the difference in lung tissue thickness and surface area between birds and mammals to deal with differences in avian and mammalian inhalation toxicity ([U.S. EPA, 2004a](#)). The model uses a conservative assumption for field active inhalation rate of a bird as three-fold greater than the rate at rest ([U.S. EPA, 1993b](#)). For additional information, please see *STIR Version 1.0 User's Guide for Pesticide Inhalation Risk* ([U.S. EPA, 2010](#)).

The mammalian-oral, mammalian-inhalation, and avian-oral empirical toxicity values which served as inputs parameters in STIR are shown in Table_Apx H-1. These toxicity values were chosen because they were the most sensitive endpoints for test species from the available data. Only mortality data were available for avian taxa for acute exposure to ethylene dibromide, so mortality health outcomes were utilized for consistency in mammalian studies. Additionally, the Mineau default scaling factor of 1.15 was accepted for use in the model. Ethylene dibromide's molecular weight of 187.9 g/mol and vapor pressure of 11.0 mmHg was used as input into the model. The author-reported average weight of Japanese quail of 0.0786 kg was used for the avian weight in the model and 0.35 kg was used as the estimated rat weight.

Table_Apx H-1. Terrestrial Avian and Mammalian Empirical Acute Toxicity Values Used as Input Parameters in STIR

Species	Exposure Route	Effect, Endpoint	Acute Toxicity Value LD/LC50	Reference
Rat	Oral	Mortality, LD50	124.4 mg/kg-bw ^a	Dow Chemical (1992a)
Rat	Inhalation	Mortality, 4-hour LC50	2.1 mg/L ^b	Rowe et al. (1952)
Japanese Quail	Oral	Mortality, LD50	130 mg/kg-bw	Westlake et al. (1981)
LC50 = concentration that is lethal to 50% of test organisms; LD50 = dose that is lethal to 50% of test organisms				
^a Represents geometric mean of male and female oral toxicity values.				
^b Calculated from author-reported data (see Appendix G).				

As shown below, Table_Apx H-2 lists the estimated terrestrial avian adjusted inhalation hazard value. STIR estimated an avian adjusted inhalation hazard value of 13.87 mg/kg-bw.

Table_Apx H-2. Terrestrial Avian and Mammalian Adjusted Inhalation Hazard Values Estimated Using STIR

Taxa	Exposure Route	Acute Predicted Toxicity Value LD50
Avian	Inhalation	13.87 mg/kg-bw
Abbreviation: LD50 = Lethal Dose (dose which is lethal to 50% of test organisms)		

For this modeling approach using STIR, there are several assumptions which may introduce uncertainty in the calculations performed in STIR. STIR assumes a vapor concentration at saturation at a temperature of 25 °C, which could differ depending on varying environmental conditions and time of application which may result in different temperatures. Furthermore, the assumption that the chemical vapor concentration is at saturation means that the vapor concentration represents the highest concentration at which the chemical can exist, thus this represents an upper-bound exposure value, providing a conservative estimate of exposure. Additionally, differences in the absorption of a vapor may alter the toxic effects. Differences in vascularization of mammalian and avian lungs may influence diffusion rates and differences in enzymatic activities in lung tissues across taxa may affect rates of chemical formation.

Appendix I ENVIRONMENTAL TERRESTRIAL STUDIES: LOW AND UNINFORMATIVE OVERALL QUALITY DETERMINATION

This appendix provides information from environmental terrestrial studies which underwent systematic review and received overall quality determinations of low or uninformative.

Studies in Vertebrates

As shown in Section 3.3.1, Table 3-6, reproductive effects were identified in bulls exposed to ethylene dibromide via diet. Four bull calves were fed 2 mg/kg-bw from 4 days of age, which increased to 4 mg/kg-bw after 12 months of age. Although statistical analysis was not conducted, Amir and Volcani (1965) found reduced sperm density and motility, and spermatozoa exhibited abnormal alterations, particularly in the outer membrane and acrosome. Recovery was observed after removal of ethylene dibromide over 10 days to 3 months. The results of this study were qualitative, and EPA assigned an overall quality determination rating of low to this study. In a separate study, Amir and Ben-David (1973) identified sperm abnormalities (*i.e.*, acrosomal defects, absent or broken tails, degenerating heads) and decreased motility in cattle exposed to 10 doses of 4 mg/kg-bw on alternating days or single intraperitoneal injections ranging from 110 to 120 mg, however no control was reported. EPA assigned an overall quality determination rating of uninformative to this study.

A study of five-week-old chickens found cellular effects following exposure to 110 mg/kg-bw ethylene dibromide administered via gavage (Table 3-10) (Broda et al., 1976). Histological examination of chick liver at 12- and 22-hours post-exposure to ethylene dibromide found a higher number of eosinophilic granulocytes in the portal region compared to control and small lesions around the central vein of the liver. This study was not used for quantitative assessment because the data presented was qualitative and statistical analysis of the results was not performed. EPA assigned this study an overall quality determination rating of low.

Studies in Invertebrates

In addition to the terrestrial invertebrate studies reported in Section 3.3.2, studies reporting acute and chronic toxicity to ethylene dibromide which were considered by EPA but received overall quality determination ratings of low or uninformative are shown below in Table_Apx I-1.

Table_Apx I-1. Terrestrial Invertebrate Toxicity of Ethylene Dibromide with Low or Uninformative Overall Quality Determinations

Test Organism	Endpoint	Hazard Value	Effect (Developmental Stage at Exposure)	Citation (Overall Quality Determination)
Skin beetle (<i>Trogoderma granarium</i>)	No statistical analysis conducted	3.0 mg/L	Mortality (larvae)	Shivanandappa and Rajendran (1987) (Low)
Rice moth (<i>Corcyra cephalonica</i>)	No statistical analysis conducted	24.66 mg/L	Mortality (eggs)	Bowry (1985a) (Uninformative)
Mite (<i>Tyrophagus longior</i>)	Endpoints could not be determined	9–15 mg/L	Mortality (embryo)	Bowley and Bell (1981) (Uninformative)
Grain mite (<i>Acarus siro</i>)				
Long hairy mite (<i>Glycyphagus destructor</i>)				

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Test Organism	Endpoint	Hazard Value	Effect (Developmental Stage at Exposure)	Citation (Overall Quality Determination)
Skin beetle (<i>Trogoderma granarium</i>)	LD50	6.1 mg/L (male), 7.9 mg/L (female)	Mortality (pupa)	Punj and Verma (1970) (Uninformative)
Sugarcane chafer beetle (<i>Cochliotus melolonthoides</i>)	LOEL	118.8 AI kg/ha	Development/Growth(larvae)	Saidi et al. (1992) (Low)
Silkworm (<i>Bombyx mori</i>)	No statistical analysis conducted	1.3 ppm	Mortality	Sugiyama (1980) (Low)
Granary weevil (<i>Sitophilus granarius</i>)	LT50 ^b	4-<8 mg/eu	Mortality	Ellis (1972b) (Uninformative)
Queensland fruit fly (<i>Bactrocera tryoni</i>)	No statistical analysis conducted	16 g/m ³	Mortality (egg to pupation)	Swaine et al. (1980) (Uninformative)
		20 g/m ³	Mortality (larva to pupa)	
Fruit fly (<i>Anastrepha suspensa</i>)	Statistical analysis not adequately conducted	8.0 g/m ³	Mortality (larvae)	von Windeguth and King (1982) (Low)
Fruit fly (<i>Anastrepha suspensa</i>)	No control group	1.4 oz/1,000 ft ³	Mortality (larvae)	Von Windeguth et al. (1984) (Uninformative)
Confused flour beetle (<i>Tribolium confusum</i>)	LD50	0.96 (0.93–0.99) ^a mg/L	Mortality (adult)	Monro et al. (1966) (Low)
Cadelle beetle (<i>Tenebroides mauritanicus</i>)	LD50	3.2 (3.0–3.4) ^a mg/L	Mortality (adult)	
Mediterranean fruit fly (<i>Ceratitis capitata</i>)	Statistical analysis not adequately conducted	8 g/m ³	Mortality (larvae)	Seo et al. (1972) (Low)
Oriental fruit fly (<i>Bactrocera dorsalis</i>)		12 g/m ³		
Fruit fly (<i>Tephritidae</i>)	LD50	1.2 g/m ³		
Fruit fly (<i>Anastrepha suspensa</i>)	LD50/ LD95	0.29 (0.26–0.32) ^a mg/L/ 0.71 (0.60–0.91) ^a mg/L	Mortality (larvae; without fruit rind)	Brueck and Burditt (1977) (Low)
	LD50/ LD95	2.92 (2.09–3.74) ^a mg/L/15.92 (10.89–30.81) ^a mg/L	Mortality (larvae; with fruit rind)	
Mediterranean fruit fly (<i>Ceratitis capitata</i>)	No statistical analysis conducted	≈5 to <10 g/m ³	Mortality (egg)	Bussel and Kamburov (1976) (Uninformative)
		≈5 to <10 g/m ³	Mortality (larvae)	
		≈5 to <10 g/m ³	Development/Growth (egg)	

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Test Organism	Endpoint	Hazard Value	Effect (Developmental Stage at Exposure)	Citation (Overall Quality Determination)
		≈5 to <10 g/m ³	Development/Growth (larvae)	
Weevil (<i>Curculio caryae</i>)	LOEL	100 kg/ha	Development/Growth (adult)	Cocke et al. (1984) (Uninformative)
Oriental fruit fly (<i>Bactrocera dorsalis</i>)	No statistical analysis conducted	8 g/m ³	Mortality (adult)	Havens et al. (1979) (Uninformative)
Rust-red flour beetle (<i>Tribolium castaneum</i>)	LD50	2.3 mg/L	Mortality (adult)	Bond (1973) (Uninformative)
Blueberry maggot (<i>Rhagoletis mendax</i>)	No statistical analysis conducted	2–4 mg/L	Mortality (larvae)	Roth and Richards (1970) (Uninformative)
Apple maggot (<i>Rhagoletis pomonella</i>)		2 mg/L	Mortality (larvae)	
Oriental fruit fly (<i>Bactrocera dorsalis</i>)	No statistical analysis conducted	2–8 g/m ³	Mortality	Seo et al. (1979) (Uninformative)
Mango tree borer (<i>Batocera rufomaculata</i>)	No statistical analysis conducted	3 mL/tree bore	Mortality (larvae)	Sharma and Tara (1986) (Uninformative)
Fruit fly (<i>Anastrepha suspensa</i>)	No data reported/No statistical analysis was conducted	2.2 mg/L	Mortality (larvae)	Weber et al. (1987) (Uninformative)
Southern root-knot nematode (<i>Meloidogyne incognita</i>)	LOEL/NOEL	110 kg/ha / 110 kg/ha	Development/Growth	Stirling (1989) (Low)
Javanese root-knot nematode (<i>Meloidogyne javanica</i>)	LOEL/NOEL	140–160 AI kg/ha / 140–160 AI kg/ha	Development/Growth	Stirling and Nikulin (1993) (Low)
Steiner's spiral nematode (<i>Helicotylenchus dishystera</i>)				
Nematode (<i>Criconemella onoensis</i>)				
Citrus root nematode (<i>Tylenchulus semipenetrans</i>)	No control group	1,000 ppm	Mortality	Evans and Thomason (1971) (Uninformative)
Javanese root-knot nematode (<i>Meloidogyne javanica</i>)				
Nematode (<i>Aphelenchus avenae</i>)				
Cereal cyst nematode (<i>Heterodera avenae</i>)	NOEL	3.7 L/ha	Development/Growth	Stanton and Fisher (1985) (Uninformative)
Nematode (<i>Heterodera glycines</i>)	NOEL	18.6 L/ha	Development/Growth	

Test Organism	Endpoint	Hazard Value	Effect (Developmental Stage at Exposure)	Citation (Overall Quality Determination)
Peanut root-knot nematode (<i>Meloidogyne arenaria</i>)	LOEL/NOEL	9.3 L/ha / 4.7 L/ha	Development/Growth	Rodríguez-Kábana et al. (1981) (Uninformative)
Nematode (<i>Heterodera glycines</i>)	NOEL	1.28 mL/m	Development/Growth	Schmitt and Nelson (1987) (Uninformative)
Lance nematode (<i>Hoplolaimus galeatus</i>)	LOEL	1.28 mL/m		
Stunt nematode (<i>Tylenchorhynchus claytoni</i>)	LOEL	1.28 mL/m		
Javanese root-knot Nematode (<i>Meloidogyne javanica</i>)	25 °C LD50/LD95	23 / 36 ppm/day	Mortality	Thomason and Mckenry (1974) (Low)
	15 °C LD50/LD95	55 / 81 ppm/day		
	5 °C LD50/LD95	213 / 290 ppm/day		
	5 °C/15 °C/25 °C LD99.9	39 / 87 / 300 ppm/day	Mortality (soil vapor phase)	
Beet cyst eelworm (<i>Heterodera schachtii</i>)	15 °C LD99.9	23 ppm/day	Mortality (soil vapor phase)	
Nematode (<i>Aphelenchus avenae</i>)	25 °C LD50/LD95	382 / 735 ppm/day	Mortality	
	25 °C LD99.9	29.5 ppm/day	Mortality (soil vapor phase)	
Southern root-knot nematode (<i>Meloidogyne incognita</i>)	No statistical analysis was conducted	10–1,000 ppm	Development/Growth	Tayal and Agarwal (1982) (Low)
Cereal cyst nematode (<i>Heterodera avenae</i>)	LOEL	3 µL/1.2 kg soil	Development/Growth	Spiegel et al. (1989) (Uninformative)
Citrus root nematode (<i>Tylenchulus semipenetrans</i>)	LOEL	3 µL/1.2 kg soil	Development/Growth	
Ring nematode (<i>Mesocriconema xenoplax</i>)	Statistical analysis not adequately conducted	42 µL/L soil	Development/Growth Respiratory	Mojtahedi and Lownsbery (1975) (Uninformative)
Nematode (<i>Caenorhabditis</i> sp.)	No statistical analysis conducted	0.0026–0.0106 M	Development/Growth	Marks (1971) (Uninformative)
Nematode (<i>Aphelenchus avenae</i>)	Statistical analysis not adequately conducted	0.0053 M		
Southern root-knot nematode (<i>Meloidogyne incognita</i>)	No statistical analysis conducted	18 mL/m ²	Development/Growth	Hussaini (1989) (Uninformative)
LD50 = dose that is lethal to 50% of test organisms; LOEL = lowest-observed-effect level; LT50 = lethal time (time when 50% of test organisms died); LD95 = dose that is lethal to 95% of test organisms; NOEL = no-observed-effect level				

Test Organism	Endpoint	Hazard Value	Effect (Developmental Stage at Exposure)	Citation (Overall Quality Determination)
^a 95% confidence interval around the LD50 as reported by the study authors.				
^b Median lethal time (time when 50% of the organisms died).				

Studies in Plants and Fungi

As shown in Section 3.3.3, Table 3-15, EPA evaluated a study which measured seed germination for barley (*Hordeum vulgare*) kernels exposed to ethylene dibromide ([Ehrenberg et al., 1974](#)). The authors reported mortality (LC50 = 1.1 mM) for seed germination exposed via direct application after a 24-hour exposure was carried out in sealed glass ampoules containing ethylene dibromide dissolved in distilled water. The study evaluated seed exposure only. Following exposure, seeds were rinsed in distilled water, sown in natural soil, and survival at maturity was observed. Chromosomal aberrations were found in metaphase in the first mitosis in root tips following treatment of the barley kernels with 1.2 mM ethylene dibromide for 24 hours. Aberrations were observed in 19.2% of cells compared to 0 in the control. EPA assigned an overall quality determination rating of low to this study.

Genotoxicity was also measured in the common onion (*Allium cepa*) exposed to ethylene dibromide hydroponically for 3 hours starting at a concentration of 0.025%, including clastogenic and aneugenic effects (disturbed meta/anaphases, chromosome stickiness, bridges, C-metaphases, laggard/vagrant chromosomes) ([Suryakumari and Vaidyanath, 1989](#)). EPA assigned an overall quality determination rating of low to this study.