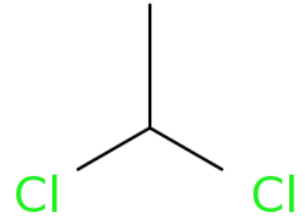
Charge to the Panel:
Peer Review of 2024 Draft Risk Evaluation for 1,1-Dichloroethane and 2024 Draft Human Health Hazard Assessment for 1,2-Dichloroethane

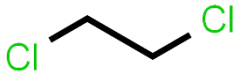
OFFICE OF POLLUTION PREVENTION AND TOXICS (OPPT)
U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA)
AUGUST 27, 2024

BACKGROUND

- 1,1-Dichloroethane is a colorless, oily liquid with a chloroform-like odor,
- Primarily used in organic chemical manufacturing
- Volatile and soluble in water
- Not imported
- Total production volume (PV) for 2015 to 2020 between 100 million and 1 billion pounds.
- A high percentage used for processing as a reactive intermediate, and a small percentage is used for commercial use as a laboratory chemical.
- EPA did not identify any consumer uses of 1,1-dichloroethane.

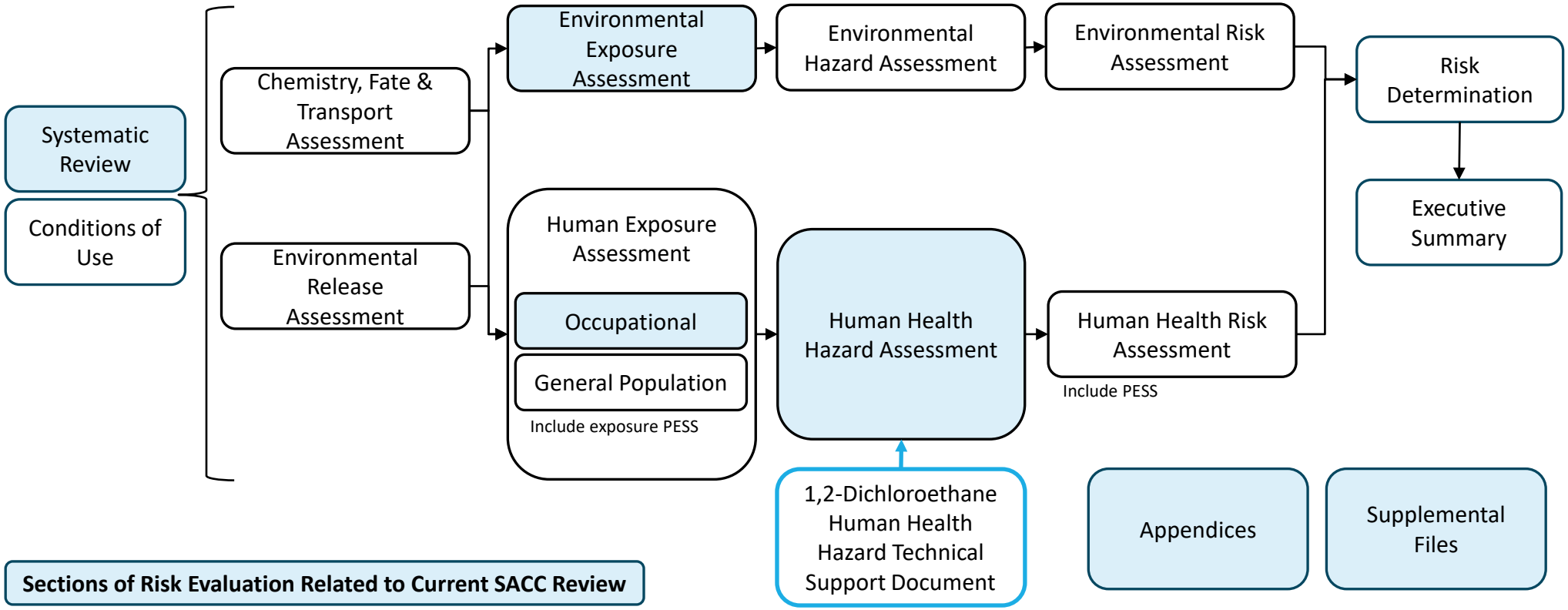


1,1-Dichloroethane
Representative Structure
CASRN: 75-34-3



1,2-Dichloroethane
Representative Structure
CASRN: 107-06-2

1,1-DICHLOROETHANE DOCUMENT MAP



1,2-DICHLOROETHANE DOCUMENT MAP

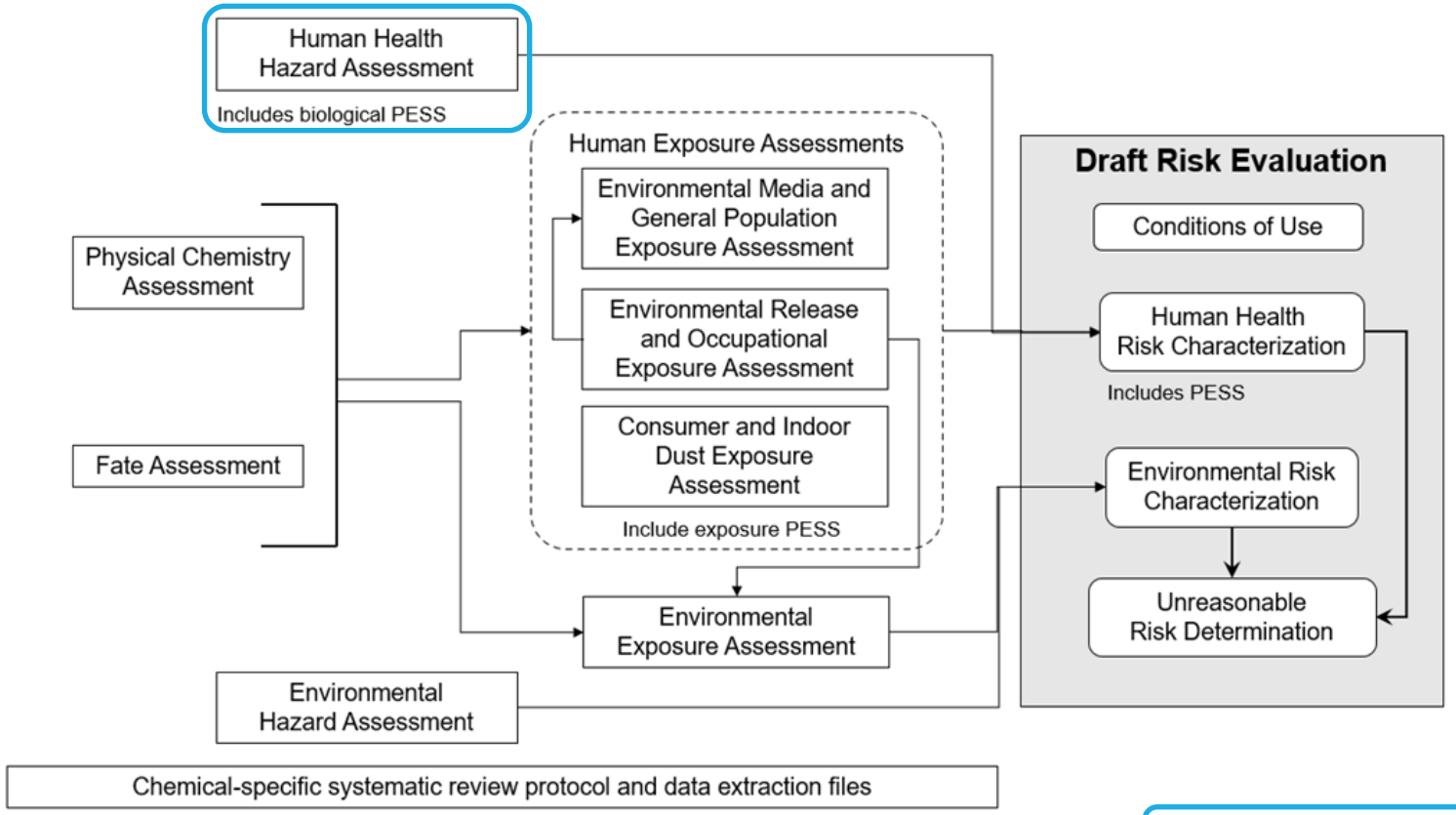


Figure 1-2. Draft 1,2-Dichloroethane Risk Evaluation

Technical Support Document (TSD) included as part of current SACC Review

Environmental Exposure: Charge Question 1

As described in Section 2 of the draft risk evaluation, 1,1-dichloroethane is an oily, high density volatile liquid with appreciable water solubility. Depending on which environmental compartment(s) receive the release, 1,1-dichloroethane is expected to partition primarily to air; however, environmental partitioning analysis shows continuous releases of 1,1-dichloroethane to water have the potential to remain in water. Additional discussion of the evidence of 1,1-dichloroethane in various media, including water is presented in Sections 1.1.2.1 and 2.2.2 of the draft risk evaluation. As described in Section 3.3.3.2.1 of the draft risk evaluation, to estimate exposures from releases to surface water for the one facility representing the manufacturing condition of use, EPA used this facility's second highest recorded release, which took place in 2016, as more representative of release conditions for this facility. The highest release from this facility located in Lake Charles, Louisiana, was associated with a storm event that is not representative of usual operating conditions and was considered an outlier in the analysis. The analysis includes consideration of the facility's operating days.

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Environmental Exposure: Charge Question 1

However, since extreme storm events do occur with regularity in the region of the country where the manufacturing facility is located (and may be expected to occur with higher frequency and intensity in the future due to climate change), EPA is seeking comments on this approach. The analysis also includes consideration of the facility's operating days.

Please comment on the use, representativeness, and relevancy of the 2016 annual release data for estimating environmental exposure in the draft risk evaluation via surface water for this facility over its operating days.

Read-Across Analysis for Environmental Assessment: Charge Question 2a

Limited empirical toxicity data are available for 1,1-dichloroethane in aquatic organisms for developing the environmental hazard values (see Appendix J.1 of the draft risk evaluation*)*. EPA selected 1,2-dichloropropane and 1,1,2-trichloroethane as analogs to read-across environmental hazard to 1,1-dichloroethane.

a) Please comment on the strengths and uncertainties related to the read-across approaches used for the selection of the analogs for aquatic organisms and environmental assessment as outlined in Appendix J.1 of the draft risk evaluation. If appropriate, please provide additional methodologies that EPA could use to identify analogs for 1,1-dichloroethane for use in the ecological risk assessment.

EPA United States Environmental Protection Agency

Read-Across Analysis for Environmental Assessment: Charge Question 2b

b) Please comment on the selection of 1,2-dichloropropane and 1,1,2-trichloroethane as analogs to support the 1,1-dichloroethane aquatic hazard database. Please also comment on the steps in the analysis, robustness, transparency of assumptions, and uncertainties of the conclusions, as well as the overall clarity with which the results are communicated.

Read-Across Analysis for Human Health Assessment: Charge Question 3a-c (Introduction)

Limited non-cancer empirical toxicity data are available for 1,1-dichloroethane for oral exposures and ECRAD did not identify available data for dermal and inhalation exposures. The Agency for Toxic Substances and Disease Registry (ATSDR) completed a *Toxicological Profile for 1,1-Dichloroethane* in August 2015 (ATSDR, 2015). EPA identified 1,2-dichloroethane as an analog for reading-across to 1,1-dichloroethane non-cancer human health using the methodology found in Section 5.2.1.3 of the draft risk evaluation.

Read-Across Analysis for Human Health Assessment: Charge Question 3a

a) Please comment on strengths and uncertainties related to the read-across approach and methodologies (Appendix J.2) used for structural similarities (Section 5.2.1.3.1), physical and chemical properties (Section 5.2.1.3.2), metabolic similarities (Section 5.2.1.3.3), and non-cancer toxicological similarities (Sections 5.2.1.3.5) in the draft risk evaluation. If appropriate, please provide additional methodologies that EPA could use to identify analogs for 1,1-dichloroethane for use in the human health risk assessment.

Read-Across Analysis for Human Health Assessment: Charge Question 3b

b) Please comment on the selection of 1,2-dichoroethane as the analog to support the 1,1-dichloroethane non-cancer hazard database. Please also comment on the steps in the analysis, robustness, transparency of assumptions and uncertainties of the conclusions, as well as the overall clarity with which the results are communicated.

Read-Across Analysis for Human Health Assessment: Charge Question 3c

c) Please include in your comments the extent to which the ATSDR (2015) Toxicological Profile for 1,1-Dichloroethane provides information relevant to support the risk evaluation under TSCA.

Human Health Assessment: Oral, Non-Cancer (Acute): Charge Question 4a

As described in Section 5.2.3 and Section 5.2.6 of the draft risk evaluation, ECRAD is proposing to rely on dose-related changes in kidney weights from Storer et al. (1984) for the acute oral point of departure (Table 5-42).

a) Please comment on the study quality, study protocol, study conduct, and data interpretation of the Storer et al. (1984) for 1,2-dichloroethane. Please include in your comments information about the appropriateness of using the findings from Storer et al. (1984) for deriving an acute oral point of departure(s) (PODs) for extrapolating non-cancer risk to 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Oral, Non-Cancer (Acute): Charge Question 4b

b) Please also include comments on the selection of the benchmark response (BMR) selected, benchmark dose (BMD) analyses models used, and those selected. Please comment, on clarity and completeness of the description of the BMD analysis.

Human Health Assessment: Oral, Non-Cancer (Acute): Charge Question 4c

c) If appropriate, please suggest alternative study or studies for use in deriving an acute oral point of departure (POD) for 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Oral, Non-Cancer (Short-Term and Chronic): Charge Questions 5a-d (Introduction)

As described in Section 5.2.3 and Section 5.2.6 of the draft risk evaluation, ECRAD is proposing to rely on the immunological effects identified in the 1,2-dichloroethane 14-day gavage study within Munson et al. (1982) for the oral non-cancer short-term and chronic points of departure (LOAEL = 4.89 mg/kg/day).

ECRAD's conclusion about the Munson et al. drinking water study (1982) differs from EPA's Office of Research and Development (ORD) 2010 Provisional Peer-Reviewed Toxicity Value (PPRTV) (U.S. EPA, 2010) and the 2022 Draft Toxicological Profile from the ATSDR (2022). For example, the ORD PPRTV (p. 33) provides a summary of Munson et al. (1982) and concluded: "The NOAEL for this study would be the highest dose tested, 189 mg/kg-day."

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Human Health Assessment: Oral, Non-Cancer (Short-Term and Chronic): Charge Questions 5a-d (Introduction)

ATSDR (2022; pp. 166–168) did not select the Munson et al. (1982) study for POD derivation and provided an explanation of why the immunological findings were not selected for sub-chronic or chronic POD derivation (ATSDR) defines a 14-day study as acute) that included scientific issues surrounding human relevance, dose selection, metabolism and unknown mechanistic understanding.

The U.S. EPA (2010) PPRTV relied on the drinking water study within the NTP (1991) study for the provisional reference dose (RfD). Similarly, ATSDR (2022) in their 2022 Toxicological Profile for 1,2-dichloroethane relied on the increase in kidney weight from the same drinking water study within NTP (1991) for their oral intermediate minimal risk level (MRL) for 1,2-dichloroethane (LOAEL = 58 mg/kg/day). ECRAD evaluated the drinking water study within Munson et al. (1982) and NTP (1991) to be “uninformative.”

Human Health Assessment: Oral, Non-Cancer (Short-Term and Chronic): Charge Question 5a

a) Please comment on the study quality of drinking water and gavage experiments in the same study, study protocol, study conduct, and data interpretation of the Munson et al. (1982) for 1,2-dichloroethane. Please include in your comments information about the appropriateness of using the findings from Munson et al. (1982) for deriving short-term and chronic POD(s) for extrapolating non-cancer risk to 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Oral, Non-Cancer (Short-Term and Chronic): Charge Question 5b

b) Please comment on the study quality, study protocol and conduct, and data interpretation of the drinking water study within NTP (1991). Please include in your comments information about the appropriateness of using the findings from the drinking water study within NTP (1991) for deriving short-term and chronic POD(s) for extrapolating non-cancer risk to 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Oral, Non-Cancer (Short-Term and Chronic): Charge Question 5c

c) Pending your comments on 4.a and 4.b and if appropriate, please suggest any alternative study or studies [*e.g.,* ATSDR (2015) Toxicological Profile for 1,1-Dichloroethane] for use in deriving oral short-term and chronic PODs for 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Oral, Non-Cancer (Short-Term and Chronic): Charge Question 5d

d) Please comment on the extent to which there is potential for uncertainty associated using short-term and sub-chronic studies for assessing chronic, long-term exposure to 1,1-dichloroethane.

Human Health Assessment: Inhalation, Non-Cancer (Acute): Charge Question 6a-c (Introduction)

As described in Section 5.2.6 of the draft risk evaluation, Appendix F in the draft human health hazard Technical Support Document (TSD) for 1,2-dichloroethane, and in *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling* (U.S. EPA, 2024c), BMD modeling was completed and used for several non-cancer points of departure inhalation (Dow Chemical, 2006). In these cases, the statistical benchmark concentration lower confidence limit (BMCL) on the concentration at the Benchmark Concentration (BMC) used as the POD is lower than the No Observed Adverse Effect Levels (NOAELs)of each of the studies (See Table 5-43; Appendix F of the draft TSD). The U.S. EPA (2012) Benchmark Dose Technical Guidance states (p. 20): "extrapolation sufficiently below the observable range may be too uncertain to reliably estimate the (BMCs/BMCLs) for the selected BMR (e.g., when all the dosed groups have near-maximal responses). In such cases, BMD modeling is not recommended and obtaining more data or using the NOAEL/Lowest Observed Adverse Effect Level (LOAEL) approach, while recognizing the inabilities of that approach to resolve the data limitations, may be warranted."

Human Health Assessment: Inhalation, Non-Cancer (Acute): Charge Question 6a

a) Please comment on the study quality, study protocol, study conduct, and data interpretation of the Dow Chemical (2006) for 1,2-dichloroethane. Please include in your comments information about the appropriateness of using the findings from Dow Chemical (2006) for deriving an acute inhalation point of departure(s) for extrapolating non-cancer risk to 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Inhalation, Non-Cancer (Acute): Charge Question 6b

b) Please also include comments on the selection of the BMR selected, BMC analyses used, and the clarity and completeness of the description of the BMC analysis.

Human Health Assessment: Inhalation, Non-Cancer (Acute): Charge Question 6c

c) If appropriate, please suggest alternative study or studies for use in deriving an acute inhalation POD for 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Inhalation, Non-Cancer (Short-Term and Chronic): Charge Question 7a

As described in Section 5.2.6 of the draft risk evaluation, Appendix F in the draft human health hazard TSD for 1,2-dichloroethane, and in *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling* (U.S. EPA, 2024c), BMD modeling was completed and used for short-term and chronic inhalation (Zhang et al., 2017) exposure durations (See Table 5-45; Appendix F of the draft TSD).

a) Please comment on the study quality, study protocol, study conduct, and data interpretation of the Zhang et al. (2017) for 1,2-dichloroethane. Please include in your comments information about the appropriateness of using the findings from Zhang et al. (2017) for deriving short-term and chronic inhalation PODs for extrapolating non-cancer risk to 1,1-dichloroethane and 1,2-dichloroethane.

Human Health Assessment: Inhalation, Non-Cancer (Short-Term and Chronic): Charge Question 7b

b) Please also include comments on the selection of the BMR selected, BMC analyses used, and the clarity and completeness of the description of the BMC analysis.

Human Health Assessment: Inhalation, Non-Cancer (Short-Term and Chronic): Charge Question 7c

c) If appropriate, please suggest alternative study or studies [e.g., ATSDR (2015) ATSDR Toxicological Profile for 1,1-Dichloroethane] for use in deriving short-term and chronic inhalation points of departure for 1,1-dichloroethane and 1,2-dichloroethane.

Dermal Absorption: Interpretation and Use of the New *in vitro* Study: Charge Question 8

As described in Section 5.1.1.1.5, of the draft risk evaluation, new data are available for an *in vitro* dermal absorption study using frozen human skin for conducted in accordance with (OECD TG) 428 and conditions of use information. The *1,1-Dichloroethane Test Order – Rates of Penetration through Human Skin Using a Flow Through in vitro System Study Report* (Labcorp Early Development, 2024), the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information: in vitro Dermal Absorption Study Analysis* (U.S. EPA, 2024e), and *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information: in vitro Dermal Absorption Calculation Sheet* (U.S. EPA, 2024f) are available for review. As described in the study analysis, ECRAD has proposed to use a dermal absorption factor 0.3% in the oral to dermal route to route extrapolation. In the neat COU exposure portion of the *in vitro* study, a total of 0.13% was recovered in the receptor fluid over 24 hours with an overall recovery of 58.42%. For the draft risk evaluation, ECRAD adjusted the dermal absorption factor to 0.3% to develop an upper bound value to account for mass recovery. In the other non-COU components of the study (*e.g.,* diluted in isopropyl myristate [IPM] and 1,2-dichloroethane at various concentrations) where the recovery was >80% the dermal absorption ranged from <0.01 to 0.06%.

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Dermal Absorption: Interpretation and Use of the New *in vitro* Study: Charge Question 8

The OECD 2022 *Guidance Notes On Dermal Absorption Studies* (OECD, 2022) states the following: “If recovery is <95% but a robust explanation demonstrating the missing material would not have been or is very unlikely to have been absorbed, then the inclusion of the missing material might not be required.” Similarly, the European Food Safety Authority *Guidance on Dermal Absorption* (EFSA, 2017) states that (p. 13) “Losses that are considered to be from non-absorbed material will have no impact on the results.” In the case of 1,1-dichloroethane, loss is expected to be due to volatility. The study authors did not conduct the recovery calculations (which were performed by ECRAD) “The missing radioactivity was most likely due to loss of volatile test item at sampling. It is therefore considered that the losses would be associated with the non-absorbed fraction and no correction for the losses has been made to the absorption value (p. 31).”

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Dermal Absorption: Interpretation and Use of the New *in vitro* Study: Charge Question 8

With regard to overall recovery, EFSA (2017) (p. 13) states that "If no clear conclusion can be drawn, only values from high recovery samples should be used to derive the absorption and replicates with low recoveries should be excluded entirely." OECD (2022) (p. 39) provide similar guidance. In the case of the 1,1-dichloroethane study where the recovery was >80%, the non-COU dermal absorption ranged from <0.01 to 0.06%.

a) Please comment on the selection and derivation of ECRAD's 0.3% dermal absorption factor and its appropriateness for developing the dermal exposure and risk assessments for 1,1-dichloroethane, considering the range of replicate values for conditions of use testing, % mass recovery and data variability. If appropriate, please provide comments on an alternative dermal absorption factor.

Cancer Assessment: Charge Question 9a-g

The available rodent cancer studies for 1,1-dichloroethane have been determined to be inappropriate for deriving quantitative cancer risk estimates. EPA identified 1,2-dichloroethane as a proposed analog for reading-across to 1,1-dichloroethane based on the methodology found in Section 5.2.1.3 of the draft risk evaluation. The 1,1-dichloroethane draft risk evaluation includes a review of the cancer hazard data gaps identified for 1,1-dichloroethane (Section 5.2.1.2.2) and outlines cancer hazard identification and evidence integration for 1,1-dichloroethane and 1,2-dichloroethane (Section 5.2.5). Additional relevant information on 1,2-dichloroethane can be found in the draft TSD. In the fall of 2023, ECRAD conducted an internal peer review of the available rodent cancer studies available for 1,1-dichloroethane and 1,2-dichloroethane by agency experts outside OPPT. While the internal peer reviewers and the ECRAD assessment team came to the same conclusion about the quality and utility of most of the rodent cancer studies, there was a differing scientific opinion (DSO) about the NTP (1978) mouse study with 1,2-dichloroethane. Three documents are available for review by the SACC related to this internal peer review within *EPA Peer Review of Carcinogenicity Studies for 1,1-Dichloroethane and 1,2-Dichloroethane* (2024) available on EPA-HQ-OPPT-2024-0114: the original charge to the independent EPA reviewers, a review memo developed by those internal peer reviewers, and a response developed by the ECRAD assessment team.

Cancer Assessment: Charge Question 9a

a) Please comment on strengths and uncertainties related to the read-across methodology used for selection of the analog for the cancer assessment as outlined in Section 5.2.1.3 and Appendix J.2. of the draft risk evaluation. If appropriate, please provide additional methodologies which EPA could use to identify analogs for 1,1-dichloroethane.

Cancer Assessment: Charge Question 9b

b) Please comment on the selection of 1,2-dichoroethane as the analog to support the 1,1-dichloroethane cancer hazard database. Please also comment on the steps in the analysis, robustness, and uncertainties of the conclusions, and the clarity with which they are communicated.

Cancer Assessment: Charge Question 9c

c) Please comment on EPA's preliminary conclusion that the NTP (1978) mouse and rat cancer studies for 1,1-dichloroethane are not appropriate for use to quantitative risk assessment. Please also comment on the extent to which the 1,1-dichloroethane rat and mouse studies are or are not useful qualitatively in hazard identification and characterization.

Cancer Assessment: Charge Question 9d

d) Please comment on the strengths and uncertainties and use of the Nagano et al. (2006) study with 1,2-dichloroethane to develop an Inhalation Unit Risk for inhalation cancer assessment of 1,1-dichloroethane and 1,2-dichloroethane.

Cancer Assessment: Charge Question 9e

e) Please comment on EPA's preliminary conclusion that the NTP rat cancer study for 1,2-dichloroethane is not appropriate for use to quantitative risk assessment. Please also comment on the extent to which the 1,2-dichloroethane rat study is or is not useful qualitatively in hazard identification and characterization.

Cancer Assessment: Charge Question 9f

f) Although internal peer reviewers recommended against using the NTP (1978) mouse cancer study to develop quantitative risk estimates. ECRAD has proposed to use it in the draft risk evaluation. Please comment on the quality, study protocol, study conduct, and data interpretation of the NTP (1978) mouse cancer study for 1,2-dichloroethane. Please include in your comments on the extent to which the 1,2-dichloroethane NTP (1978) mouse study is or is not useful qualitatively and/or quantitatively in hazard identification, dose-response, and characterization.

Cancer Assessment: Charge Question 9g

g) Pending your comments on 9.c, 9.e, and 9.f and if the panel determines that NTP (1978) rat and mouse cancer studies are not appropriate for use in human health risk assessment, please provide additional comment on the extent to which the oral cancer risk can be and/or needs to be assessed for in the risk evaluations for 1,1-dichloroethane and 1,2-dichloroethane.

Occupational Exposure: Charge Question 10a

a) As described in Section 5.1.1.1.2 of the draft risk evaluation and in the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Environmental Releases and Occupational Exposure Assessment* (U.S. EPA, 2024d), EPA obtained primary inhalation exposure monitoring data for 1,1-dichloroethane for the occupational exposure scenario (OES) of Manufacture through a Test Order. EPA prioritized the use of these occupational inhalation monitoring data for the intended condition of use and other appropriate exposure scenarios (*e.g.,* Processing as a Reactant and Laboratory Use OESs). Please comment on the study protocol and conduct of the study. Please also comment on ECRAD's interpretation, use, and representativeness of the manufacturing inhalation empirical exposure monitoring data received through the OPPT Test Order as applied to other exposure scenarios.

Occupational Exposure: Charge Question 10b

b) As described in Section 5.1.1.1.3 of the draft risk evaluation and in the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Environmental Releases and Occupational Exposure Assessment* (U.S. EPA, 2024d), EPA used surrogate chlorinated solvent inhalation monitoring data to estimate occupational exposures for the General waste handling, treatment, and disposal OES where there were a lack of inhalation monitoring data. EPA also applied a vapor pressure correction factor to account for vapor pressure differences between 1,1-dichloroethane and the surrogate chemicals methylene chloride and 1,2-dichloroethane. Please comment on the appropriateness and representativeness of the surrogate data to estimate occupational exposures.

Occupational Exposure: Charge Question 10c

c) As described in Section 5.1.1.1.5 of the draft risk evaluation and in the Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Environmental Releases and Occupational Exposure Assessment (U.S. EPA, 2024d), EPA used the Dermal Exposure to Volatile Liquids Model (DEVL) and applied the model to all OESs; however, values for fraction absorbed and weight fraction of the chemical can differ among OESs (fraction absorbed estimate is 0.6%). In particular, a key parameter in the model is the dermal loading on the skin per exposure event. The values that EPA currently uses are based on experimental studies done with oils of different viscosities (U.S. EPA, 1992).

Occupational Exposure: Charge Question 10c.i

i. Please comment on the appropriateness of using a dermal loading value based on generic scenario of oils for risk assessment of 1,1-dichloroethane which PubChem classifies as a high-density oily liquid. If appropriate, please provide any information on dermal loading values that may be more applicable for 1,1-dichloroethane in the conditions of use assessed in this draft risk evaluation.

Occupational Exposure: Charge Question 10c.ii

ii. Please also provide comment on additional available data, models and/or references on dermal exposure assessment, dermal loading, and/or dermal fraction absorbed, which could be used in the future to improve and refine the dermal exposure potential in risk evaluation of other chemicals and across various conditions of use.