OVERVIEW OF THE 2024 DRAFT 1,1-DICHLOROETHANE RISK EVALUATION & DRAFT 1,2-DICHLOROETHANE HUMAN HEALTH HAZARD TECHNICAL SUPPORT DOCUMENT

Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency

INTRODUCTION TO TSCA

Seema Schappelle, Ph.D.; OCSPP/OPPT/ECRAD/RAB4

ACKNOWLEDGEMENTS

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PRESENTATION OUTLINE

Presenter	Presentation Section	Charge Question
Seema Schappelle	Introduction to TSCA	N/A
Janet Burris	1,1- and 1,2-Dichloroethane Background	
Nerija Orentas	1,1-Dichloroethane Environmental Exposure	1
Jennifer Brennan	1,1-Dichloroethane Environmental Hazard Read-Across Approach	2a, 2b
Janet Burris/ William Irwin	Introduction to Human Health Hazard Assessment 1,1-Dichloroethane Human Health Hazard Read-Across Approach	3a, 3b, 3c, 9a, 9b
Ali Shohatee	1,1- and 1,2-Dichloroethane Non-Cancer Oral Human Health Hazard Assessment	4a, 4b, 4c, 5a, 5b, 5c, 5d, 11, 12
Katherine Anitole	1,1- and 1,2-Dichloroethane Non-Cancer Inhalation Human Health Hazard Assessment	6a, 6b, 6c, 7a, 7b, 7c
Katherine Anitole	1,1- and 1,2-Dichloroethane Cancer Assessment	9c, 9d, 9e, 9f, 9g, 12
William Irwin	Dermal Absorption: Interpretation and Use of the *In Vitro* Study	8
Greg Macek	Occupational Exposure	10a, 10b, 10c

REGULATORY CONTEXT

TSCA Section 6(b) requires EPA to conduct risk evaluations to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to potentially exposed or susceptible subpopulation(s) (PESS) identified by EPA as relevant to the risk evaluation under the conditions of use (COU)

EPA REQUIREMENTS UNDER TSCA

- Evaluate existing chemicals with clear and enforceable deadlines
- Must use **best available science** using **reasonably available information** and make decisions based on the **weight of scientific evidence**
- Develop a risk-based chemical assessment without consideration of costs or other non-risk factors
- Consider risks to potentially exposed or susceptible subpopulations (PESS) determined to be relevant to the evaluation
- Address unreasonable risks identified in risk evaluation

TSCA RISK EVALUATIONS OVERVIEW

- The risk evaluation considers exposure and hazard to determine whether a chemical substance presents an unreasonable risk to human health or the environment under the conditions of use (COUs)
- The risk evaluation is the **primary science support document** the Agency uses if it is necessary to issue regulations to address unreasonable risks identified as part of the evaluation
- To the extent the Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science… **[Section 26(h)]**

SOME KEY TERMS FROM TSCA

- EPA will document that the risk evaluation is consistent with the **best available science** and based on the **weight of scientific evidence**. In determining best available science, EPA shall consider as applicable:

  (i) The extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information

  (ii) The extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture

  (iii) The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented

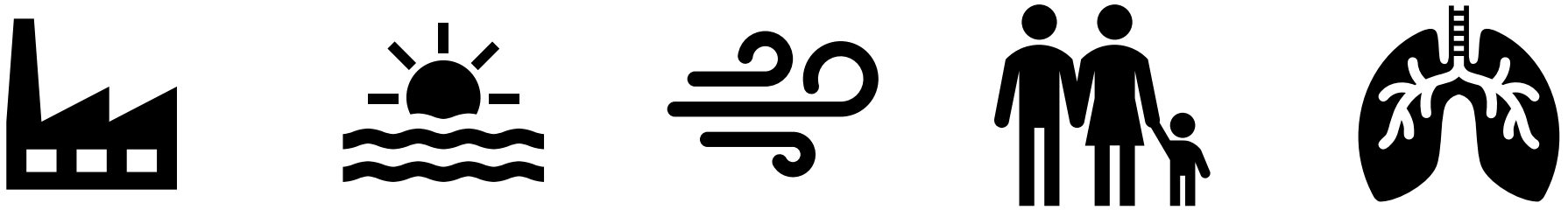
  (iv) The extent to which the variability and uncertainty in the information—or in the procedures, measures, methods, protocols, methodologies, or models—are evaluated and characterized

  (v) The extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies or models

WEIGHT OF SCIENTIFIC EVIDENCE

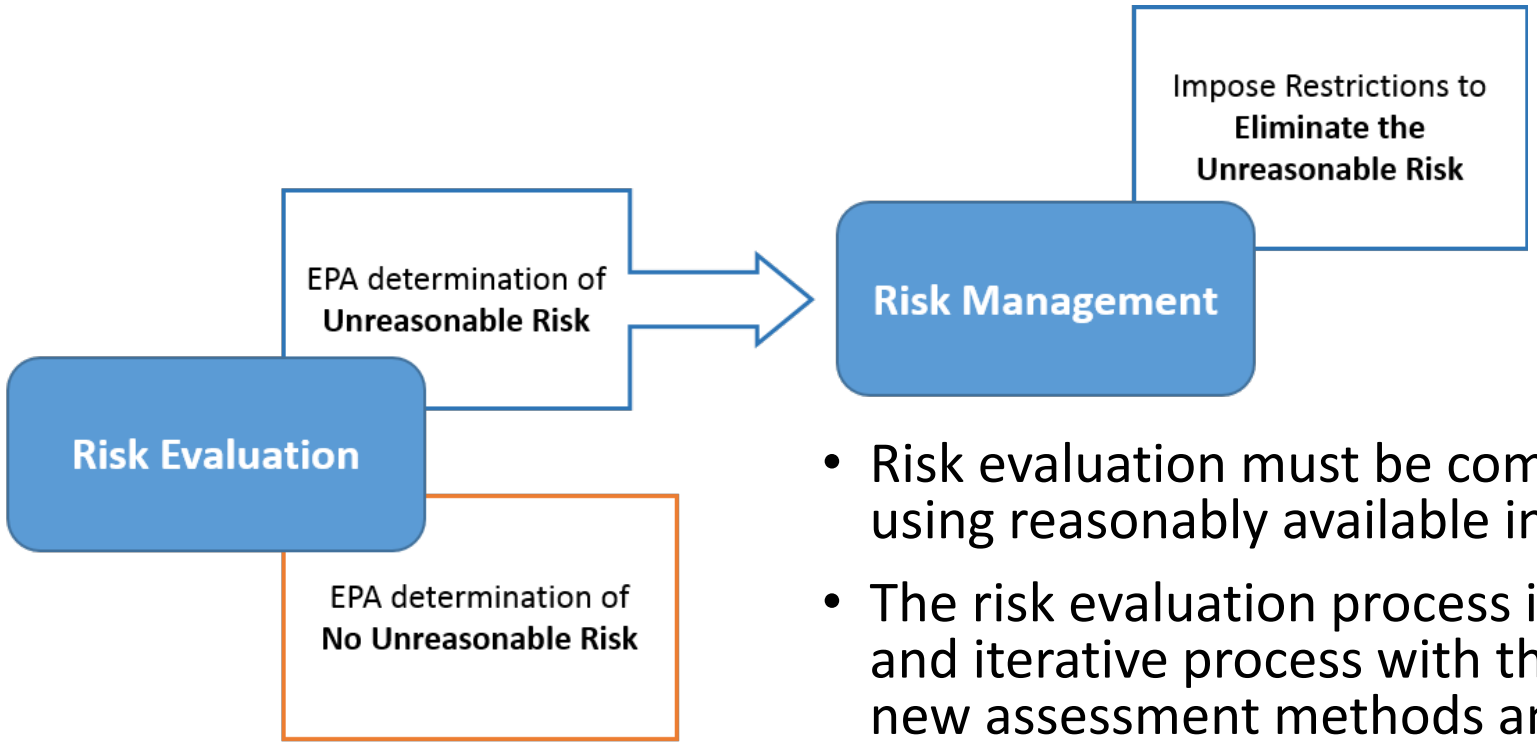
- To meet the law's requirement to base decisions in TSCA risk evaluations on the **weight of scientific evidence (WOSE)**, EPA relies on established Agency guidance documents which provide consistency and formality to a process that looks to integrate multiple and often heterogenic lines of evidence
- The WOSE assessment is based on the strengths, limitations, and interpretation of data available, information across multiples lines of evidence and how these different lines of evidence may or may not fit together when drawing conclusions
- The WOSE assessment examines multiple lines of evidence from scientifically relevant published or publicly available studies in the peer reviewed scientific journals, studies conducted in accordance with OECD or EPA guidelines, gray literature, and/or any other studies, scientific information, or lines of evidence that are of sufficient quality, relevance, and reliability, are evaluated across studies and endpoints into an overall assessment
- EPA has provided a summary WOSE narrative or characterization to accompany a detailed analysis to transparently describe the conclusion(s), as well as explain the selection of the studies or effects used as the main lines of evidence and relevant basis for conclusions. EPA encourages differing scientific opinions or DSOs as a necessary part of the scientific process (https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions)

TSCA RISK ASSESSMENT CONSIDERATIONS



Source	Pathway	Media	Humans and Environment	Routes
• Articles and Products • Industrial Releases to Air, Land and Water	• Ambient Air • Land • Water • Indoor Air	• Air • Biosolids • Groundwater • Sediment • Soil • Surface Water • Food chain	• Environmental Organisms • Consumers • General Population • Workers	• Oral • Dermal • Inhalation • Ingestion

TSCA RISK EVALUATIONS FOR RISK MANAGEMENT



- Risk evaluation must be completed in 3 years using reasonably available information
- The risk evaluation process is an incremental and iterative process with the development of new assessment methods and approaches over time

SCIENCE QUALITY AND TRANSPARENCY

Internal

- Peer Review
  - Technical Teams
  - Senior Scientists
  - Management
- Collaboration
  - Office of Pesticide Programs (OPP)
  - Office of Research and Development (ORD)
  - Office of Water (OW)
  - Office of Air and Radiation (OAR)
  - Science Policy Council (OCSPP)

External

- Public Comment
- Peer Review
  - Science Advisory Committee on Chemicals (SACC)
  - Human Studies Review Board (HSRB)
  - National Academies of Sciences, Engineering, and Medicine (NASEM)
  - Journal publications
  - Contract review
  - Letter peer review
- Stakeholder Engagements (examples)
  - TSCA Occupational Exposure Workshops (2023/2024)

FEEDBACK WILL HELP EPA DECIDE…

When and how EPA will use different approaches to estimate potential exposure to chemicals

How to assist the Agency in quickly identifying readily available data best suited for use in risk evaluations

How to define conditions when specific approaches can or should be applied to risk evaluation

Future steps in method development, and utilization in ongoing and future risk evaluations

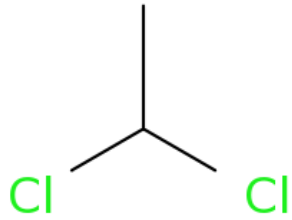
Thank you for your attention

Overview of the 2024 Draft Risk Evaluation for 1,1-Dichloroethane and Draft Human Health Hazard Assessment for 1,2-Dichloroethane and Questions

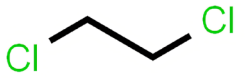
Janet Burris, MSPH; OCSPP/OPPT/ECRAD/RAB4

BACKGROUND

- 1,1-Dichloroethane is a colorless, oily liquid with a chloroform-like odor, which is primarily used in organic chemical manufacturing
- Volatile and soluble in water
- Not imported and the reported total production volume (PV) for 2015 to 2020 is 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 is regulated under:
  - Resource Conservation and Recovery Act
  - Clean Water Act
  - Clean Air Act (as Hazardous Air Pollutant)
  - Determination under Safe Drinking Water Act: **not** to regulate 1,1-dichloroethane

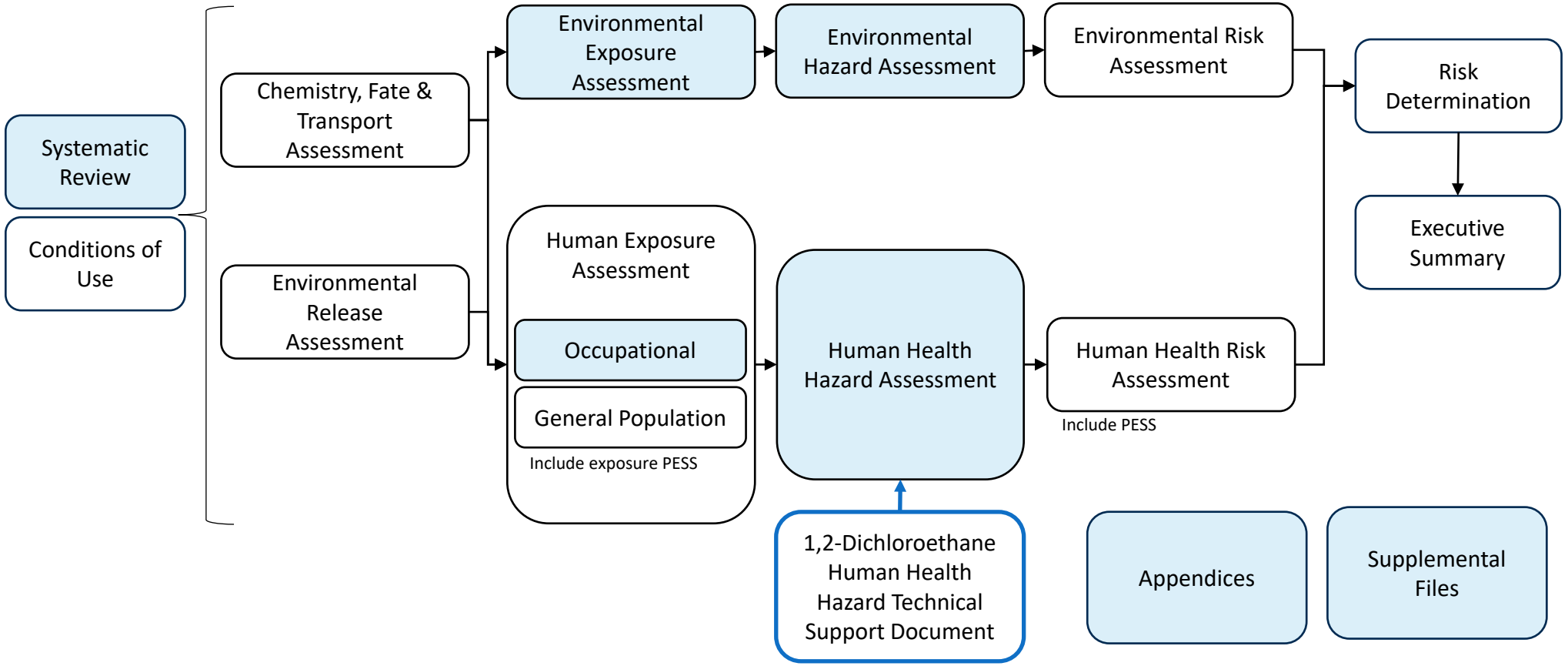


1,1-Dichloroethane
Representative Structure
CASRN: 75-34-3



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

1,1-DICHLOROETHANE DOCUMENT MAP



1,2-DICHLOROETHANE DOCUMENT MAP

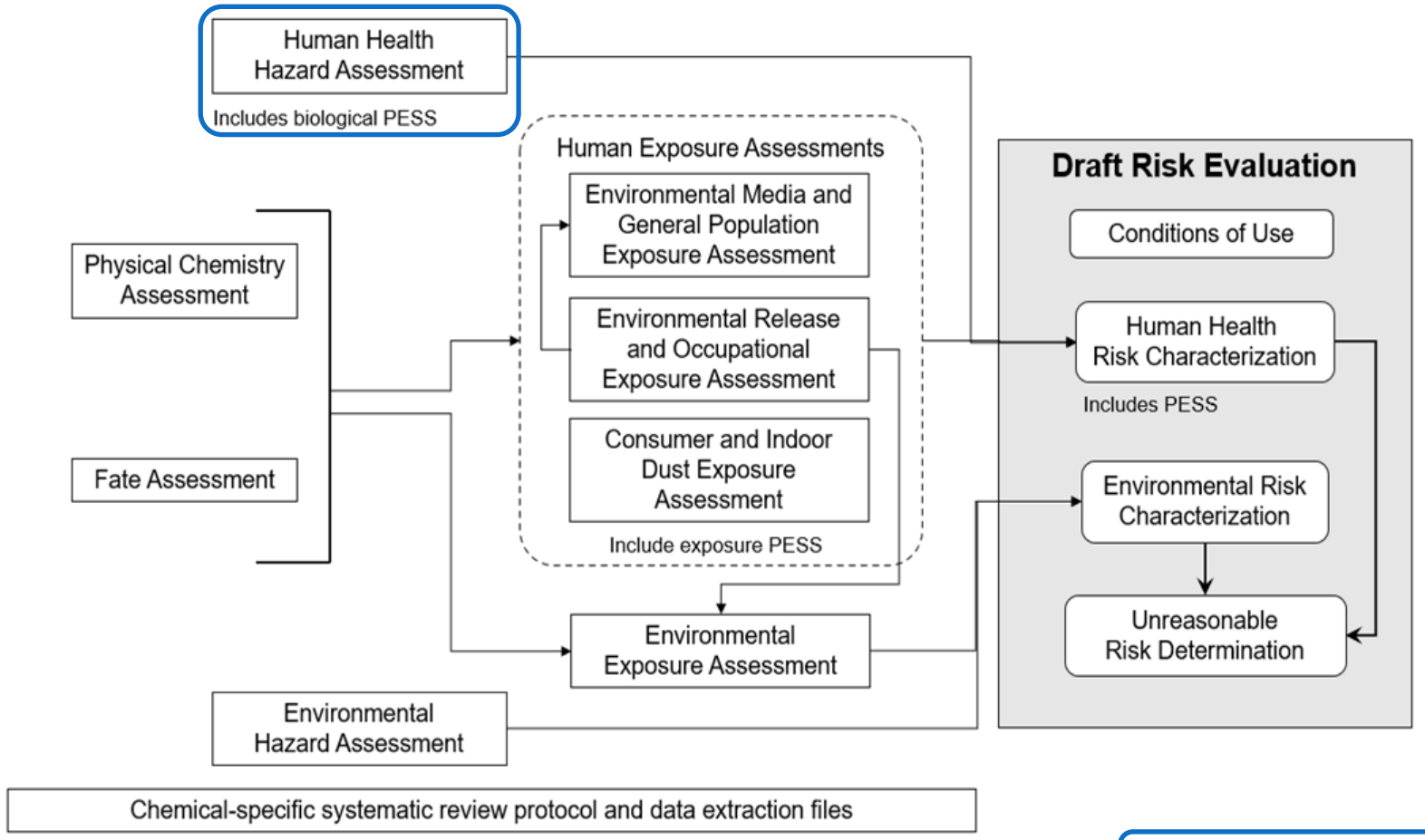


Figure 1-2. Draft 1,2-Dichloroethane Risk Evaluation

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

1,1-DICHLOROETHANE RISK EVALUATION

- EPA seeks early feedback on approaches used through this SACC review of the 1,2-Dichloroethane Human Health Hazard Assessment
- EPA seeks input on both documents based on the charge questions

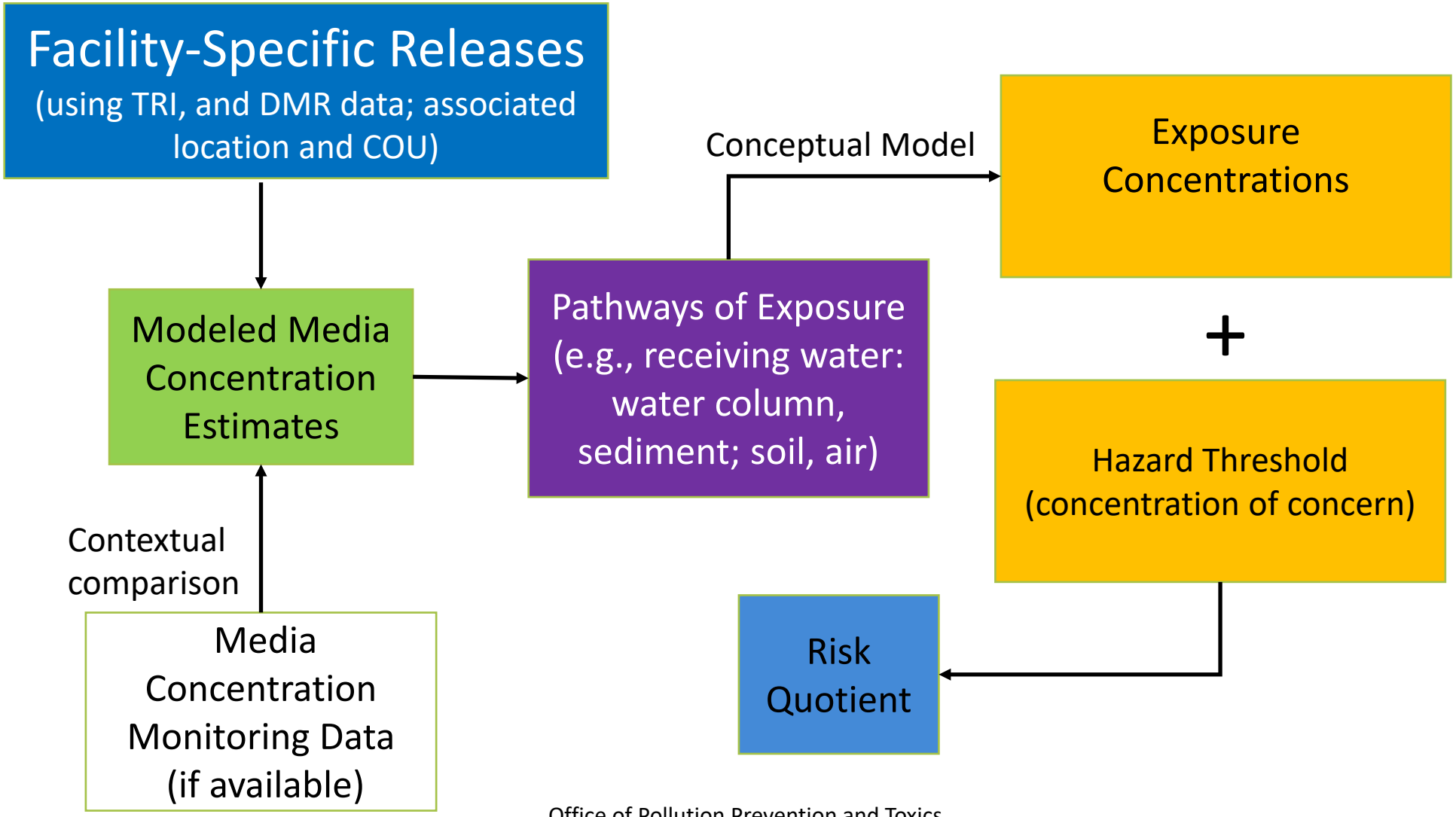
Thank you for your attention

1,1-DICHLOROETHANE ENVIRONMENTAL EXPOSURE

Nerija Orentas, Ph.D.; OCSPP/OPPT/ECRAD/RAB4

Charge Question	Location in 1,1-Dichloroethane Draft Risk Evaluation
1	Section 3.3.3.2.1

ENVIRONMENTAL EXPOSURE



ENVIRONMENTAL EXPOSURE

Charge Q 1

- Facility releases are reported via Discharge Monitoring Reports (DMR) per National Pollutant Discharge Elimination System (NPDES) requirements
- Receiving water was identified through permit information and flow parameters from National Hydrography Dataset Plus (NHDPlus)
- Highest release across five years (2015-2020) was used to model receiving water column and sediment concentrations and corresponding low flow – conservative estimate
- One exception for Louisiana Westlake facility: instead of highest release in 2020, second highest in 2016 was used

ENVIRONMENTAL EXPOSURE

Charge Q 1

			Event #1:	Event #2	Event #3	Event #4		
			12/3-4/2016	8/13-14/2016	4/30/2016	5/1/2016		
301 Organics		Flow:	1042 GPM	1115 GPM	42 GPM	2916 GPM	301 Totals (lbs/yr)	
1,1-DCA	**75-34-3**		0.55	0	0.02	4.69	**5.26**	

				Power Failure	**200 yr Rain**			
			Event #1:	Event #2	Event #3	Event #4		
			3/29/2017	4/28/2017	5/3/2017	6/21/2017		
301 Organics		Flow:	7 GPM	76 GPM	2764 GPM	208 GPM	301 Totals (lbs/yr)	
1,1-DCA	**75-34-3**		0.1	0.2	2	0	**2.3**	

			Event #1:	Event #2	Event #3	Event #4		
			10/9/2018	10/15/2018	10/16/2018	10/31/2018		
301 Organics		Flow:	1.6 GPM	59 GPM	144 GPM	2 GPM	301 Totals (lbs/yr)	
1,1-DCA	**75-34-3**		0.1	1	2	0	**3.1**	

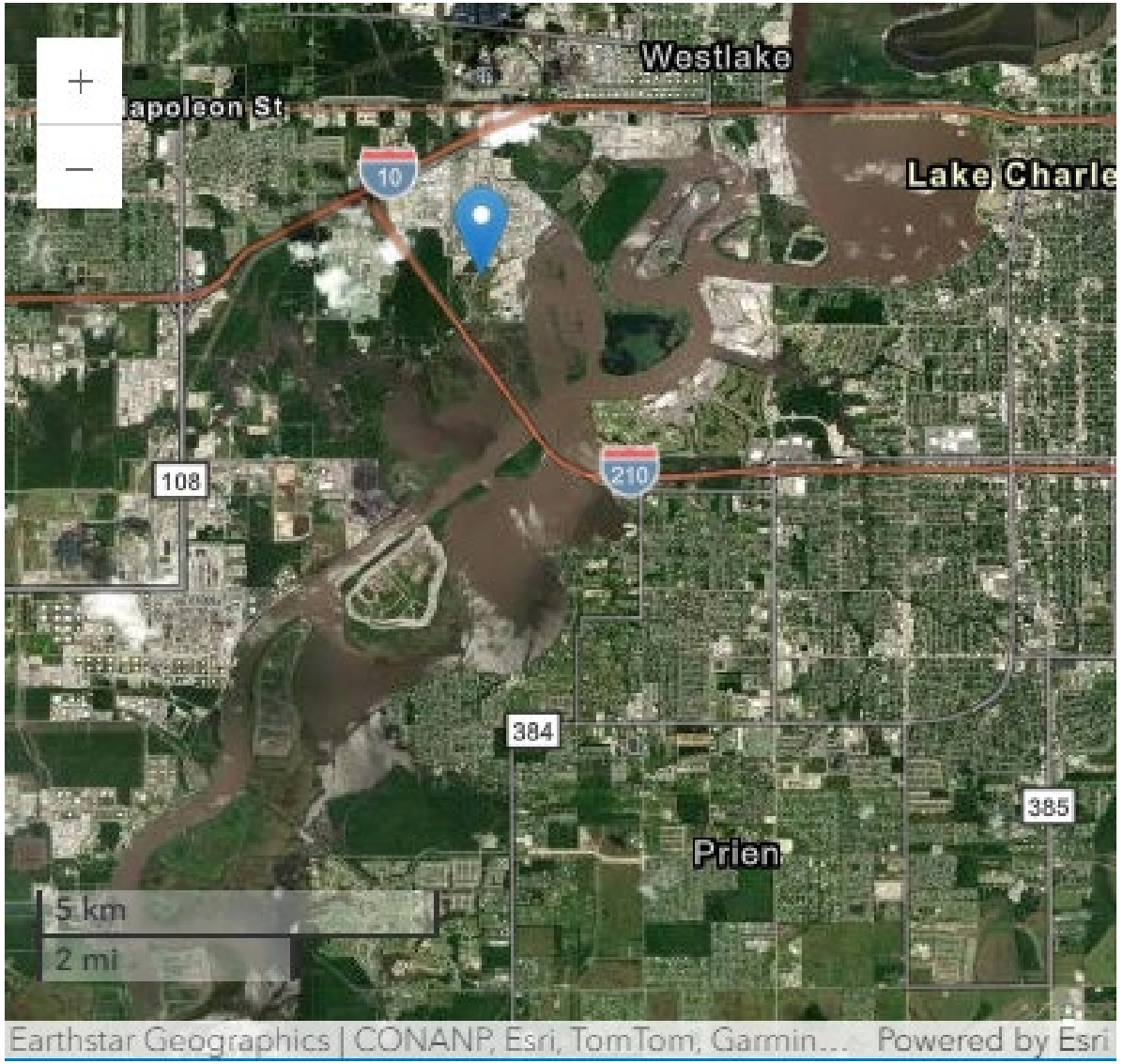
			Event #1:	Event #2	Event #3	Event #4		
			4/4/2019	8/13-14/2016				
301 Organics		Flow:	333 GPM	729 GPM			301 Totals (lbs/yr)	
1,1-DCA	**75-34-3**		0.4	0	0	0	0.4	

				Post Hurricane Laura		**Hurricane Delta**			
			Event #1:	Event #2	Event #3	Event #4	Event #5		
			4/29/2020	9/21-25/2020	9/28/2020	10/9/2020	10/20/2020		
301 Organics		Flow:	7 GPM	1651 GPM	44 GPM	2640 GPM	17 GPM	301 Totals (lbs/yr)	
1,1-DCA	**75-34-3**		0	987	16.4	35	0	**1038.4**	

			Winter Storm Uri					
			Event #1:	Event #2	Event #3	Event #4		
			2/16-17/2021	5/19/2021				
301 Organics		Flow:	2900 GPM	430 GPM	42 GPM	2916 GPM	301 Totals (lbs/yr)	
1,1-DCA	**75-34-3**		171	4	0	0	**175**	

ENVIRONMENTAL EXPOSURE

Charge Q 1



Thank you for your attention

1,1-DICHLOROETHANE ENVIRONMENTAL HAZARD READ-ACROSS APPROACH

Jennifer Brennan, Ph.D.; OCSPP/OPPT/ECRAD/RAB6

Charge Question	Location in 1,1-Dichloroethane Draft Risk Evaluation
2a, 2b	Appendix J.1

1,1-DICHLOROETHANE ENVIRONMENTAL HAZARD READ-ACROSS APPROACH

Charge Q 2a-b

- Few empirical data were reasonably available on aquatic species for 1,1-dichloroethane
  - Initial aquatic dataset consisted of a 1-hour respiratory study in fish
  - Japanese National Institute of Technology and Evaluation (NITE) studies identified during development of draft risk evaluation provided additional 1,1-dichloroethane aquatic hazard data but were not comprehensive across aquatic taxa and exposure durations
- EPA used 1,2-dichloropropane and 1,1,2-trichloroethane data to supplement the aquatic and benthic hazard characterization for 1,1-dichloroethane

USE OF ANALOGS TO SUPPLEMENTAL 1,1-DICHLOROETHANE ENVIRONMENTAL HAZARD

Charge Q 2a-b

- 1,2-Dichloropropane was selected as an analog for read-across of aquatic environmental hazard data (fish, mysid, algae) to supplement the 1,1-dichloroethane aquatic environmental hazard
  - 1,1-dichloroethane and analog 1,2-dichloropropane acute aquatic vertebrate and invertebrate hazard data were combined to generate Web-ICE predictions for additional aquatic taxa representation (*e.g.*, benthic invertebrates and amphibians)
- No chronic benthic hazard data were reasonably available for 1,1-dichloroethane or its primary analog, 1,2-dichloropropane, therefore, 1,1,2-trichloroethane was selected as an analog for read-across of chronic benthic environmental hazard to 1,1-dichloroethane

USE OF ANALOGS FOR ENVIRONMENTAL HAZARD THRESHOLDS IN 1,1-DICHLOROETHANE DRAFT RE

Charge Q 2a-b

Environmental Toxicity	Analog	COC (ppb) or Hazard Threshold	Assessment Medium
Acute aquatic exposure: Lower 95% CI of HC05 from SSD	1,1-dichloroethane and **1,2-dichloropropane**	7,898	Water column
Acute benthic exposure: Lower 95% CI of HC05 from SSD	1,1-dichloroethane and **1,2-dichloropropane**	7,898	Benthic pore water
Chronic aquatic exposure: based on aquatic invertebrate ChV	1,1-dichloroethane	**93**	Water column
Chronic benthic exposure: based on benthic invertebrate EC10	**1,1,2-trichloroethane**	6,800	Benthic pore water
Chronic benthic exposure: based on benthic invertebrate ChV	**1,1,2-trichloroethane**	2,900	Sediment
Aquatic plant exposure: based on algae ChV	**1,2-dichloropropane**	**1,000**	Water column
Mammal: TRV	1,1-dichloroethane	1,189 mg/kg-bw/day	Dietary (Trophic Transfer)
Avian	NA	No data	No data
Soil invertebrate	NA	No data	No data
Terrestrial plant (*Populus x canadensis*): based on EC50	1,1-dichloroethane	802 mg/L	Soil porewater

Table 4-6 from the 1,1-Dichloroethane Draft Risk Evaluation

OVERVIEW OF ENVIRONMENTAL HAZARD ANALOG SELECTION

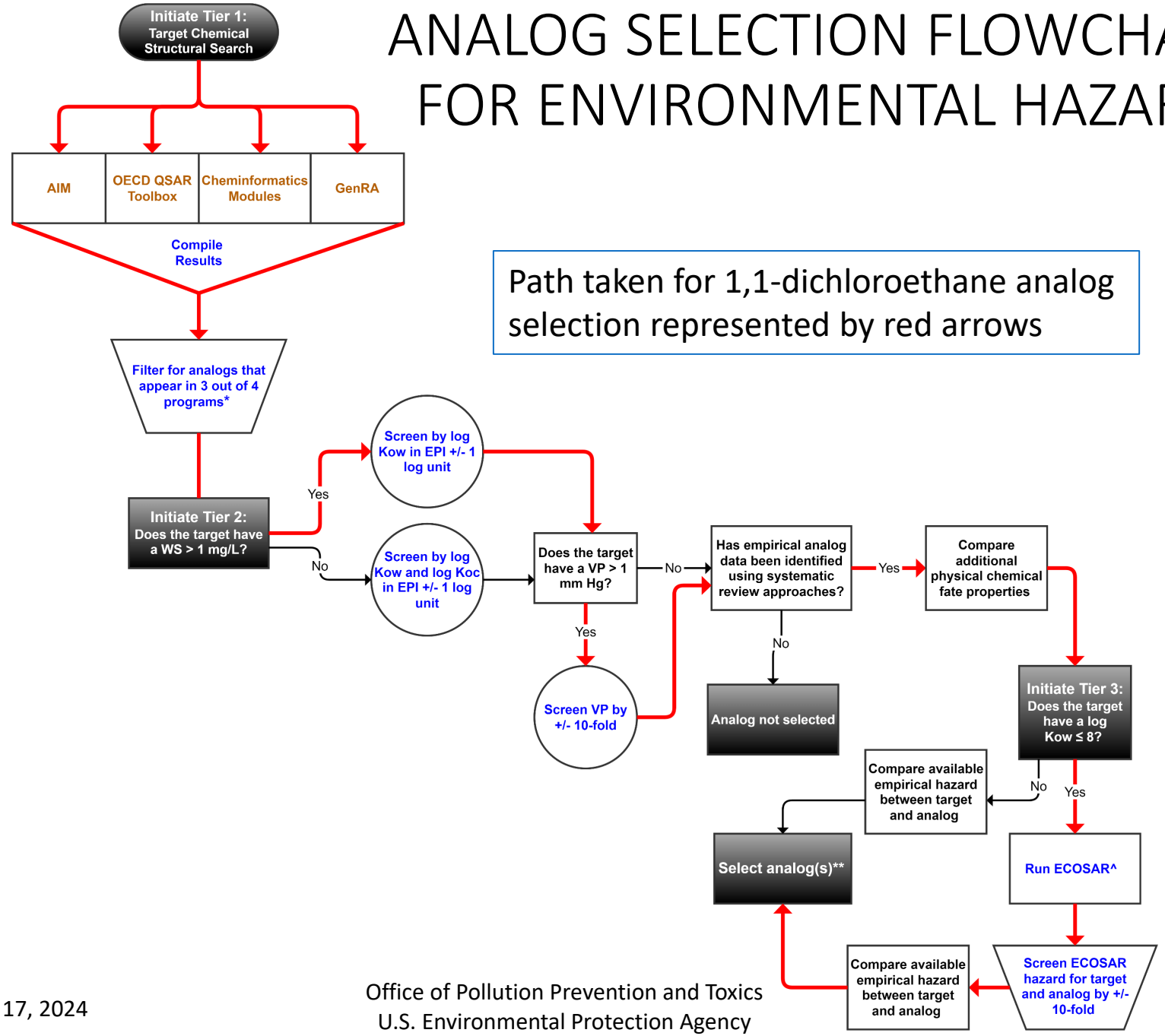
Charge Q 2a-b

- Analog selection for environmental hazard read-across based on:
  1. Structural similarity
     - Screening thresholds applied
  2. Physical, chemical, environmental fate and transport similarity
     - Screened by
       - Log Kow (within +/- 1 log unit)
       - Vapor Pressure (within 10-fold)
       - Data availability in Systematic Review
  3. Ecotoxicological similarity
     - Predicted toxicity comparisons (ECOSAR)
     - Available empirical hazard comparisons

ANALOG SELECTION FLOWCHART FOR ENVIRONMENTAL HAZARD

Charge Q 2a-b

Path taken for 1,1-dichloroethane analog selection represented by red arrows



STRUCTURAL SIMILARITY OF 1,1-DICHLOROETHANE AND OTHER HIGH-PRIORITY SOLVENTS

Charge Q 2a-b

Chlorinated Solvent	AIM	OECD QSAR Toolbox	GenRA	Cheminformatics
1,1-Dichloroethane (target)	Exact Match	1.00	1.00	1.00
1,2-Dichloropropane	2nd pass	0.75	0.45	0.42
1,1,2-Trichloroethane	2nd pass	0.79	–	0.78
1,2-Dichloroethane	2nd pass	0.79	–	0.63

Table Apx J-1 from the 1,1-Dichloroethane Draft Risk Evaluation

PHYSICAL-CHEMICAL SIMILARITY OF 1,1-DICHLOROETHANE AND OTHER HIGH-PRIORITY SOLVENTS

Charge Q 2a-b

Property	1,1-Dichloroethane (Target)	1,2-Dichloropropane	1,1,2-Trichloroethane	1,2-Dichloroethane
Water solubility	5,040 mg/L	2,800 mg/L	4,590 mg/L	8,600 mg/L
Log K_{OW}	1.79	1.99	1.89	1.48
Log K_{OC}	1.48	1.67	1.9–2.05, 2.2–2.32	1.28–1.62
BCF	7	0.5–6.9	0.7–6.7	2
BAF	6.8	7.1	6.9	3.8
Hydrolysis t½	61.3 years	15.8 years	85 days	65 years, 72 years
Henry's Law constant (atm-m^3/mol)	5.62E−03	2.82E−03	8.24E−04	1.18E−03
Vapor pressure (mm Hg)	227	40	23	79
Molecular weight	98.95 g/mol	112.99 g/mol	133.41 g/mol	98.96 g/mol
Physical state of the chemical	Colorless liquid	Colorless liquid	Colorless liquid	Colorless liquid

Table Apx J-2 from the 1,1-Dichloroethane Draft Risk Evaluation

ECOTOXICOLOGICAL SIMILARITY OF 1,1-DICHLOROETHANE AND OTHER HIGH-PRIORITY SOLVENTS

Charge Q 2a-b

- ECOSAR hazard predictions for acute and chronic exposures to aquatic taxa used as first comparison of ecotoxicological similarity between 1,1-dichloroethane and candidate analogs (1,2-dichloropropane, 1,1,2-trichloroethane, and 1,2-dichloroethane)
- Aquatic hazard predictions for 1,2-dichloropropane and 1,1,2-trichloroethane agreed very well with 1,1-dichloroethane aquatic hazard predictions
  - 1,2-dichloroethane aquatic hazard predictions less protective, therefore 1,2-dichloroethane did not move forward for further comparison

Average ratio of analog to target predicted hazard; mean ± S.E. (range)

1,2-dichloropropane	1,1,2-trichloroethane	1,2-dichloroethane
0.77 ± 0.02 (0.62-1.09)	**1.10** ± 0.02 (1.00-1.32)	**1.88** ± 0.11 (1.08-2.57)

MEASURED AQUATIC HAZARD DATA INDICATE 1,1-DICHLOROETHANE IS MOST TOXICOLOGICALLY SIMILAR TO ANALOG 1,2-DICHLOROPROPANE FOLLOWED BY ANALOG 1,1,2-TRICHLOROETHANE

Charge Q 2a-b

Species	Endpoint	1,1-Dichloroethane (Target)	**1,2-Dichloropropane (Analog)**		**1,1,2-Trichloroethane (Analog)**	
		Empirical Toxicity (mg/L)	Empirical Toxicity (mg/L)	**Ratio to 1,1-Dichloroethane**	Empirical Toxicity (mg/L)	**Ratio to 1,1-Dichloroethane**
Poecila reticulata [a]	96-h LC50	202	116	**0.57**	94.4	**0.47**
Daphnia magna	48-h EC50	34	29.5	**0.87**	81.6	**2.40**
Pseudokirchneriella subcapitata [a]	48-h EC50	49.92	34.42	**0.69**	105.42	**2.11**
Daphnia magna	21-d ChV	0.93	1.52	**1.63**	3.2	**3.44**

[a] These studies were rated uninformative for not stating the doses and/or number of doses utilized in the dose-response (Tsai and Chen, 2007; Könemann, 1981) and not stating inclusion of a control group (Könemann, 1981); however, EPA finds other aspects of both studies otherwise useful for comparing the relative toxicity of 1,1-dichloroethane and 1,2-dichloropropane or 1,1,2-trichloroethane.

Adapted from Table Apx J-4 from 1,1-Dichloroethane Draft Risk Evaluation

UNCERTAINTIES IN THE ENVIRONMENTAL HAZARD READ-ACROSS

Charge Q 2a-b

- Relatively small chemical structures of 1,1-dichloroethane and its analogs could result in lower structural similarity scores
  - Addressed by looking for concordance across multiple structure programs
- Lower vapor pressure of analog candidates 1,2-dichloropropane and 1,1,2-trichloroethane relative to 1,1-dichloroethane (although still within 10-fold) which could result in volatility differences between target and analog.
  - Addressed using experimental design considerations in the analog's empirical hazard dataset (chemical measurement, flow-through, etc.)
- ECOSAR hazard predictions do not include prediction for benthic invertebrate
  - Ability to read-across to benthic hazard was inferred from similar physical chemical and fate properties of 1,1-dichloroethane and 1,1,2-trichloroethane relevant to sediment and similar hazard in aquatic invertebrate

CONCLUSION AND KEY POINTS

Charge Q 2a-b

- 1,1-dichloroethane relatively data poor for aquatic and benthic hazard
- Analog selection was performed to supplement 1,1-dichloroethane's aquatic and benthic hazard dataset
- Similarity analyses for structure and physical/chemical behavior in water and sediment indicated three High-Priority Substances (1,2-dichloropropane, 1,1,2-trichloroethane, and 1,2-dichloroethane) as suitable analogs for 1,1-dichloroethane
- Further comparison for ecotoxicological similarity indicated 1,2-dichloropropane as the most suitable analog for read-across followed by 1,1,2-trichloroethane
- 1,2-dichloropropane was selected as analog for supplementing 1,1-dichloroethane's aquatic hazard dataset
- 1,1,2-trichloroethane was selected as analog for supplementing 1,1-dichloroethane's benthic hazard dataset

Thank you for your attention

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD INTRODUCTION

Janet Burris, MSPH; OCSPP/OPPT/ECRAD/RAB4

Charge Question	Location in 1,1-Dichloroethane Draft Risk Evaluation
3a, 3b, 3c, 9a, 9b, 12	Sections 5.2.1.3.1, 5.2.1.3.2, 5.2.1.3.3, and 5.2.1.3.5; Appendix J.2

OPPT SYSTEMATIC REVIEW PROCESS

Charge Q 12

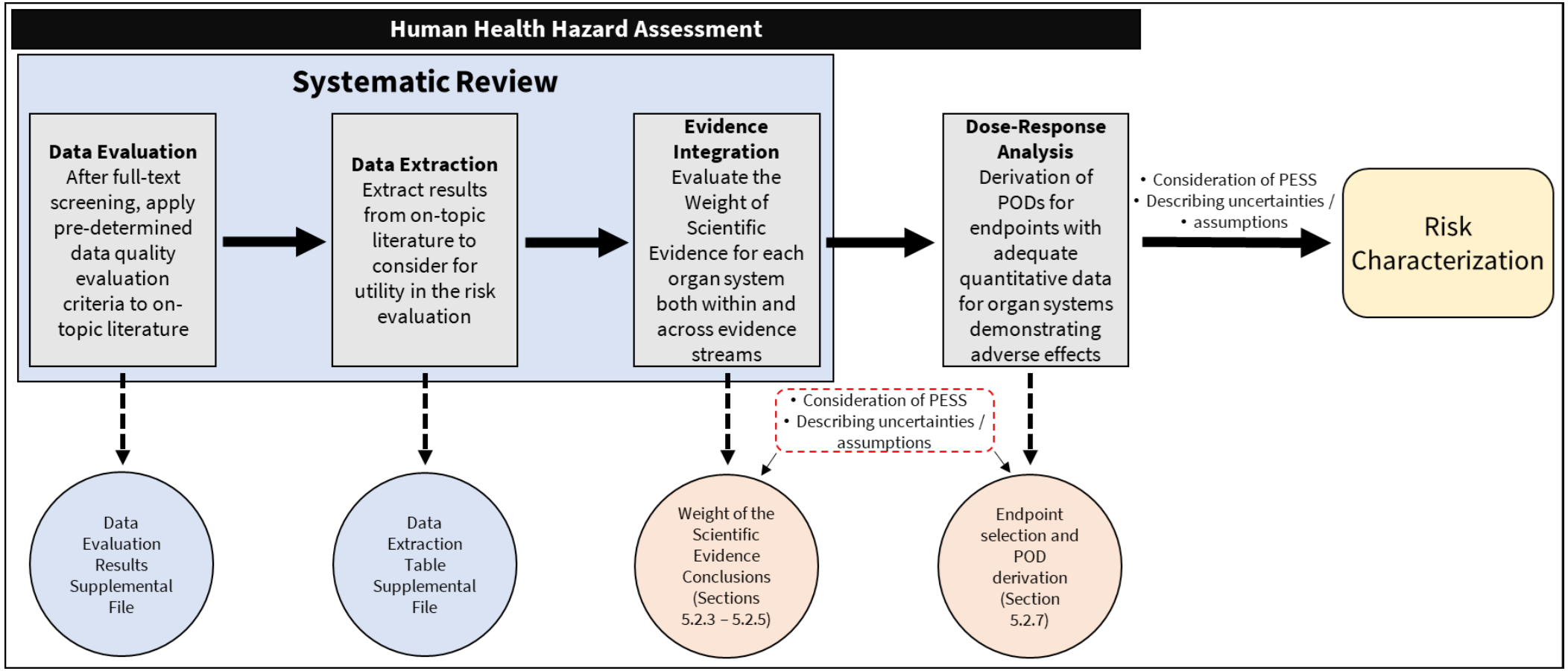


Figure 5-6 from 1,1-Dichloroethane Draft RE

OPPT SYSTEMATIC REVIEW PROCESS

Charge Q 12

- Full data evaluation of the studies within these existing assessments and other studies that passed initial title/abstract screening underwent the full text screening phase of systematic review and data evaluation
  - A summary of the studies not considered or considered suitable for PODs/dose-response assessment for 1,1-dichloroethane and 1,2-dichloroethane can be found in Sections M.2.1 and M.2.2 in the *1,1-Dichloroethane Draft RE*, respectively
  - The *1,1-Dichloroethane - Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology supplemental file provides the data evaluation results of these studies*

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD INTRODUCTION

Charge Q 3c, 12

- 1,1-Dichloroethane Hazard Identification and Evidence Integration (based on systematic review, SR)
  - No adequate data for non-cancer oral and inhalation, and no available data for dermal, for all exposure durations (acute, short-term and chronic)
  - No adequate data for cancer by the oral route, and no available data for cancer by the inhalation and dermal routes
- Data gaps filled by read-across from the identified human health hazard analog 1,2-dichloroethane
  - Based on an analyses of similarities of structure, physical-chemical properties, metabolism and toxicological endpoints (non-cancer and cancer)
  - Necessitated completion of the SR process, hazard identification, data quality evaluation, data extraction and evidence integration for both 1,1- and 1,2-dichloroethane

OPPT SYSTEMATIC REVIEW PROCESS

- Historically, offices across EPA and other agencies (*e.g.*, ATSDR), have developed their own assessments for 1,1- and 1,2-dichloroethane
  - Comparison of identified assessments is outlined in *Table 5-53 of the 1,1-Dichloroethane Draft Risk Evaluation* for non-cancer based on exposure duration and route
  - EPA reviewed the 1,1-and 1,2-dichloroethane toxicological profiles by ATSDR (ATSDR, 2015; 2022 Draft, respectively)
  - EPA reviewed the 1,1 and 1,2-dichloroethane U.S. EPA's Provisional Peer-Reviewed Toxicity Values Assessments (U.S. EPA, 2010; 2006b).
  - 1,1- and 1,2-dichloroethane were not assessed for non-cancer exposure durations/routes by U.S. EPA's Integrated Risk Information System (IRIS) program (U.S. EPA, 1990; 1987b, respectively)

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

William Irwin, Ph.D., DABT, ERT, FATS; OCSPP/OPPT/ECRAD/RAB4

Charge Question	Location in 1,1-Dichloroethane Draft Risk Evaluation
3a, 3b, 3c, 9a, 9b	Sections 5.2.1.3.1, 5.2.1.3.2, 5.2.1.3.3, and 5.2.1.3.5; Appendix J.2

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b & 9a-b

- Adequate human health hazard data were not available to assess non-cancer and cancer risks for 1,1-dichloroethane, EPA chose to use a “read-across” approach using data available for a closely related chemical or analog to evaluate the human health non-cancer/cancer hazard of 1,1-dichloroethane
- The analyses resulted in the identification of 1,2-dichloroethane (an isomer of 1,1-dichloroethane) as the most appropriate analog with acceptable and available data to fill data gaps
- General principles for read-across as outlined in Lizarraga et al. (2019):
  1. Structural Similarity
  2. Physical and Chemical Similarities
  3. Metabolic Similarities
  4. Toxicological Similarity

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b & 9a-b

1. Structural Similarity

	Chlorinated Solvent	AIM	OECD QSAR Toolbox	GenRA	HCD
Target	1,1-Dichloroethane	Exact match	1.00	1.00	1.00
Candidate Analogs	1,2-Dichloroethane	2nd pass	0.79	–	0.63
	1,1,2-Trichloroethane	2nd pass	0.79	0.27	0.78
	1,2-Dichloropropane	2nd pass	0.75	0.45	0.42
	Trichloroethylene	–	0.73	–	0.33
	Dichloromethane	2nd pass	0.46	–	0.57
	trans-1,2-dichloroethylene	–	0.63	–	0.30
	Perchloroethylene	–	0.47	–	0.33
	Carbon tetrachloride	2nd pass	0.29	–	0.44

Table 5-35 in the 1,1-Dichloroethane Draft RE

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b & 9a-b

2. Physical and Chemical Similarities of Candidate Chemicals

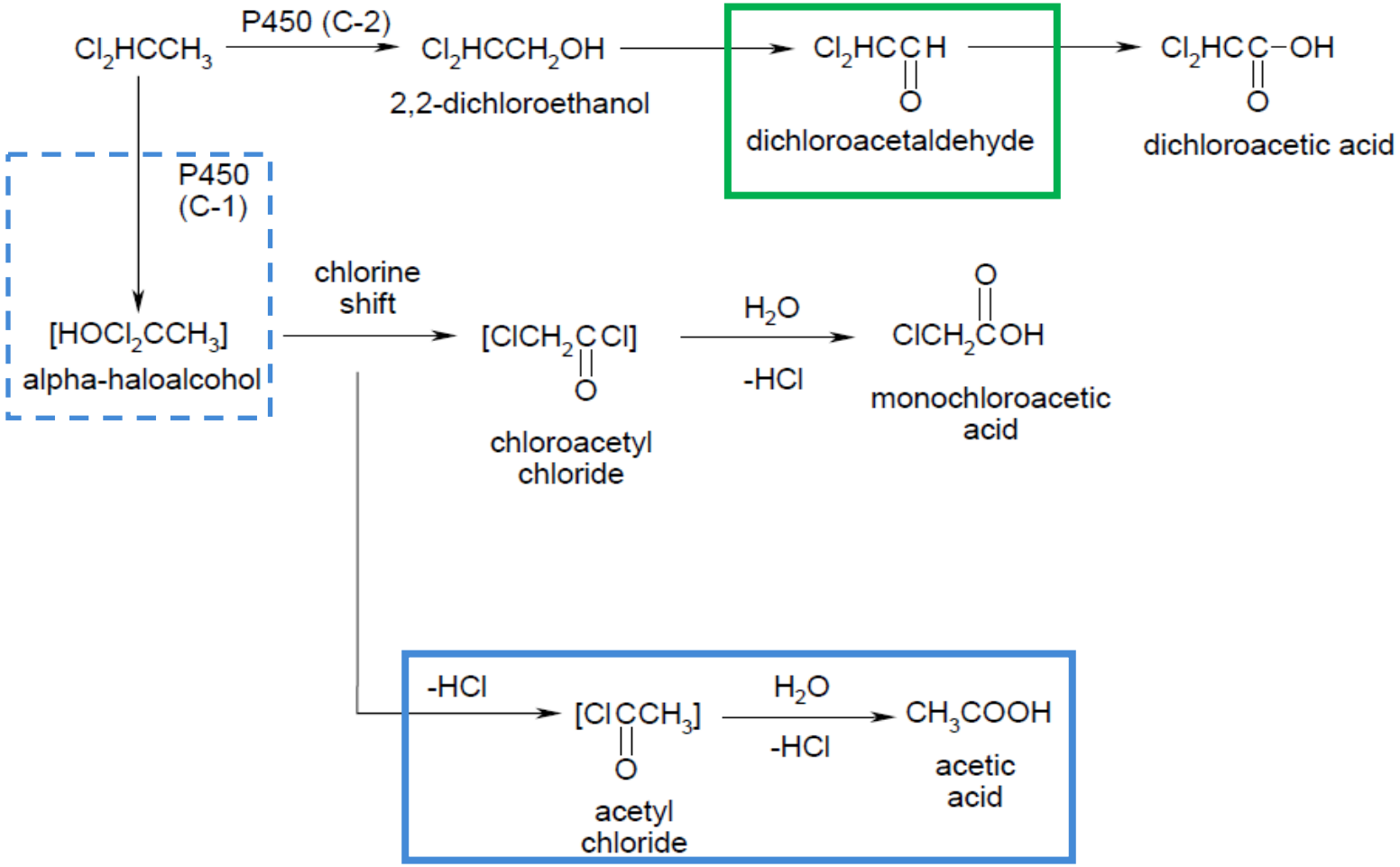
Chlorinated Solvent	Water Solubility (mg/L)	Log K_{OW}	Molecular Weight	Physical State	Henry's Law Constant (atm-m^3/mol)	Vapor Pressure (mm Hg)
1,1-Dichloroethane	5,040	1.79	98.95	Liquid	0.00562	227
1,2-Dichloroethane	8,600	1.48	98.96	Liquid	0.00118	79
1,1,2-Trichloroethane	4,590	1.89	133.41	Liquid	0.00082	23
1,2-Dichloropropane	2,800	1.99	112.99	Liquid	0.00282	40

Table 5-36 in the 1,1-Dichloroethane RE

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b & 9a-b

3. Metabolic Similarities

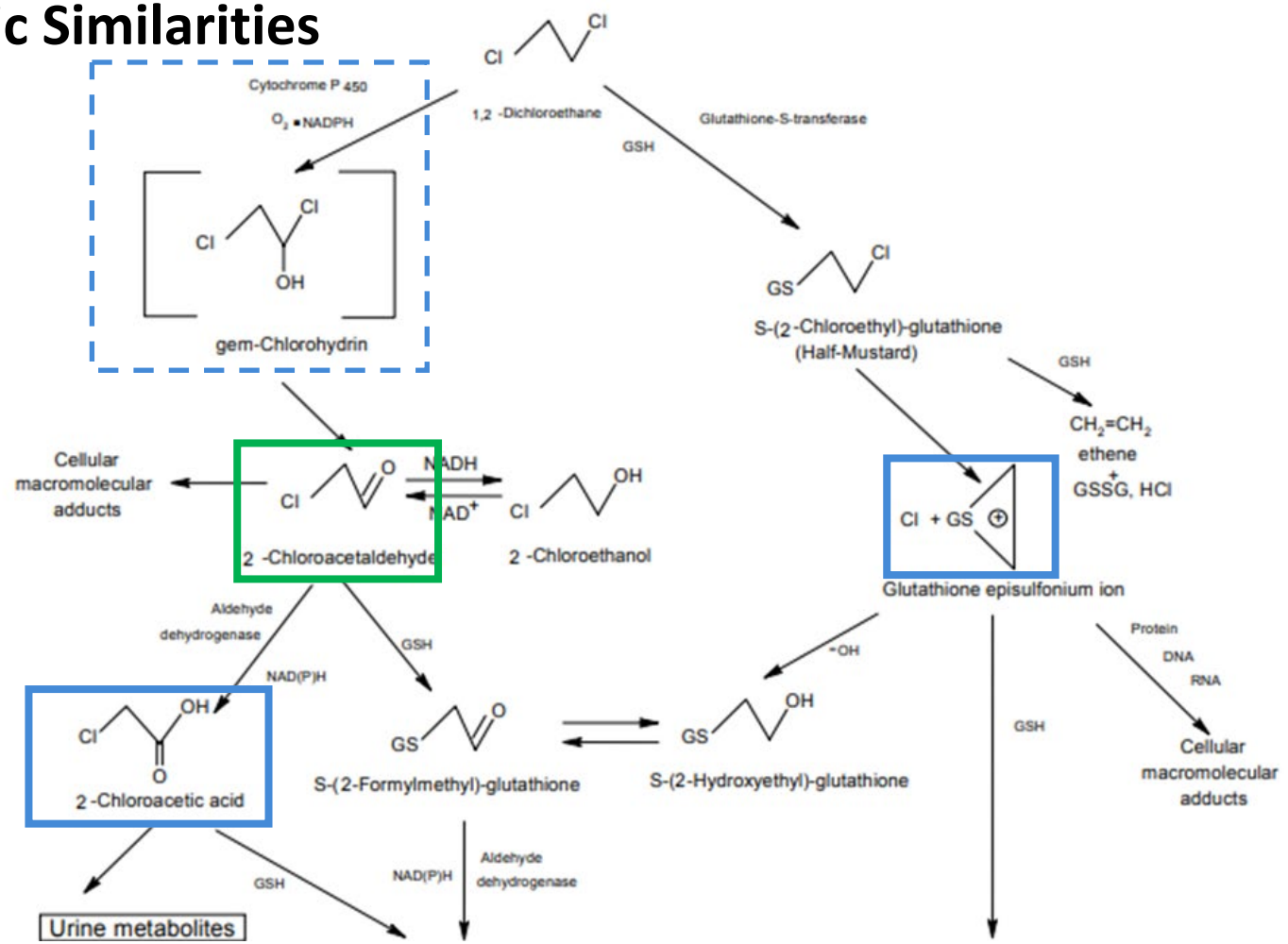


Adapted from Figure Apx J-1. Proposed Metabolic Scheme for 1,1-Dichloroethane (McCall et al., 1983) in the 1,1-Dichloroethane Draft RE

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b & 9a-b

3. Metabolic Similarities



Adapted from Figure Apx J-2. Proposed Metabolic Scheme for 1,2-Dichloroethane (IPCS, 1995) in the 1,1-Dichloroethane Draft RE

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a/b & 9a/b

3. Metabolic Similarities

- As depicted in Figures Apx J-1 and Apx J-2 of the 1,1-dichloroethane draft RE, in terms of metabolic similarities between 1,1-dichloroethane and 1,2-dichloroethane, both chemicals are directly reactive and both form ***chloroaldehydes***, which can form persistent DNA crosslinks (OECD, 2015) and produce HCl and decrease glutathione levels

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b, 9a-b

4. Toxicological Similarities – Non-Cancer/Cancer

Hazard-Property	1,1-Dichloroethane	1,2-Dichloroethane
Chemical Reactivity	+	+
Dichloroethane Isomers	+	+
Irritation	+	+
Narcosis	+	+
Cardiotoxicity	+	+
Genotoxicity without Metabolic Activation	+	+
Immunotoxicity	+	+
Nephrotoxicity	+	+
Hepatoxicity	+	+
Nutritional/Metabolic Toxicity	+	+
Endometrial Polyps	+	+
Hepatocellular Carcinoma	+	+
Hemangiosarcomas	+	+
Mammary Gland Tumors	+	+

Adapted from Table Apx J-15 in the 1,1-Dichloroethane Risk Evaluation

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b, 9a-b, 12

4. Toxicological Similarity - Cancer

Studies	1,1-Dichloroethane	1,2-Dichloroethane
NTP Oral Rat Studies ("uninformative" SR rating)	Mammary gland adenocarcinomas, hemangiosarcoma (NTP, 1978a)	Mammary gland adenocarcinomas, hemangiosarcoma (NTP, 1978b)
NTP Oral Mouse Studies ("high" SR rating)	Endometrial stromal polyps (precursor) NTP (1978a)	Endometrial stromal polyps (precursor), NTP (1978b) Hepatocarcinomas; basis for IRIS calculated cancer slope factor (NTP, 1978b)
Inhalation Studies	Chronic study, but not a cancer study, (Hofmann et al., 1971b, "uninformative" SR rating)	Mammary gland adenomas; fibroadenomas, adenocarcinomas; subcutaneous fibromas; bronchioalveolar adenoma & carcinoma; endometrial stromal polyps; hepatocellular adenoma (Nagano et al., 2006, "high" SR rating)
Dermal Study	None	Bronchioalveolar adenomas and adenocarcinomas (mice, 1 dose) (Suguro et al., 2017, "high" SR rating)
Human Studies	Indeterminate	Indeterminate

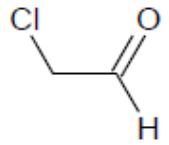
Adapted from Table Apx J-9 in the 1,1-Dichloroethane Draft RE

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b, 9a-b

Cancer Risk Evaluation Resources

- **EPA OncoLogic™ Model**
  - An expert system that mimics the judgment of human experts by following sets of knowledge rules based on studies of how chemicals cause cancer in animals and humans. EPA OncoLogic™ was developed by cancer experts Dr. Yintak Woo and Dr. David Lai (https://www.epa.gov/tsca-screening-tools/oncologictm-expert-system-evaluate-carcinogenic-potential-chemicals).
- **OECD Fundamental and Guiding Principles for (Q)SAR Analysis of Chemical Carcinogens with Mechanistic Considerations (2015)**
  - **Bifunctional Persistent DNA Crosslinkers Tend Have Higher Potential for Carcinogenicity**
    - **Monofunctional vs. bifunctional vs. polyfunctional and intergroup distance:** Substances that contain more than one electrophilic group tend to have a higher potential for carcinogenicity than those with only one electrophilic functional group because of the possibility for crosslinking. The groups can be identical or different (e.g., chloroacetaldehyde). The ideal distance between groups appears to be in the range of 1 to 6 carbon atoms to allow the formation of DNA cyclic adducts which tend to be more persistent.



chloroacetaldehyde

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b, 9a-b

4. Toxicological Similarity Cancer

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

Adapted from Table Apx J-11 in the 1,1-Dichloroethane Draft RE

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

Adapted from Table Apx J-12 in the 1,1,-Dichloroethane Draft RE

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Charge Q 3a-b, 9a-b

KEY POINTS & CONCLUSIONS

- 1,2-Dichloroethane was identified as the best available candidate chemical to fill the identified data gaps for 1,1-dichloroethane. This conclusion is based on the following:
  - Both 1,1- and 1,2-dichloroethane are structurally similar as reactive di-chlorinated ethanes
  - Good Structural Similarity Indices: 0.63 to 0.79
  - Both are isomers of each other with identical molecular weights and formulas
  - Both have similar physical-chemical properties
  - Both are volatile liquids
  - Both have similar ADME patterns and metabolic pathways to produce reactive species
  - Both are reactive alkyl halides
  - Both possess, overall, similar non-cancer and cancer hazards (available mutagenicity, common tumor types, many common hazard endpoints)
  - EPA has the highest confidence using 1,2-dichloroethane as an analog

Thank you for your attention

1,1- AND 1,2-DICHLOROETHANE DRAFT NON-CANCER ORAL HUMAN HEALTH HAZARD ASSESSMENT

Ali Shohatee, Ph.D.; OCSPP/OPPT/ECRAD/RAB4

Charge Questions	Location in 1,1-Dichloroethane Draft Risk Evaluation
4a, 4b, 4c, 5a, 5b, 5c, 5d, 11, 12	Sections 5.2.3, 5.2.6 and 5.2.7; Appendix M.2 and M.6; Appendix F (1,2-Dichloroethane TSD) *12. 1,1-Dichloroethane - Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology* *30. 1,1-Dichloroethane - Draft Benchmark Dose Modeling*

1,1-DICHLOROETHANE NON-CANCER HUMAN HEALTH HAZARD INTRODUCTION

Charge Q 5c

Existing Assessments: EPA'S PPRTV (2006) for 1,1-Dichloroethane

Subchronic Oral Duration

- The subchronic oral exposure study by Muralidhara et al. (2001) identified the kidney as a sensitive target for 1,1-dichloroethane in male rats
  - NOAEL and LOAEL values of 1000 and 2000 mg/kg-day, respectively, estimated based on increased urinary enzyme markers for renal damage and CNS depression
  - NOAEL of 1000 mg/kg-day, administered for 5 days/week, was adjusted to 714.3 mg/kg-day for continuous exposure

Subchronic p–RfD = NOAEL ÷ UF = 714.3 ÷ 300 = **2.4 mg/kg–day**

Summary Table for the U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for 1,1-Dichloroethane (2006)

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Renal/Nervous	Sprague-Dawley Rats male only	5 days/week for 13-weeks via gavage in corn oil	$NOAEL_{adj}$ = 714.3 mg/kg-day	Increased urinary enzyme markers for renal damage and CNS depression	UF_A = 10 UF_H = 10 UF_D = 3 ***Total UF= 300***	Muralidhara et al. (2001)

UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, data evaluating susceptible human responses are insufficient
UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient
UF_D: Despite the relatively complete database, a factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies

1,1-DICHLOROETHANE NON-CANCER HUMAN HEALTH HAZARD INTRODUCTION

Charge Q 5c

Existing Assessments: EPA'S PPRTV (2006) for 1,1-Dichloroethane

Chronic Oral Duration

- The subchronic oral exposure study by Muralidhara et al. (2001) identified for the subchronic oral was used for the chronic oral duration as well
  - NOAEL of 1000 mg/kg-day, administered for 5 days/week, was adjusted to 714.3 mg/kg-day for continuous exposure

Chronic p–RfD = NOAEL ÷ UF = 714.3 ÷ 3000 = **0.2 mg/kg–day**

Summary Table for the U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for 1,1-Dichloroethane (2006)

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Renal/Nervous	Sprague-Dawley Rats male only	5 days/week for 13-weeks via gavage in corn oil	$NOAEL_{adj}$ = 714.3 mg/kg-day	Increased urinary enzyme markers for renal damage and CNS depression	UF_A = 10 UF_H = 10 UF_S = 10 UF_D = 3 ***Total UF= 3000***	Muralidhara et al. (2001)

UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, data evaluating susceptible human responses are insufficient
UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient
UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure
UF_D: Despite the relatively complete database, a factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies

1,1-DICHLOROETHANE NON-CANCER HUMAN HEALTH HAZARD INTRODUCTION

Existing Assessments: ATSDR (2015) Toxicological Profile for 1,1-Dichloroethane

- Oral MRLs were not derived for 1,1-dichloroethane as database was considered not adequate

1,1-DICHLOROETHANE NON-CANCER HUMAN HEALTH HAZARD INTRODUCTION

Charge Q 12

- Based on systematic review of 1,1-dichloroethane:
  - No adequate data for non-cancer oral hazard were identified for dose-response
    - Muralidhara et al. (2001) used to derive EPA's PPRTV (2006) subchronic and chronic p-RfD was not selected for dose-response (rated "high" by OPPT systematic review)
      - NOAEL near the limit dose of 1,000 mg/kg-day, only male rats tested
      - Histopathological effects on the kidney showed nephropathy with high incidences in the control group (7/10 animals)
      - Mortality in the highest two groups of 2,000 and 4,000 mg/kg-bw/day resulted in ceasing continuation of exposure at the highest dose
      - The methodology for CNS depression was not defined and results were only described qualitatively
  - No available data for dermal hazard for all exposure durations (acute, short-term and chronic) were identified for dose-response
  - Section 5.2.3.1 in the 1,1,-Dichloroethane Draft RE outlines the hazard identification and evidence integration associated with 1,1-dichloroethane (and 1,2-dichloroethane) exposure by health outcome
- Data gaps filled by read-across from the identified human health hazard of chemical analog 1,2-dichloroethane

1,1-DICHLOROETHANE NON-CANCER ACUTE ORAL DURATION POINT OF DEPARTURE (POD)

Charge Q 4a-b, 12

- Non-cancer POD based on the benchmark response of 10% ($BMDL_{10}$) of 153 mg/kg-day to 1,2-dichloroethane based on increased kidney weight in male mice
- Allometric body weight scaling to the ¾ power used to derive the human equivalent dose (HED) of 19.9 mg/kg-day from the $BMDL_{10}$
- Total uncertainty factor (UF) of 30 proposed as the benchmark margin of exposure (MOE)
  - Intraspecies UF (UF_H) of 10X and an interspecies UF (UF_A) of 3X (reduced from 10X), consistent with U.S. EPA Guidance (U.S. EPA, 2011)
- No suitable dermal study relevant for dose-response
  - Route-to-route extrapolation from the oral POD for the dermal POD

Adapted from Table 5-49 in the 1,1-Dichloroethane Draft RE

Target Organ/ System	Species/ Gender	Duration	Study POD/Type	Effect	Worker HED (mg/kg-bw/day)	Continuous HED (mg/kg-bw/day)	Uncertainty Factors	Reference	Data Quality
Renal	Mice (male)	1,2-dichloroethane (read-across) 1-day oral gavage	$BMDL_{10}$= 153 mg/kg BMD = 270 mg/kg	Increased kidney weight	19.9	19.9	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1 ***Total UF= 30***	Storer et al. (1984)	High

WEIGHT OF SCIENTIFIC EVIDENCE IN SUPPORT OF THE NON-CANCER ACUTE ORAL POD

Charge Q 4c, 12

- Adequate data not available to identify PODs following acute oral exposures to 1,1-dichloroethane; read-across from 1,2-dichloroethane was required to fill in this data gap
- Increased kidney weights in Storer et al. (1984) was selected as the critical endpoint from among several acute toxicity studies
- Increased L-iditol dehydrogenase and blood urea nitrogen (BUN) were considered as co-critical endpoints in the same Storer et al. (1984) study
- Damaged renal tubules were seen in Morel et al. (1999), however, uncertainties due to dose groups being above the limit dose reduced EPA's confidence for its use in the risk assessment to derive PODs
- Acute oral toxicity studies and PODs (both 1,1-dichloroethane and 1,2-dichloroethane toxicity data) used in support of the critical and co-critical endpoints are presented in *Table 5-42 in the 1,1-Dichloroethane Draft RE*

1,1-DICHLOROETHANE NON-CANCER SUBCHRONIC ORAL DURATION POINT OF DEPARTURE (POD)

Charge Q 5a, 12

- Non-cancer POD based on the LOAEL of 4.89 mg/kg-day to 1,2-dichloroethane based on suppression of immune response (antibody presenting cells (AFC)/spleen) in male mice
- Allometric body weight scaling to the ¾ power used to derive the worker and general population (continuous) human equivalent dose (HED) of 0.890 and 0.636 mg/kg-day, respectively
- Total uncertainty factor (UF) of 100 proposed as the benchmark margin of exposure (MOE)
  - Intraspecies UF (UF_H) of 10X, an interspecies UF (UF_A) of 3X (reduced from 10X), and LOAEL-to-NOAEL UF (UF_L) of 3X to account uncertainty inherent in extrapolating from the LOAEL to the NOAEL, consistent with U.S. EPA Guidance (U.S. EPA, 2011)
- No suitable dermal data available for dose response
  - Route-to-route extrapolation from the oral POD for the dermal POD

Adapted from Table 5-50 in the 1,1-Dichloroethane Draft RE

Target Organ/ System	Species/ Gender	Duration	Study POD/Type	Effect	Worker HED (mg/kg-bw/day)	Continuous HED (mg/kg-bw/day)	Uncertainty Factors	Reference	Data Quality
Immune System	Mice (male)	1,2-dichloroethane (read-across) 14-days oral gavage	LOAEL = 4.89 mg/kg-day	Suppression of immune response (AFCs/spleen)	0.890	0.636	UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 1 UF_D = 1 ***Total UF= 100***	Munson et al. (1982)	High

1,1-DICHLOROETHANE NON-CANCER CHRONIC ORAL DURATION POINT OF DEPARTURE (POD)

Charge Q 5d, 12

- The Munson et. al (1982) study identified for the subchronic oral non-cancer POD was used for the chronic oral duration as well
- Total uncertainty factor (UF) of 1000 proposed as the benchmark margin of exposure (MOE)
  - Intraspecies UF (UF_H) of 10X, an interspecies UF (UF_A) of 3X (reduced from 10X), LOAEL-to-NOAEL UF (UF_L) of 3X to account uncertainty inherent in extrapolating from the LOAEL to the NOAEL, and subchronic-to-chronic duration UF (UF_S) of 10X, consistent with U.S. EPA Guidance (U.S.EPA, 2011)
- No suitable dermal study relevant for dose-response
  - Route-to-route extrapolation from the oral POD for the dermal POD

Adapted from Table 5-51 in the 1,1-Dichloroethane Draft RE

Target Organ/ System	Species/ Gender	Duration	Study POD/Type	Effect	Worker HED (mg/kg-bw/day)	Continuous HED (mg/kg-bw/day)	Uncertainty Factors	Reference	Data Quality
Immune System	Mice (male)	1,2-dichloroethane (read-across) 14-days oral gavage	LOAEL = 4.89 mg/kg-day	Suppression of immune response (AFCs/spleen)	0.890	0.636	UF_A = 3 UF_H = 10 UF_L = 3 UF_S = 10 UF_D = 1 ***Total UF= 1000***	Munson et al. (1982)	High

WEIGHT OF SCIENTIFIC EVIDENCE IN SUPPORT OF THE NON-CANCER SUBCHRONIC/CHRONIC ORAL PODs

Charge Q 5c, 12

- The LOAEL of 4.89 mg/kg-day based on suppression of immune response in Munson et al., (1982) is supported by other findings:
  - Decrease leukocytes was considered as a co-critical endpoint in the same Munson et al. (1982) study
- The ATSDR (2022/2024) Draft/Final Toxicological Profile for 1,2-dichloroethane concluded that "the immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice."
  - 14-day Munson et al. (1982) gavage study was considered as an acute duration by ATSDR, thus not utilized for the subchronic or chronic PODs in the ATSDR assessment (acute <15 days in ATSDR assessments)
- Recommended sub-chronic/chronic oral studies and PODs (both 1,1-dichloroethane and 1,2-dichloroethane toxicity data) followed by co-critical endpoints in support of the recommended POD are presented in *Tables 5-44 & 5-46 in the 1,1-Dichloroethane Draft RE*

EXISTING ASSESSMENTS: EPA'S PPRTV (2010) FOR 1,2-DICHLOROETHANE

Charge Q 5b, 12

Subchronic Duration

- The 13-week study by NTP (1991) in male and female F344/N rats exposed to 1,2-dichloroethane in drinking water was used to derive the subchronic provisional reference dose (p-RfD) in the U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for 1,2-Dichloroethane
  - A significant dose-related increase in kidney weight and the kidney-body-ratio of female F344/N rats was identified at 58 mg/kg/day

Subchronic p–RfD = LOAEL ÷ UF = 58 ÷3000 = **0.02 mg/kg–day**

Summary Table for the U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for 1,2-Dichloroethane (2010)

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Renal	F344/N Rats (female)	13-weeks via drinking water	LOAEL = 58 mg/kg-day	Increased absolute kidney weight in females	UF_A = 10 UF_H = 10 UF_L = 10 UF_D = 3 ***Total UF= 3000***	NTP, 1991

UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, data for evaluating susceptible human responses are insufficient
UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient
UF_L: A factor of 10 is applied for using a LOAEL as the POD
UF_D: Despite the relatively complete database, a factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies

EXISTING ASSESSMENTS: EPA'S PPRTV (2010) FOR 1,2-DICHLOROETHANE

Charge Q 5b, 12

Chronic Duration

- "In the absence of suitable chronic data, the POD from the subchronic p-RfD could be used to derive the chronic p-RfD; however, the composite UF would include the additional UF_S of 10 for applying data from a subchronic study to assess potential effects from chronic exposure. This would result in the large composite UF of greater than 3,000, thereby relegating this derivation of the chronic p-RfD to an appendix screening value"

Screening Chronic p–RfD = LOAEL ÷ UF = 58 ÷10,000[a] = **0.006 mg/kg–day**

Summary Table for the U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for 1,2-Dichloroethane (2010)

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Renal	F344/N Rats (female)	13-weeks via drinking water	LOAEL = 58 mg/kg-day	Increased absolute kidney weight in females	UF_A = 10 UF_H = 10 UF_L = 10 UF_S = 10 UF_D = 3 ***Total UF= 30,000***	NTP, 1991

[a] Maximum UF of 10,000 is used to derive the screening chronic p-RfD
UF_H: A factor of 10 applied for extrapolation to a potentially susceptible human subpopulation, data for evaluating susceptible human responses are insufficient
UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient
UF_L: A factor of 10 is applied for using a LOAEL as the POD
UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure
UF_D: Despite the relatively complete database, a factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies

EXISTING ASSESSMENTS: ATSDR (2022) TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

Charge Q 5b, 12

Intermediate Duration

- The 13-week study by NTP (1991), where rats exposed to 1,2-dichloroethane in drinking water, was used to derive the intermediate-duration oral minimal risk level (MRL) for the ATSDR (2022) Draft Toxicological Profile for 1,2-Dichloroethane
  - Based on increased kidney weight in female F344/N rats

Intermediate–duration oral MRL = LOAEL ÷ UF = 58 ÷ 300 = **0.2 mg/kg–day**

Summary Table for the ATSDR (2022) Draft Toxicological Profile for 1,2-Dichloroethane

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Renal	F344/N Rats (female)	13-weeks via drinking water	LOAEL = 58 mg/kg-day	Increase in kidney weight	UF_A = 10 UF_H = 10 UF_L = 3 ***Total UF= 300***	NTP, 1991

UF_A: A factor of 10 is applied for animal-to-human extrapolation
UF_H: A factor of 10 is applied for human variability
UF_L: A factor of 3 is applied for using a LOAEL as the POD

EXISTING ASSESSMENTS: ATSDR (2024) TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

Charge Q 5b, 12

Intermediate Duration

- The 13-week study by NTP (1991), where rats exposed to 1,2-dichloroethane in drinking water, was used to derive the intermediate-duration oral minimal risk level (MRL) for the ATSDR (2024) Toxicological Profile for 1,2-Dichloroethane
  - Based on increased incidences of kidney lesions (tubule regeneration) in female F344/N rats

Intermediate–duration oral MRL = $BMDL_{10} \div UF = 70.08 \div 100 =$ **0.7 mg/kg–day**

Summary Table for the ATSDR (2024) Toxicological Profile for 1,2-Dichloroethane

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Renal	F344/N Rats (female)	13-weeks via drinking water	$BMDL_{10}$ = 70.08 mg/kg/day[a]	Increase in kidney lesions (tubule regeneration)	$UF_A = 10$ $UF_H = 10$ ***Total UF= 100***	NTP, 1991

[a] BMD modeling of incidences of tubular lesions (tubule regeneration) in female F344 rats from NTP (1991)
UF_A: A factor of 10 is applied for animal-to-human extrapolation
UF_H: A factor of 10 is applied for human variability

EXISTING ASSESSMENTS: ATSDR (2022/2024) TOXICOLOGICAL PROFILES FOR 1,2-DICHLOROETHANE

Chronic Duration

- ATSDR (2022 Draft/2024 Final) Toxicological Profiles for 1,2-Dichloroethane indicated that "available data are insufficient for derivation of a chronic-duration oral MRL for 1,2-Dichloroethane."

SOLICITING COMMENT ON RATIONALE FOR NOT SELECTING THE NTP (1991) DW STUDY FOR THE SUBCHRONIC/CHRONIC ORAL PODs

Charge Q 5c, 12

- OPPT SR rating of "uninformative" for dose-response
  - This NTP 1991 study was reviewed for POD derivation, *however*, the daily intake doses were estimated on a mg/kg body weight basis and not measured throughout the duration of exposure putting uncertainty in the doses; water consumption not corrected for spillage
  - Weight gain depression seen in male and female rats in the two higher dose groups throughout the study and likely caused by dehydration due to poor palatability of formulated drinking water
  - Study indicated water consumption was substantially decreased with increasing dose
  - Analysis of formulations remaining in the drinking water bottles after 24 hours in the animal cages showed that the concentrations of the formulations had decreased an average of 29% (range of 13% to 53%) of target concentrations.
- Due to the uncertainty regarding the delivered dose and the inherit volatility associated with 1,2-dichloroethane, it was not recommended using this drinking water study for this dose-response assessment

SOLICITING COMMENT ON RATIONALE FOR NOT SELECTING THE NTP (1991) DW STUDY FOR THE SUBCHRONIC/CHRONIC ORAL PODs

Charge Q 5c, 12

- EPA's PPRTV for 1,2-dichloroethane (U.S. EPA, 2010) identified the Munson et al. (1982) study, specifically the 90-day drinking water portion of the study where male and female CD-1 mice were exposed to 1,2-dichloroethane and suggested that "the NOAEL for this study would be the highest dose tested, 189 mg/kg-day."
  - The subchronic reference dose for oral exposure (RfD) was ultimately based on the 13-week study by NTP (1991)
- ATSDR (2022) Draft Toxicological Profile for 1,2-Dichloroethane identified the same NTP (1991) drinking water study for the intermediate-duration oral MRL of 58 mg/kg-day (NOAEL) based on increased absolute kidney weights in the female F344/N rats exposed to 1,2-dichloroethane with an uncertainty factor of 300
  - The immune system was identified as "the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice", however, ATSDR concluded that the data provide limited evidence that the immune system is a sensitive target of 1,2-dichloroethane in mice, but not rats.
  - Due to apparent interspecies differences in animal immunotoxicity, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following exposure by inhalation or ingestion
  - The mechanism by which 1,2-dichloroethane may produce immunological effects is not known
- The final ATSDR (2024) Draft Toxicological Profile for 1,2-Dichloroethane has now identified increase in kidney lesions (tubule regeneration) as the basis for intermediate-duration MRL

SOLICITING COMMENT ON RATIONALE FOR NOT SELECTING THE NTP (1991) DW STUDY FOR THE SUBCHRONIC/CHRONIC ORAL PODs

Charge Q 5c, 12

- A summary of the studies not considered or considered suitable for PODs/dose-response assessment for 1,1-dichloroethane and 1,2-dichloroethane can be found in *Sections M.2.1 and M.2.2 in the 1,1-Dichloroethane Draft RE*, respectively

- Evaluation results for studies identified from the 1,1- and 1,2-dichloroethane databases can be found in the *1,1-Dichloroethane - Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology supplemental file* and EPA's conclusions are summarized in *Section 5.2.6.4 of the 1,1-Dichloroethane Draft RE*

SOLICITING COMMENT ON RATIONALE FOR NOT SELECTING OECD Guideline 443 STUDY FOR DOSE-RESPONSE

Charge Q 11a, 12

- In 2015, OPPT received the OECD Guideline 443 study entitled “An extended one-generation drinking water reproductive toxicity study of ethylene dichloride [1,2-dichloroethane] in rats”, (WIL Research Laboratories, 2015)
  - Conducted to fulfill one of the requirements of an Enforceable Consent Agreement (ECA) under Section 4 of TSCA
  - During the Agency’s review of the draft protocol for this study, the Agency identified palatability and volatility as possible issues to be addressed and after consideration of the response from the HAP Task Force approved the protocol in November 2011

SOLICITING COMMENT ON RATIONALE FOR NOT SELECTING OECD Guideline 443 STUDY FOR DOSE-RESPONSE

Charge Q 11a, 12

- In preparation of the 1,1-Dichloroethane Draft Risk Evaluation, OPPT systematic review identified the study as “uninformative” for dose-response
  - This study was reviewed for POD derivation however, it was identified by the study authors that concentration-dependent reductions in water intake throughout the study period were likely due to issues with palatability
  - Water intake was reduced by >20% in the mid-and high-dose groups, and there were corresponding reductions in body weights
  - The authors noted that many of the effects observed (decreased body weights, organ weight changes etc.) stemmed from the reduced water intake and likely dehydration

- Due to the uncertainty regarding the delivered dose as exposure levels were below the target and the effects observed, systematic review recommended not using this drinking water study for this dose-response assessment

- Additional details regarding the study quality evaluation are available on pp. 919-938 in the *1,1-Dichloroethane - Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology* supplemental file

Thank you for your attention

1,1- AND 1,2-DICHLOROETHANE DRAFT NON-CANCER INHALATION HUMAN HEALTH HAZARD ASSESSMENT

Katherine Anitole, Ph. D.; OCSPP/OPPT/ECRAD/RAB5

Charge Questions	Location in 1,1-Dichloroethane Draft Risk Evaluation
6a, 6b, 6c, 7a, 7b, 7c, 11, 12	Sections 5.2.3, 5.2.6 and 5.2.7; Appendix M.2 and M.6; Appendix F (1,2-Dichloroethane TSD) *12. 1,1-Dichloroethane - Draft Data Quality Evaluation Information for Human Health Hazard Animal Toxicology* *30. 1,1-Dichloroethane - Draft Benchmark Dose Modeling*

1,1-DICHLOROETHANE NON-CANCER ACUTE INHALATION DURATION NON-CANCER POINT OF DEPARTURE (POD)

Charge Q 6a-c

- Non-cancer POD based on the benchmark response level of 10% ($BMCL_{10}$) of 48.9 mg/m^3 1,2-dichloroethane based on degeneration with necrosis of the olfactory mucosa in male and female rats (NOAEC of 202 mg/m3 or 71.3 mg/m^3 for an adjusted continuous exposure concentration)
- Allometric body weight scaling to the ¾ power was used to derive the human equivalent concentration (HEC) of 41.1 mg/m^3 for workers and 9.78 mg/m^3 for general population (continuous) from the $BMCL_{10}$
- Total uncertainty factor (UF) of 30 proposed as the benchmark margin of exposure (MOE)
- Intraspecies UF (UF_H) of 10X and an interspecies UF (UF_A) of 3X (reduced from 10X), consistent with U.S. EPA Guidance (U.S.EPA, 2011)

Adapted from Table 5-49 in the 1,1-Dichloroethane Draft RE

Target Organ/ System	Species/ Gender	Duration	Study POD/Type	Effect	Worker HEC [mg/m³] (ppm)	Continuous HEC [mg/m³] (ppm)	Uncertainty Factors	Reference	Data Quality
Neurological	Rats (males and females combined)	1,2-dichloroethane (read-across) 8-hour inhalation	$BMCL_{10}$ = 48.9 mg/m^3 (12.1 ppm)	Degeneration with necrosis of the olfactory mucosa	[41.1 mg/m^3] (10.14 ppm)	[9.78 mg/m^3] (2.42 ppm)	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1 ***Total UF= 30***	Dow Chemical, (2006b)	High

WEIGHT OF SCIENTIFIC EVIDENCE IN SUPPORT OF THE ACUTE INHALATION NON-CANCER POD

Charge Q 6a-c

- Adequate data were not available to identify PODs following acute inhalation exposures to 1,1-dichloroethane; read-across from 1,2-dichloroethane was required to fill in this data gap
- Degeneration with necrosis of the olfactory neuroepithelial mucosa at a NOAEC of 202 mg/m^3 (or $NOAEC_{adj}$ of 71.3 mg/m^3); ($BMCL_{10}$ = 48.9 mg/m^3, Dow Chemical, 2006b) was selected as the critical endpoint from among several acute toxicity studies
- Decreased body weight of selected F1B male weanlings at a NOAEC of 613 mg/m^3 (Rao et al., 1980) was selected as a co-critical endpoint
- Rao et al. (1980) study used for the co-critical endpoints with $BMCL_{10}$ is very close to that from the recommended critical endpoint (50 mg/m^3 vs 48.9 mg/m^3, respectively)
  - However, considering NOAECs/LOAECs, the selected critical endpoint will be protective of the decreases in pup body weight

This information is presented in *Table 5-43 of the 1,1-Dichloroethane Draft RE*

COMPARISON OF THE ACUTE INHALATION NON-CANCER POD: EPA and ATSDR

Charge Q 6a-c

EPA 1,1-Dichloroethane Draft Risk Evaluation

- Non-cancer acute inhalation POD based on degeneration with necrosis of the olfactory mucosa in male and female rats from the Dow (2006) study in 1,2-dichloroethane (based on read-across)
- RfC = $BMCL_{HEC}$ for workers ÷ UF = 41.1 mg/m^3 ÷ 30 = 1.37 mg/m^3

ATSDR (2022) Draft Toxicological Profile for 1,2-Dichloroethane

- A minimum risk level (MRL) for the acute inhalation POD was 0.3 ppm (1.2 mg/m^3) based on degeneration, with necrosis, olfactory epithelium in rats (Dow Chemical, 2006; Hotchkiss et al., 2010))
- Acute Duration Inhalation MRL = $BMCL_{HEC}$ ÷ UF = 9.2 ÷ 30 = 0.3 ppm (1.2 mg/m^3)

ATSDR (2024) Final Toxicological Profile for 1,2-Dichloroethane

- A minimum risk level (MRL) for the acute inhalation POD was 0.1 ppm (0.4 mg/m^3) based on degeneration, with necrosis, olfactory epithelium in rats (Dow Chemical, 2006; Hotchkiss et al., 2010).
- Acute Duration Inhalation MRL =$BMDL_{HEC}$ ÷ UF = 3.84 ÷ 30 = 0.1 ppm (0.4 mg/m^3)

BENCHMARK DOSE MODELING FOR THE SELECTED ACUTE INHALATION NON-CANCER POD

Charge Q 6a-c

- Benchmark dose modeling was completed and used for several non-cancer points of departure for acute inhalation, including degeneration with necrosis of the olfactory neuroepithelial mucosa, the selected critical endpoint (NOAEC of 202 mg/m^3 or 71.3 mg/m^3 for an adjusted continuous exposure concentration), with a $BMCL_{10}$ = 48.9 mg/m^3 from the Dow Chemical study (2006b).

- The modeling results are shown on the next slide

- A Benchmark response level of 10% ($BMCL_{10}$) was chosen according to EPA's BMD Technical Guidance (U.S. EPA, 2012).

This information is in the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling (U.S. EPA, 2024c).*

BENCHMARK DOSE MODELING FOR THE SELECTED ACUTE INHALATION NON-CANCER POD

Charge Q 6a-c

Model	Goodness of Fit		BMD 10%ER (mg/m^3)	BMDL 10%ER (mg/m^3)	Basis for Model Selection
	p-value	AIC			
Dichotomous Hill	1.000	23.96	131	78.1	All models provided adequate fit to the data (chi-square p-value > 0.1) except for the Multistage 1-degree/Quantal Linear model. **The BMDLs of the fit models were sufficiently close (differed by < 3-fold);** therefore, EPA chose the model with the lowest Akaike's Information Criterion (AIC).
Gamma	0.9847	24.01	112	75.2	
Log-Logistic	0.9779	24.04	114	77.5	
Multistage 3	**0.8911**	**21.80**	**81.4**	**48.9**	
Multistage 2	0.3612	26.88	57.8	34.3	
Multistage 1	0.0570	32.87	23.1	14.8	
Weibull	0.9664	22.40	106	68.2	
Logistic	0.8515	24.46	110	72.6	
Log-Probit	0.9965	23.97	114	77.8	
Probit	0.9049	24.26	110	70.5	
Quantal Linear	0.0570	32.87	23.1	14.8	

Table 2-14 from the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling*

BENCHMARK DOSE MODELING FOR THE SELECTED ACUTE INHALATION NON-CANCER POD

Charge Q 6a-c

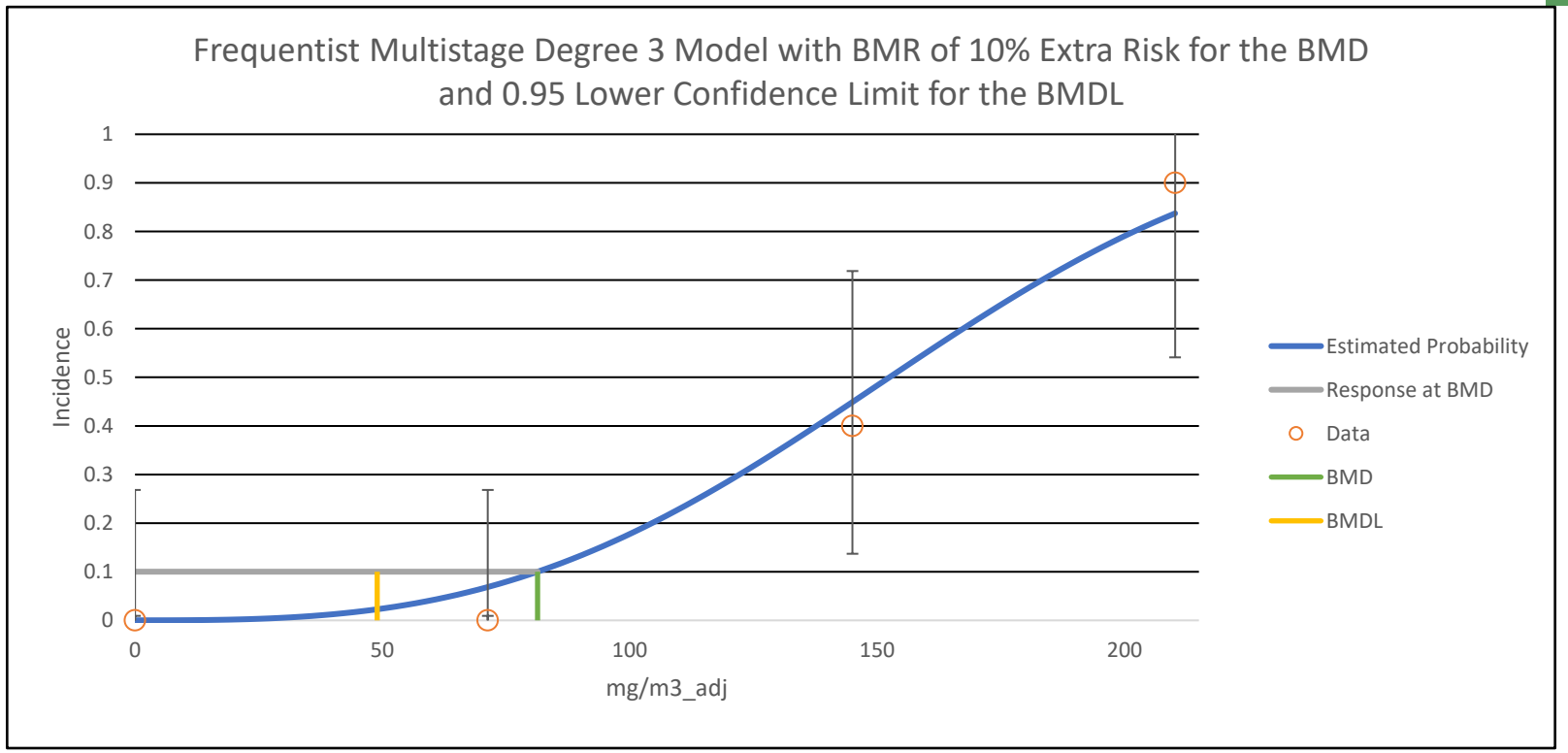


Figure 2-15. Plot of Non-Cancer Response by Concentration with Fitted Curve for the Selected Model (Multistage 3-Degree) for Degeneration with Necrosis of the Olfactory Mucosa in Male and Female Rats (Combined) Exposed to 1,2-Dichloroethane Via Inhalation for 8 Hours and BMR of 10% ER. The statistical lower confidence limit (BMCL) on the concentration at the BMC used as the POD is lower than the NOAEC (duration adjusted 71.3 mg/m^3). This information is in the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling*

SOLICITING COMMENTS ON BENCHMARK DOSE MODELING FOR THE SELECTED ACUTE INHALATION NON-CANCER POD

Charge Q 6a-c

- The statistical lower confidence limit (BMCL) on the concentration at the BMC used as the POD is lower than the NOAEC
- The U.S. EPA (2012) Benchmark Dose Technical Guidance states that extrapolation sufficiently below the observable range may be too uncertain to reliably estimate BMDs/BMDLs for the selected BMR (e.g., when all the dosed groups have near-maximal responses). However, the responses were not near maximal at all doses in this case
  - The guidance further states that in such cases, BMD modeling is not recommended and obtaining more data or using the NOAEL/LOAEL approach, while recognizing the inabilities of that approach to resolve the data limitations, may be warranted
- BMCLs of the fit models ***were sufficiently close*** (the BMCL of 48.9 mg/m^3 is less than 3-fold below the adjusted NOAEC from that study (71.3 mg/m3).
- Although the benchmark modeled data for the Dow Chemical (2006) study was lower than the study NOAEL, the BMCL can be less than the lowest dose and can be less than the NOAEL value; this is because, "the NOAEL approach can inappropriately reward underpowered studies"[a]
- Soliciting comments on the benchmark response level selected, benchmark dose analyses used, and the clarity and completeness of the description of the BMC analysis
  - This information is presented in Table 5-43 in the *1,1-Dichloroethane Draft RE*

[a]Please see the March 22, 2024 Training: https://www.epa.gov/bmds/bmds-training-videos

1,1-DICHLOROETHANE NON-CANCER SUBCHRONIC INHALATION NON-CANCER DURATION POINT OF DEPARTURE (POD)

Charge Q 7a-c

- Non-cancer POD based on the benchmark response of 5% ($BMCL_5$) of 21.2 mg/m^3 1,2-dichloroethane based on decreases in sperm concentration in male mice
- Allometric body weight scaling to the ¾ power used to derive the human equivalent concentration (HEC) of 89.0 mg/m^3 for workers and 21.2 mg/m^3 for continuous from the $BMCL_5$
- Total uncertainty factor (UF) of 30 proposed as the benchmark margin of exposure (MOE)
- Intraspecies UF (UF_H) of 10X and an interspecies UF (UF_A) of 3X (reduced from 10X), consistent with U.S. EPA Guidance (U.S.EPA, 2011)

Adapted from Table 5-50 in the 1,1-Dichloroethane Draft RE

Target Organ/ System	Species/ Gender	Duration	Study POD/Type	Effect	Worker HEC [mg/m³] (ppm)	Continuous HEC [mg/m³] (ppm)	Uncertainty Factors	Reference	Data Quality
Reproductive	Mice (male)	1,2-dichloroethane (read-across) 4-week inhalation	$BMCL_5$ = 21.2 mg/m^3	Decreases in sperm concentration	[89.0 mg/m^3] (22.0 ppm)	[21.2 mg/m^3] (5.2 ppm)	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 1 UF_D = 1 ***Total UF= 30***	Zhang et al. (2017)	High

WEIGHT OF SCIENTIFIC EVIDENCE IN SUPPORT OF SUBCHRONIC INHALATION NON-CANCER POD

Charge Q 7a-c

- Adequate data were not available to identify PODs following subchronic inhalation exposures to 1,1-dichloroethane; read-across from 1,2-dichloroethane was required to fill in this data gap
- Decreases in sperm concentration with a $BMCL_5$ 21.2 mg/m^3, from Zhang et al. (2017), was selected as the critical endpoint from among several subchronic toxicity studies
- Decreased body weight of selected F1B male weanlings with the $BMCL_5$ of 25 mg/m^3 (Rao et al., 1980) was selected as a co-critical endpoint, very close to the critical endpoint identified
- Considering NOAECs/LOAECs, using the critical endpoint will be human health protective of the decreases in pup body weight
- Benchmark response of 5% ($BMCL_5$) was conducted because EPA considers a $\geq$5% change in sperm concentration to be biologically relevant
- The $BMCL_5$ 21.2 mg/m^3 is <3-fold below the lowest concentration tested of 25.68 mg/m^3, thus a reliable extrapolation according to BMD guidance (U.S. EPA, 2022)

This information is presented in *Table 5-45 in the 1,1-Dichloroethane Draft RE*

1,1-DICHLOROETHANE NON-CANCER CHRONIC INHALATION DURATION NON-CANCER POINT OF DEPARTURE (POD)

Charge Q 7a-c

- Non-cancer POD based on the benchmark response of 5% ($BMCL_5$) of 21.2 mg/m^3 1,2-dichloroethane based on decreases in sperm concentration in male mice
- Allometric body weight scaling to the ¾ power used to derive the human equivalent concentration (HEC) of 89.0 mg/m^3 for workers and 21.2 mg/m^3 for continuous from the BMC_5
- Total uncertainty factor (UF) of 300 proposed as the benchmark margin of exposure (MOE)
- Intraspecies UF (UF_H) of 10X, an interspecies UF (UF_A) of 3X (reduced from 10X), and a UFs of 10x for subchronic to chronic duration, consistent with U.S. EPA Guidance (U.S.EPA, 2011)

Adapted from Table 5-51 in the 1,1-Dichloroethane Draft RE

Target Organ/ System	Species/ Gender	Duration	Study POD/Type	Effect	Worker HEC [mg/m^3] (ppm)	Continuous HEC [mg/m^3] (ppm)	Uncertainty Factors	Reference	Data Quality
Reproductive	Mice (male)	1,2-dichloroethane (read-across) 4-week inhalation	$BMCL_5$ = 21.2 mg/m^3	Decreases in sperm concentration	[89.0 mg/m^3] (22.0 ppm)	[21.2 mg/m^3] (5.2 ppm)	UF_A = 3 UF_H = 10 UF_L = 1 UF_S = 10 UF_D = 1 ***Total UF= 300***	Zhang et al. (2017)	High

WEIGHT OF SCIENTIFIC EVIDENCE IN SUPPORT OF THE CHRONIC INHALATION NON-CANCER POD

Charge Q 7a-c

- Adequate data were not available to identify PODs following chronic inhalation exposures to 1,1-dichloroethane; read-across from 1,2-dichloroethane was required to fill in this data gap
- Decreases in sperm concentration with a BMCL5 21.2 mg/m^3, from Zhang et al. (2017), was selected as the critical endpoint from among several subchronic toxicity studies
- Decreased body weight of selected F1B male weanlings with the BMCL5 of 25 mg/m^3 (Rao et al., 1980) was selected as a co-critical endpoint, very close to the critical endpoint identified
- Using the critical endpoint will be protective of the decreases in pup body weight
- A duration extrapolation from the 4-week short-term/subchronic to a chronic duration was conducted to account for uncertainty, using a subchronic to chronic UF of 10
- Although an uncertainty regarding study duration may have been reduced while performing read-across by use of the chronic (Nagano et al., 2006) study that evaluated 1,2-dichloroethane cancer endpoints, that study did not adequately evaluate non-cancer effects, precluding the determination of a non-cancer chronic POD
- Benchmark response of 5% ($BMCL_5$) was conducted because EPA considers a >5% change in sperm concentration to be biologically relevant
- The $BMCL_5$ 21.2 mg/m^3 is <3-fold below the lowest concentration tested of 25.68 mg/m^3

This information is presented in *Table 5-47 in the 1,1-Dichloroethane Draft RE* and in the *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Benchmark Dose Modeling*

EXISTING ASSESSMENTS: EPA'S PPRTV (2010) FOR 1,2-DICHLOROETHANE

Charge Q 7c

Acute Duration

- A provisional (p-RfC) value was not derived for an acute inhalation POD

Subchronic Duration

- A p-RfC is based on neurobehavioral impairment (Kozik, 1957), with an UF = 300
- Confidence in the study (Kozik, 1957) is very low (UF_D of 3 was added); overall confidence is low.
- This study rated as "uninformative" for dose-response by OPPT's systematic review.

Subchronic Duration p–RfC = LOAEL÷ UF = 22 ÷300 = **0.07 mg/m^3**

Summary Table for the U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for Subchronic Duration for 1,2-Dichloroethane (2010)

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Neurobehavioral Function	Humans	Unknown/Occupational Exposure	LOAEL = 22 mg/m^3	Neurobehavioral Impairment	UF_A = 1 UF_H = 10 UF_L = 10 UF_D = 3 ***Total UF= 300***	Kozik, 1957

UF_A: A factor of 1 is applied for animal-to-human extrapolation because a human study served as the basis for the p-RfC
UF_H: A factor of 10 applied for extrapolation to a potentially susceptible human subpopulation, data for evaluating susceptible human responses are insufficient
UF_L: A factor of 10 is applied for using a LOAEL as the POD
UF_D: A factor of 3 is applied for database inadequacies, lack of a comprehensive animal bioassay of potential neurotoxicity , and lack of a high-quality key study

EXISTING ASSESSMENTS: EPA'S PPRTV (2010) FOR 1,2-DICHLOROETHANE

Charge Q 7c

Chronic Duration

- A p-RfC is based on neurobehavioral impairment (Kozik, 1957), with an UF = 3000
- Confidence in the study (Kozik, 1957) is very low (UF_D of 3 was added); overall confidence is low.
- This study rated as "uninformative" for dose-response by OPPT systematic review.

Screening Chronic p–RfC = LOAEL ÷ UF = 22 ÷3,000 = **0.007 mg/m³**

Summary Table for the 2010 U.S. EPA's Provisional Peer-Reviewed Toxicity Value (PPRTV) for Chronic Duration for 1,2-Dichloroethane

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Neurobehavioral Function	Humans	Unknown/Occupational Exposure	LOAEL = 22 mg/m³	Neurobehavioral Impairment	UF_A = 1 UF_H = 10 UF_L = 10 Ufs = 10 UF_D = 3 ***Total UF= 3000***	Kozik, 1957

UF_H: A factor of 10 applied for extrapolation to a potentially susceptible human subpopulation, data for evaluating susceptible human responses are insufficient
UF_A: A factor of 1 is applied for animal-to-human extrapolation because a human study served as the basis for the p-RfC
UF_L: A factor of 10 is applied for using a LOAEL as the POD
UFs: A factor of 10 is applied for subchronic to chronic
UF_D: A factor of 3 is applied for database inadequacies, lack of a comprehensive animal bioassay of potential neurotoxicity , and lack of a high-quality key study

EXISTING ASSESSMENTS: ATSDR (2022) DRAFT TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

Charge Q 7c

Acute Duration

- A minimum risk level (MRL) for the acute inhalation POD was 0.3 ppm (1 mg/m^3) based on degeneration, with necrosis, olfactory epithelium in rats (Dow Chemical, 2006; Hotchkiss et al., 2010).

Subchronic and Chronic Duration

- MRLs were not derived in the ATSDR (2022) Toxicological Profile for 1,2-Dichloroethane

Acute Duration Inhalation MRL = $BMCL_{HEC} \div UF = 9.2 \div 30 =$ **0.3 ppm (1 mg/m^3)**

Summary Table for the 2022 Agency for Toxic Substances and Disease Registry (ATSDR) MRL for the Acute Duration for 1,2-Dichloroethane

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Neurological	Rats (Females)	4-hour Inhalation[a]	$BMCL_{10}$ = 230.7 mg/m^3 $BMCL_{HEC}$ = 37.24 mg/m^3	Degeneration/Necrosis of the Nasal Epithelium	UF_A = 3 UF_H = 10 UF_L = 1 Ufs = 1 UF_D = 1 ***Total UF= 30***	Dow Chemical, 2006; Hotchkiss et al., 2010

[a]4-hour inhalation at 50 ppm (NOAEC); 8-hours at 100 and 150 ppm.
UF_A: A factor of 3 for extrapolation from animals to humans.
UF_H: A factor of 10 for human variability.

EXISTING ASSESSMENTS: ATSDR (2024) FINAL TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

Charge Q 7c

Acute Duration

- A minimum risk level (MRL) for the acute inhalation POD was 0.1 ppm (0.4 mg/m^3) based on degeneration, with necrosis, olfactory epithelium in rats (Dow Chemical, 2006; Hotchkiss et al., 2010).

Acute Duration Inhalation MRL =$BMDL_{HEC}$ ÷ UF = 3.84 ÷ 30 **= 0.1 ppm (0.4 mg/m^3)**

Summary Table for the 2024 Agency for Toxic Substances and Disease Registry (ATSDR) MRL for the Acute Duration for 1,2-Dichloroethane

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Neurological	Rats (Males and Females Combined)	8-hour Inhalation	$BMCL_{10}$ = 233.21 mg/m^3 $BMCL_{HEC}$ = 0.95 mg/m^3	Degeneration/Necrosis of the Nasal Epithelium	UF_A = 3 UF_H = 10 UF_L = 1 Uf_S= 1 UF_D = 1 ***Total UF= 30***	Dow Chemical, 2006; Hotchkiss et al., 2010
UF_A: A factor of 3 for extrapolation from animals to humans. UF_H: A factor of 10 for human variability.						

EXISTING ASSESSMENTS: ATSDR (2024) FINAL TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

Charge Q 7c

Intermediate Duration

- A minimum risk level (MRL) for the intermediate inhalation POD was 0.1 ppm (0.4 mg/m^3) based on altered behavior in an open field test in mice in a 28-day inhalation study by Zhong et al. (2022)

Chronic Duration

- MRLs were not derived in the ATSDR (2024) Toxicological Profile for 1,2-Dichloroethane

Intermediate Duration Inhalation MRL = $BBMCL_{1std-HEC} \div UF = 3.70 \div 30 =$ **0.1 ppm (0.4 mg/kg–day)**

Summary Table for the 2024 Agency for Toxic Substances and Disease Registry (ATSDR) MRL for Intermediate Duration for 1,2-Dichloroethane

Target Organ/ System	Species/ Gender	Duration/Route	Study POD/Type	Effect	Uncertainty Factors	Reference
Neurological	Mice (male)	28-day whole-body inhalation	$BBMCL_{1std}$ = 59.9 mg/m^3 $BBMCL_{1std-HEC}$ = 14.98 mg/m^3	Altered behavior in open field (decreased distance and time in central area); vacuolization and demyelination in the cerebral cortex	UF_A = 10 UF_H = 3 ***Total UF= 30***	Zhong et al., 2022

[a] The Bayesian benchmark response of 1 standard deviation ($BBMCL_{1SD}$).
UF_A: A factor of 10 is applied for animal-to-human extrapolation.
UF_H: A factor of 10 is applied for human variability.

1,1- AND 1,2-DICHLOROETHANE NON-CANCER HUMAN HEALTH HAZARD ASSESSMENT

Overall Summary:

- EPA identified kidney toxicity, immunotoxicity, neurotoxicity and male reproductive toxicity as the most sensitive critical human health hazard non-cancer outcomes associated with 1,2-dichloroethane.
- Inferences across evidence streams and the overall WOSE judgement for these critical endpoints indicates that 1,2-dichloroethane is *likely* to cause these effects. (*Appendix M.6 in the 1,1-Dichloroethane Draft Risk Evaluation*)
- Overall, 1,2-dichloroethane provides human health protective PODs for 1,1-dichloroethane

Thank you for your attention

1,1- AND 1,2-DICHLOROETHANE DRAFT CANCER HUMAN HEALTH HAZARD ASSESSMENT

Katherine Anitole, Ph.D.; OCSPP/OPPT/ECRAD/RAB5

Charge Question	Location in 1,1-Dichloroethane Draft Risk Evaluation
9c, 9d, 9e, 9f, 9g, 12	Sections 5.2.1.2.2, 5.2.1.3, 5.2.5, Appendix J.2; *EPA Peer Review of Carcinogenicity Studies for 1,1-Dichloroethane and 1,2-Dichlorothane* (2024)

1,1- AND 1,2-DICHLOROETHANE DRAFT CANCER HUMAN HEALTH HAZARD ASSESSMENT

Charge Q 9c, 12

ORAL CANCER DATA FOR 1,1-DICHLOROETHANE

- EPA identified a single cancer study by the oral route in rats and mice for 1,1-NTP (1978a)
  - The rat portion of this study was rated as "***uninformative***" by SR review based on rats from all study groups (including both sexes and controls) exhibited high incidences of pneumonia (up to 95%) and decreased survival rates
    - This aspect was not discussed nor mentioned by the study authors
    - These data were not appropriate for use to quantitative risk assessment
  - The mouse portion of this study was rated as "***high***" by SR based on a statistically significant increase in benign uterine endometrial stromal polyps (4/46) in high-dose females, which were not observed in any other group
    - No other statistically significant evidence of cancer was observed
    - Pre-cancerous endometrial polyps are **NOT** a tissue growth amenable to calculate cancer slope factors
- As a result, EPA did **NOT** use the NTP (1978a) oral cancer study on 1,1-dichloroethane in rats and mice to calculate cancer slope factors for 1,1-dichloroethane

INHALATION and DERMAL CANCER DATA FOR 1,1-DICHLOROETHANE

- Cancer studies via the inhalation or dermal exposure routes for 1,1-dichloroethane were not available.

1,1- AND 1,2-DICHLOROETHANE DRAFT CANCER HUMAN HEALTH HAZARD ASSESSMENT

Charge Q 9e, 12

ORAL CANCER DATA FROM 1,2-DICHLOROETHANE

- EPA identified the oral cancer data on 1,2-dichloroethane from one study in rats and mice, NTP (1978b)
  - The rat portion of this study was rated as "**uninformative**" by SR review based on rats from all study groups (including both sexes and controls) exhibited high incidences of pneumonia (up to 95%) and decreased survival rates
    - This aspect was not discussed nor mentioned by the study authors
    - These data were not appropriate for use to quantitative risk assessment
  - The mouse portion of this study was rated as "**high**" by SR review based on:
    - Statistically significant increase in significantly increased incidence of forestomach squamous-cell carcinomas and circulatory system hemangiosarcomas in male mice
    - Significant increases in mammary adenocarcinoma incidence in mice
    - Alveolar/bronchiolar adenomas developed in mice
    - Female mice developed endometrial stromal polyps and sarcomas
    - Males developed hepatocellular carcinomas

- As a result, EPA used the NTP (1978b) oral cancer study on 1,2-dichloroethane as read-across based on hepatocellular carcinomas in male B6C3F1 mice to calculate cancer slope factor (CSF) for 1,1-dichloroethane (IRIS (1987) also utilized this study to calculate a CSF)

1,1- AND 1,2-DICHLOROETHANE DRAFT CANCER HUMAN HEALTH HAZARD ASSESSMENT

Charge Q 9c, 9e-g

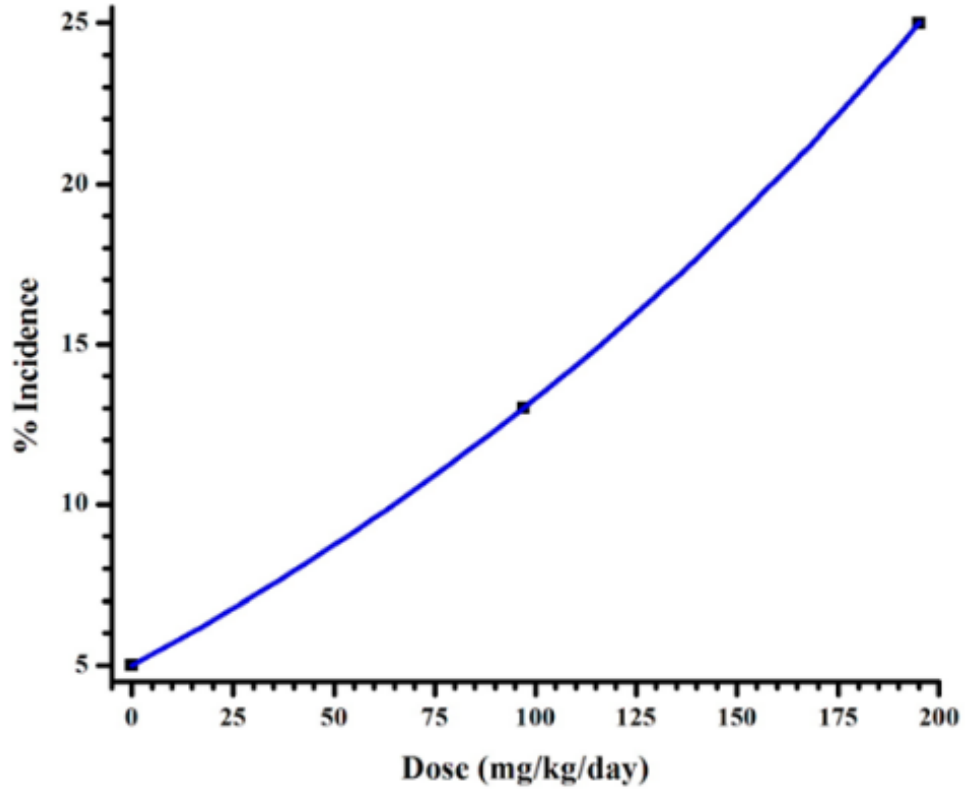


Figure 5-7. Hepatocellular Carcinoma Dose Response in Male Mice for Oral Exposure to 1,2-Dichloroethane NTP (1978) from the 1,1-Dichloroethane Draft RE

1,1- AND 1,2-DICHLOROETHANE DRAFT CANCER HUMAN HEALTH HAZARD ASSESSMENT

Charge Q 9d

INHALATION CANCER DATA FROM 1,2-DICHLOROETHANE

- No inhalation cancer study for 1,1-dichloroethane was available, therefore, cancer data for 1,2-dichloroethane was required for the inhalation route by the same read-across rationale as for the oral route
- The Nagano et al. (2006) 1,2-dichloroethane inhalation cancer study produced some of the same tumors as observed in the 1,2-dichloroethane oral cancer study (High SR rating)
  - Mammary gland adenomas, fibroadenomas, adenocarcinomas, subcutaneous fibromas, bronchioalveolar adenoma & carcinoma, hepatocellular adenoma
  - Systematic review which received a “high” quality rating and could be used quantitatively for the carcinogenicity assessment via the inhalation route in both rats and mice
- As a result, EPA used the Nagano et al. (2006) inhalation cancer study on 1,2-dichloroethane as read-across based on combined mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas in female rats to calculate the inhalation unit risk (IUR) for 1,1-dichloroethane.

1,1- AND 1,2-DICHLOROETHANE DRAFT CANCER HUMAN HEALTH HAZARD ASSESSMENT

Charge Q 9d

- The oral cancer slope factor (CSF) relied on read-across from 1,2-dichloroethane, based on hepatocellular carcinomas in male mice (NTP 1978b, "high" SR)
  - This oral CSF was used to calculate a drinking water unit risk of 1.8 E−06 per ug/L
  - Due to scarcity of cancer data by the dermal route, route-to-route extrapolation from the oral slope factor was used for the dermal route
- Inhalation Unit Risk (IUR) relied on read-across from 1,2-dichloroethane, based on combined mammary gland adenomas, fibroadenomas, and adenocarcinomas and subcutaneous fibromas in female rats (Nagano et al., 2006, "high" SR)

Exposure Assumption	Oral Slope Factor	Dermal Slope Factor	Inhalation Unit Risk	Drinking Water Unit Risk
Continuous Exposure	0.062 per mg/kg/day	0.062 per mg/kg/day	7.1E−06 (per µg/m^3) 2.9E−2 (per ppm)	1.8E−06 per ug/L
Worker	0.062 per mg/kg/day	0.062 per mg/kg/day	2.4E−06 (per µg/m^3) 9.5E−3 (per ppm)	1.8E−06 per ug/L

Adapted from Table 5-52 in the 1,1-Dichloroethane Draft Risk Evaluation

CONSULATION WITH AN INTERNAL EPA AD-HOC COMMITTEE

Charge Q 9c, 9e-g

- EPA consulted with an internal EPA ad-hoc committee of four staff to evaluate the individual study quality and use of the available carcinogenicity studies for 1,1-dichloroethane and 1,2-dichloroethane. These studies were:
  1. **NTP. (1978a). Bioassay of 1,1-dichloroethane for possible carcinogenicity.** (NCI-CG-TR66). Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr066.pdf.
  2. **NTP. (1978b). Bioassay of 1,2-dichloroethane for possible carcinogenicity.** (NCI-CG-TR55). Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr055.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tr055.
  3. **Carcinogenicity and chronic toxicity in rats and mice exposed by inhalation to 1,2-dichloroethane for two years.** Nagano, K; Umeda, Y; Senoh, H; Gotoh, K; Arito, H; Yamamoto, S; Matsushima, T. (2006). J Occup Health 48: 424-436. http://dx.doi.org/10.1539/joh.48.424. https://www.jstage.jst.go.jp/article/joh/48/6/48_6_424/_pdf

The internal EPA ad-hoc committee memorandum is available in the *1,1-Dichloroethane - EPA Peer Review of Carcinogenicity Studies* supplemental file

1. NTP (1978a). ORAL BIOASSAY OF 1,1-DICHLOROETHANE FOR POSSIBLE CARCINOGENICITY

Charge Q 9c, 9e-g

Internal EPA Ad-Hoc Committee Conclusions:

- Rats:
  - Data in rats from this study are not appropriate for use for in quantitative risk assessment based on the following:
    - High incidences for pneumonia
    - Poor survival in all dosed groups as well as the control groups
- Mice:
  - Data in mice are not appropriate for use in quantitative risk assessment since there was no conclusive evidence of carcinogenicity.
  - In addition, qualitative use of the data is not appropriate

Additional details regarding the evaluation of this study are outlined in the *1,1-Dichloroethane - EPA Peer Review of Carcinogenicity Studies* supplemental file

2. NTP (1978b). ORAL BIOASSAY OF 1,2-DICHLOROETHANE FOR POSSIBLE CARCINOGENICITY

Charge Q 9c, 9e-g

Internal EPA Ad-Hoc Committee Conclusions:

- Rats:
  - Data in rats from this study are not appropriate for use for quantitative risk assessment based on the following:
    - High incidences for pneumonia
    - Poor survival in all dosed groups as well as the control groups
- Mice:
  - Data in mice from this study are not appropriate for use for quantitative risk assessment based on several guideline and methodological reasons.

Additional details regarding the evaluation of this study are outlined in the *1,1-Dichloroethane - EPA Peer Review of Carcinogenicity Studies* supplemental file

3. NAGANO ET AL. (2006). INHALATION TWO-YEAR CARCINOGENICITY STUDY WITH 1,2-DICHLOROETHANE

Charge Q 9c, 9e-g

Internal EPA Ad-Hoc Committee Conclusions:

- Data in rats and mice from this study are appropriate for use for quantitative risk assessment

Additional details regarding the evaluation of this study are outlined in the *1,1-Dichloroethane - EPA Peer Review of Carcinogenicity Studies* supplemental file

CONSULTATION WITH AN INTERNAL EPA AD-HOC COMMITTEE

KEY POINTS AND CONCLUSIONS

Charge Q 9c, 9e-g

- The NTP (1978a and 1978b) oral rat studies for 1,1- and 1,2-dichloroethane *are not* appropriate for use for quantitative risk assessment in the weight of evidence for evaluating carcinogenicity
- The NTP (1978a) oral mouse study for 1,1-dichloroethane *is not* appropriate for quantitative or qualitative risk assessment in the weight of evidence for evaluating 1,2-dichloroethane carcinogenicity
  - However, ECRAD is proposing to use the study in mice for 1,1-dichloroethane qualitatively since this study rated “high” in OPPT's SR
- The NTP (1978b) oral mouse study for 1,2-dichloroethane *is not* appropriate for quantitative risk assessment in the weight of evidence for evaluating 1,2-dichloroethane carcinogenicity.
  - However, OPPT’s SR rated the mouse study in 1,2-dichloroethane as “high”
  - Additionally, IRIS (1987) concluded that 1,2-dichloroethane as a probable carcinogen and used the NTP (1978b) study as the basis for the oral slope factor
  - ECRAD is proposing to use this same study for this draft risk evaluation
- The Nagano et al. (2006) *is* appropriate for use in quantitative risk assessment in the weight of evidence for evaluating 1,2-dichloroethane carcinogenicity

1,1-DICHLOROETHANE HUMAN HEALTH HAZARD READ-ACROSS APPROACH

Studies	1,1-Dichloroethane	1,2-Dichloroethane
NTP Oral Rat Studies ("uninformative" SR rating)	Mammary gland adenocarcinomas, hemangiosarcoma (NTP, 1978a)	Mammary gland adenocarcinomas, hemangiosarcoma (NTP, 1978b)
NTP Oral Mouse Studies ("high" SR rating)	Endometrial stromal polyps (precursor) NTP (1978a)	Endometrial stromal polyps (precursor), NTP (1978b) Hepatocarcinomas; basis for IRIS calculated cancer slope factor (NTP, 1978b)
Inhalation Studies	Chronic study, but not a cancer study, (Hofmann et al., 1971b, "uninformative" SR rating)	Mammary gland adenomas; fibroadenomas, adenocarcinomas; subcutaneous fibromas; bronchioalveolar adenoma & carcinoma; endometrial stromal polyps; hepatocellular adenoma (Nagano et al., 2006, "high" SR rating)
Dermal Study	None	Bronchioalveolar adenomas and adenocarcinomas (mice, 1 dose) (Suguro et al., 2017, "high" SR rating)
Human Studies	Indeterminate	Indeterminate

Adapted from Table Apx J-9 in the 1,1-Dichloroethane Draft RE

OVERALL NON-CANCER and CANCER HUMAN HEALTH HAZARD KEY POINTS & CONCLUSIONS

Charge Q 9c, 9e-g

- As acceptable human health hazard data were not available to assess non-cancer or cancer risks for 1,1-dichloroethane, EPA needed to use a “read-across” approach using data available for a closely related chemical or analog 1,2-dichloroethane to evaluate the human health hazard of 1,1-dichloroethane
- An analysis of other chlorinated solvents as potential analogs for read-across data were performed following the general principles for read-across as outlined in Lizarraga et al. (2019), taking into consideration, structural similarities, physical-chemical properties, metabolism, and toxicological similarities and adequate data availability
- The analyses resulted in the identification of 1,2-dichloroethane (a close structural isomer of 1,1-dichloroethane) as the most appropriate analog to fill the identified data gaps for 1,1-dichloroethane and a consultation with the EPA Office of Research and Development (ORD) agreed
- EPA has high confidence that the 1,2-dichloroethane data will accurately reflect both the non-cancer & cancer hazards of 1,1-dichloroethane and be human health protective for 1,1-dichloroethane exposures

Thank you for your attention

DERMAL ABSORPTION: INTERPRETATION AND USE OF THE NEW *IN VITRO* STUDY

William Irwin, PhD, DABT, ERT, FATS; OCSPP/OPPT/ECRAD/RAB4

Charge Question	**Location in 1,1-Dichloroethane Draft Risk Evaluation**
8	Document 32. *1,1-Dichloroethane - Draft Dermal Absorption Study Analysis* supplemental file

In Vitro Dermal Absorption Results

Charge Q 8

- OECD 428 Testing: "that to which humans or other potential target species may be exposed".
  - Conditions of Use (COU) is neat or pure 1,1-dichloroethane
- Neat or pure 1,1-dichloroethane raw mean dermal absorption is 0.13% at 58.4% average mass recovery
- Neat 1,1-dichloroethane raw dermal absorption replicates range is 0.08-0.21%
- EPA corrected absorption so that only a portion of the missing mass is considered absorbed: Mean corrected absorption is 0.22%, Corrected absorption range is 0.14-0.36% (PESS)
- The dermal absorption of the analog 1,2-dichloroethane is 0.21% (ATSDR, 2022)
- OECD GD156 on data variability: “The use of the upper confidence limit (95% confidence interval) addresses uncertainty about mean absorption due to sampling variability. This approach is reasonably conservative and could reduce the need to repeat studies.” 1,1-Dichloroethane coefficient of variation cohorts all exceeded the OECD limit of 25%.
- For neat 1,1-Dichloroethane the 95% upper confidence level is 0.31% dermal absorption
- See docket Document 32 for details on the dermal absorption calculations

Methods of Dermal Absorption Calculations

Charge Q 8

1. Assume missing mass is not absorbed

- OECD GD156 (2022): “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”
- EFSA (2017): “Losses that are considered to be from non-absorbed material will have no impact on the results”
- However, the 1,1-dichloroethane testing utilized a vapor trap, donor chamber washings and skin washings to quantify known non-absorbed material

2. Assume only a portion of the missing mass is absorbed

- OECD GD156: “One approach would be to normalise the measured dermal absorption value [for losses]. This approach assumes that losses occurred in all matrices equally”
- For neat 1,1-dichloroethane results all replicates were less than 80% recovery, EPA chose this approach as reasonable

3. Assume all of the missing mass is absorbed

- OECD GD156 (2022): “As second approach would be to include all the unrecovered material in the amount that is potentially absorbed”
- EFSA (2017): "Adding the missing material should certainly apply when the calculated dermal absorption value is < 5% and recovery is < 95%" (This approach is very conservative)

There were no high recovery data >80% mass balance for the neat 1,1-dichloroethane COU testing to base the calculations, so lower recovery data replicates could not be excluded

1,1-DICHLOROETHANE DERMAL ABSORPTION RESULTS

Charge Q 8

Sample	Low Value	High Value	Mean Value	% CV	% Mass Balance
1% 1,1-DCA in IPM Vehicle	ND	0.101	0.02	200.0	88.87
10% 1,1-DCA in IPM Vehicle	ND	0.015	0.01	100.0	87.68
50% 1,1-DCA in IPM Vehicle	0.003	0.09	0.06	66.7	87.66
1% 1,1-DCA in 1,2-DCA Vehicle	ND	0.135	0.05	120.0	55.42
10%1,1-DCA in 1,2-DCA Vehicle	ND	0.045	0.02	100.0	92.76
50% 1,1-DCA in 1,2-DCA Vehicle	0.044	0.267	0.12	75.0	54.36
Neat, 100% 1,1-DCA	0.080	0.212	0.13	38.5	58.42
Red text indicates values outside the recommended range.					

Adapted from *Table 1 in Document 32. 1,1-Dichloroethane - Draft Dermal Absorption Study Analysis*

- OECD GD156 Guidance Document Cited in Test Order Followed for Data Calculations
- An Intermediate Dermal Absorption of 0.3% was Utilized for Risk Calculations, Data in IPM vehicle and at 1% or 10% concentrations are not conditions of use. TSCA is not required to follow EU EFSA policies.

1,1-DICHLOROETHANE DERMAL ABSORPTION RESULTS

Corrected % Absorption = Raw % Absorption/(% Recovery/100)

Charge Q 8

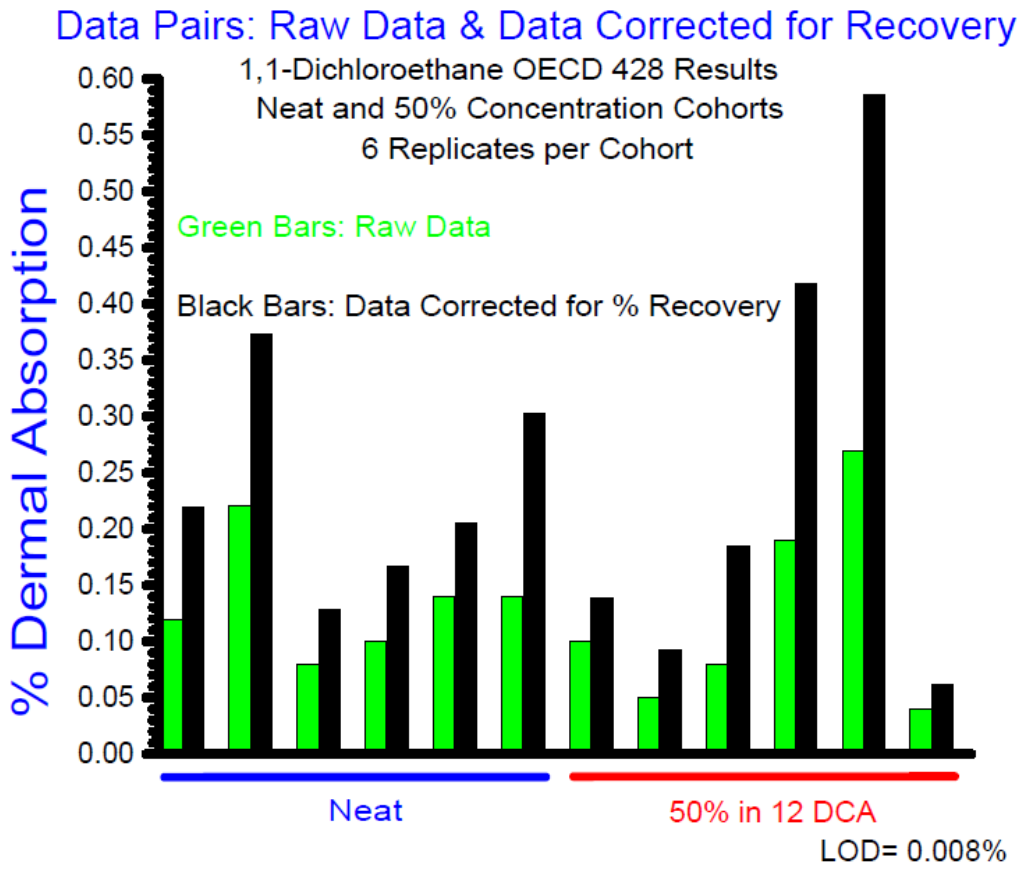


Figure 1. 1,1-Dichloroethane Dermal Absorption Data: Raw Data and Data Corrected for Recovery
OECD GD156 comments on correcting data for mass balance rather than repeating the study
Exposure model predicts 0.6% dermal absorption

Thank you for your attention

OCCUPATIONAL EXPOSURE

Greg Macek, OCSPP/OPPT/ECRAD/RAB4

Charge Question	Location in 1,1-Dichloroethane Draft Risk Evaluation
10a, 10b, 10c	Sections 5.1.1.1.2, 5.1.1.1.3 and 5.1.1.1.5 *Draft Risk Evaluation for 1,1-Dichloroethane – Supplemental Information File: Environmental Releases and Occupational Exposure Assessment*

OBJECTIVES OF THE OCCUPATIONAL EXPOSURE ASSESSMENT

- Identify Occupational Exposure Scenarios (OES) for each condition of use of 1,1-dichloroethane
- Identify Similar Exposure Groups (SEGs) to assess for each OES
  - Dependent on the amount of detail in the data source
  - If detail unavailable, assess for generic SEGs of “workers” and “occupational non-users” (ONU)
- Estimate occupational inhalation exposure and dermal exposure
  - Provide high-end and central tendency exposure results
- Evaluate the weight of scientific evidence for the exposure assessment for each OES

IDENTIFY AND DESCRIBE OESs

- OES determinations are largely driven by:
  - Similarities and differences in release and exposure potential between Conditions of Use (COUs)
  - Availability of data and modeling approaches to assess releases and exposures
- Generally, three approaches are followed:
  - Designate the COU as an OES to assess
  - Group multiple similar COUs into one OES
  - Take one COU and subdivide into multiple OES

IDENTIFY AND DESCRIBE OES

- 8 OESs identified for 1,1-dichloroethane:
  - Manufacturing
  - Processing as a Reactive Intermediate
  - Processing - Repackaging
  - Distribution in Commerce
  - Commercial Use as a Laboratory Chemical
  - General Waste Handling, Treatment, and Disposal
  - Waste Handling, Treatment, and Disposal (POTW)
  - Waste Handling, Treatment, and Disposal (Remediation)

ASSESSING INHALATION EXPOSURE: GENERAL APPROACH

Charge Q 10a

1. Monitoring Data
   a. Full-shift Personal Breathing zone (PBZ) data
   b. Chemical-Specific data for the OES being assessed
   c. Chemical-Specific data for use as analogous data (same chemical, similar OES)
   d. Surrogate monitoring data (similar chemical for the same OES)
   e. Area monitoring data
2. Modeling Approaches:
   a. Deterministic modeling approaches
   b. Probabilistic modeling approaches
3. Occupational Exposure Limits:
   a. Company-specific OELs (for site-specific assessments)
   b. OSHA PEL
   c. Voluntary Limits (ACGIH TLVs, NIOSH RELs)

ASSESSING INHALATION EXPOSURE TO 1,1-Dichloroethane

Charge Q 10a

- **1,1-Dichloroethane Monitoring Data – Collecting Primary Inhalation Monitoring Data**
  - Data on inhalation exposure to 1,1-dichloroethane during manufacture provided to EPA through Test Order
  - Used for the OES of Manufacture
  - Test Order data considered primary exposure data
    - Collected for the purpose of Risk Evaluation
    - EPA reviewed and approved sampling protocol
    - EPA received and reviewed Summary report
    - Includes all key metadata
  - Test Order Monitoring Study
    - Monitored 4 different SEGs
      - Operators/Process Technicians
      - Maintenance Technicians
      - Laboratory Technicians
      - ONUs
    - 62 Full-Shift PBZ samples were collected
  - Data rated as “high” quality per EPA data quality ratings for occupational exposure

ASSESSING INHALATION EXPOSURE TO 1,1-Dichloroethane

Charge Q 10a

- **Additional 1,1-Dichloroethane Monitoring Data from Test Orders**
  - Data on 1,1-dichloroethane inhalation exposure during production as a byproduct during manufacture of 1,2-dichloroethane
  - These data will be included in the *1,2-Dichloroethane Risk Evaluation*
  - Decision was made during scoping for 1,2-dichloroethane that byproducts of 1,2-dichloroethane manufacturing would be assessed in the *1,2-Dichloroethane Risk Evaluation*

ASSESSING INHALATION EXPOSURE TO 1,1-Dichloroethane

- **1,1-Dichloroethane Monitoring Data – Search for Secondary Exposure Data**
  - These monitoring data have been previously collected
  - No connection to EPA risk evaluations
  - Available to EPA through public databases such as OSHA CEHD (Chemical Exposure Health Data), NIOSH publications, scientific literature, comments on risk evaluation documents
  - Can still be rated as “high” quality but often lacks key metadata resulting in “lower” data quality rating
  - No secondary 1,1-dichloroethane monitoring data were identified

ASSESSING INHALATION EXPOSURE TO 1,1-Dichloroethane

Charge Q 10a

- **1,1-Dichloroethane Monitoring Data Used as Analogous Data**
  - *Processing as a Reactive Intermediate* OES considered as analogous to *Manufacture* OES
  - 1,1-Dichloroethane Test Order Inhalation Monitoring Data during Manufacture were used for this OES
  - This approach is consistent with one EPA has used previously (Ex. Perchloroethylene Risk Evaluation)
  - 1,1-Dichloroethane Test Order included a SEG for Laboratory Technicians
    - These data were used for the OES of Laboratory Chemical Use

ASSESSING INHALATION EXPOSURE TO 1,1-Dichloroethane

Charge Q 10b

FILLING DATA GAPS

- **Surrogate Monitoring Data**
  - Inhalation Monitoring Data for a similar chemical but same (or similar OES)
  - Search for surrogate data limited to:
    - EPA published Risk Evaluations – Draft or Final
    - Results from Systematic Review for chemicals EPA is currently working on – RE's not yet published
  - EPA's method for applying surrogate data to the chemical being assessed
    - Accounts for vapor pressure differences
    - Does not include combining chemical-specific data with surrogate data to estimate the exposures for an OES
  - Use of Surrogate Data for 1,1-Dichloroethane
    - Data on methylene Chloride and 1,2-dichloroethane were used for:
      - OES of Waste handling treatment, disposal (General)
      - OES of Waste handling treatment, disposal (POTW)

ASSESSING INHALATION EXPOSURE TO 1,1-DICHLOROETHANE

FILLING DATA GAPS

- **Probabilistic Modeling Approaches**
  - Used for the OES of Repackaging
  - EPA has a generic scenario for Repackaging which aids in model set-up and execution
  - Generic Scenario models inhalation exposure for worker activities of unloading, container cleaning and loading
  - Individual activity models are executed in a probabilistic mode with Monte Carlo using 100,000 iterations representing different combinations of parameter values.
  - Exposures for individual activities are then added together and averaged over 8-hr to estimate full-shift exposure

ASSESSING DERMAL EXPOSURE

Charge Q 10c

- Dermal Exposure Assessment for 1,1-Dichloroethane
  - 1,1-dichloroethane is a highly volatile chemical
  - No dermal monitoring data relevant to the Occupational Dermal Exposure Assessment for 1,1-Dichloroethane were identified from review of the scientific literature
  - For highly volatile chemicals, EPA uses the Dermal Exposure to Volatile Liquids (DEVL) model to estimate dermal exposure
  - This model was applied for all OES
  - EPA received data for the *1,1-Dichloroethane Test Order: In vitro OECD 428 dermal absorption study*
    - Proposed Dermal fraction absorption (f_{abs}) of 0.3 percent derived from test order study data
    - These data are one of the parameters in the DEVL model

DERMAL EXPOSURE MODEL

Charge Q 10c.i & c.ii

EPA Dermal Exposure to Volatile Liquids Model (DEVL)

$$D_{\text{exp}} = (S \; x \; Q_u \; x \; f_{abs} \; x \; Y_{derm} \; x \; FT)$$

Where:

D_{exp} = Dermal retained dose (mg/kg-day)

S = Surface area of contact (cm^2)

Q_u = Dermal Loading (mg/cm^2)

f_{abs} = Fraction of applied mass that is absorbed (%)

Y_{derm} = Weight fraction of the chemical of interest

FT = Frequency of events (default: 1)

DERMAL EXPOSURE MODEL

Charge Q 10c.i & c.ii

- Deterministic
- High-end skin surface areas and dermal loading values used for high-end dermal exposure estimate
- Mid-range skin surface areas and dermal loading values used for central-tendency dermal exposure estimates
- Model estimates exposure to the hands and does not account for dermal exposure to other parts of the body

DERMAL EXPOSURE MODEL

Charge Q 10c.i & c.ii

- Skin Surface Area (*S*)
  - Model Default Parameter
  - EPA uses values from Chapter 7 of the Exposure Factors Handbook (U.S. EPA, 2011)
  - High-end value of 1,070 cm^2 is based on the mean two-hand surface area for adult males ages 21 or older
  - For central tendency, EPA assumes surface area equal to half of high-end estimate

$$D_{\text{exp}} = (\boldsymbol{S}\ x\ Q_u\ x\ f_{abs}\ x\ Y_{derm}\ x\ FT)$$

DERMAL EXPOSURE MODEL

Charge Q 10c.i & c.ii

- Dermal Loading (Q_u)
  - Default Dermal Loading Values are from (U.S. EPA, 1992)
  - Experimental studies of non-aqueous liquids
  - Objective was to measure the quantity remaining on the skin after contact
  - Initial wipe test performed of subjects wiping their hands with a cloth saturated in the liquid
  - Amount of liquid retained on the hands was measured immediately after application
  - High-end value of 2.1 mg/cm^2 and 1.4 mg/cm^2 for central tendency

$$D_{\text{exp}} = (S \; x \; \boldsymbol{Q_u} \; x \; f_{abs} \; x \; Y_{derm} \; x \; FT)$$

DERMAL EXPOSURE MODEL

Charge Q 10c.i & c.ii

- Fraction Absorbed Value (f_{abs})
  - 1,1-Dichloroethane expected to be handled in neat (100%) form for all OES
  - Fraction absorbed value for neat form of 1,1-dichloroethane from the test order is 0.3%

$$D_{\text{exp}} = (S \; x \; Q_u \; x \; \boldsymbol{f_{abs}} \; x \; Y_{derm} \; x \; FT)$$

DERMAL EXPOSURE MODEL

Charge Q 10c.i & c.ii

- Weight Fraction of the Chemical (Y_{derm})
  - EPA approach is to use the highest concentration for each OES
  - For all OES, 1,1-dichloroethane could be in neat form (weight fraction = 1)

$$D_{\text{exp}} = (S \; x \; Q_u \; x \; f_{abs} \; x \; \boldsymbol{Y_{derm}} \; x \; FT)$$

DERMAL EXPOSURE MODEL RESULTS

Charge Q 10c.i & c.ii

- Dermal Model Results for 1,1-Dichloroethane
  - High-end: 6.7 mg/day for all OES
  - Central Tendency: 2.3 mg/day for all OES

- For comparison:
  - Results for non-volatile liquid
  - Assume Fraction absorbed value of 1
    - High-end: 2,247 mg/day
    - Central-tendency: 749 mg/day

Additional Components of the Occupational Exposure Assessment

- **Estimating number of workers and ONUs**
  - Data on specific chemicals such as 1,1-dichloroethane are available from the Chemical Data Reporting Rule (CDR)
  - NAICS or SIC level information for the OES assessed can be found in data from:
    - Bureau of Labor Statistics (BLS)
    - U.S. Census data
- **Estimating Number of days per year of worker exposure**
  - In general, the exposure frequency is the same as the number of operating days per year for a given OES.
  - EPA typically assumes that a single worker would not work more than 250 days per year.

SUMMARY INFORMATION FOR OCCUPATIONAL EXPOSURE ASSESSMENT: ORGANIZED BY OES

Charge Q 10

OES	Inhalation Exposure												Dermal Exposure		
	1,1-Dichloroethane Monitoring					Surrogate Monitoring					Modeling		Monitoring		Modeling
	Worker	# Data Points	ONU	# Data Points	Data Quality Ratings	Worker	# Data Points	ONU	# Data Points	Data Quality Ratings	Worker	ONU	Worker	Data Quality Rating	Worker
Manufacturing	✓	57	✓	5	H	✓	172	X	N/A	H	X	X	X	N/A	✓
Processing as a reactive intermediate	✓	57	✓	5	H	✓	46	X	N/A	M	X	X	X	N/A	✓
Processing – repackaging	X	N/A	X	N/A	N/A	X	N/A	X	N/A	N/A	✓	X	X	N/A	✓
Commercial use as a laboratory chemical	✓	9	X	N/A	H	✓	76	X	N/A	H	X	X	X	N/A	✓
Distribution in commerce	Not estimated														
Waste handling, treatment, and disposal (POTW)	X	N/A	X	N/A	N/A	✓	3	X	N/A	M	X	X	X	N/A	✓
General waste handling, treatment, and disposal	X	N/A	X	N/A	N/A	✓	22	X	N/A	M	X	X	X	N/A	✓

X = no data available; ✓ = data available

Where EPA was not able to estimate ONU inhalation exposure from monitoring data or models, this was assumed equivalent to the central tendency experienced by workers for the corresponding OES; dermal exposure for ONUs was not evaluated because they are not expected to be in direct contact with 1,1-dichloroethane.

DETERMINING WEIGHT OF SCIENTIFIC EVIDENCE RATINGS

- **Based on the strengths, limitations, and uncertainties associated with the occupational assessment**
  - Example: Strength of having primary chemical-specific data monitoring data for manufacture from test order
  - Example: Uncertainty in applying exposure data on lab workers at MFG facility to commercial laboratories
  - Example: Strength of using Monte Carlo modeling approach in capturing range of parameter input values

	Weight of Scientific Evidence Rating – Inhalation Exposure
Manufacturing	Moderate to Robust
Processing as a reactive intermediate	Moderate
Processing – repackaging	Moderate
Commercial use as a laboratory chemical	Moderate
Waste handling, treatment, and disposal (general)	Moderate
Waste handling, treatment, and disposal (POTW)	Moderate

Thank you for your attention