United States
Environmental Protection Agency

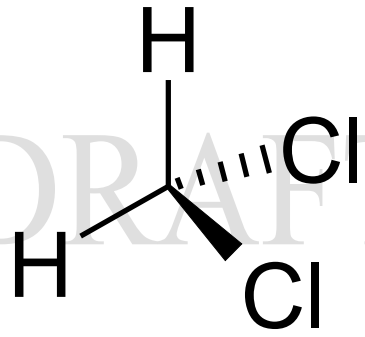
Office of Chemical Safety and
Pollution Prevention

Risk Evaluation for Methylene Chloride

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Animal Studies

CASRN: 75-09-2



October 2019, DRAFT

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NOTE: This supplemental file includes the evaluations of key and supporting studies identified in previous assessments as well as new studies published after the completion of previous assessments. The studies are identified as key or new (and new study header rows are shaded).

1. Acute and Short-Term Toxicity Studies

1.1. Dow et al 1988, acute inhalation - neurotoxicity/behavior, clinical chemistry

Study reference:	**Dow Chemical Co (1988). Initial Submission: Evaluation of the Acute Neuropharmacologic Effects of Dichloromethane in Rats (Final Report) with Attachments and Cover Letter Dated 050792** **HERO ID: 4214025** **STUDY TYPE: New**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified definitively.	High	1	2	2
	2. Test Substance Source	The source of the test substance and lot number were provided. Analytical verification of the test substance was performed by infrared spectroscopy.	High	1	1	1
	3. Test Substance Purity	Purity was reported (99.97% as reported by source, and 99.94%, as determined by gas chromatography).	High	1	1	1

Study reference:	Dow Chemical Co (1988). Initial Submission: Evaluation of the Acute Neuropharmacologic Effects of Dichloromethane in Rats (Final Report) with Attachments and Cover Letter Dated 050792 HERO ID: 4214025 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Design	4. Negative and Vehicle Controls	The study authors reported using an appropriate concurrent negative control group (exposed to filtered air) for some of the tests (e.g., Probe 3); however, other tests did not have a true negative control group (e.g., were pre-exposed to DCM for 3 days [conditioning phase] and were then exposed to filtered air on 4th day).	Medium	2	2	4
	5. Positive Controls	Positive control is not indicated by the study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study authors did not report how animals were allocated to study groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation methods of the test substance were reported and were suitable for the test substance. Storage methods were not reported but this is not considered to have a substantial impact on the results for this acute study.	Medium	2	1	2

Study reference:	Dow Chemical Co (1988). Initial Submission: Evaluation of the Acute Neuropharmacologic Effects of Dichloromethane in Rats (Final Report) with Attachments and Cover Letter Dated 050792 HERO ID: 4214025 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	The study authors reported adequate details of exposure administration and exposures were administered consistently across study groups.	High	1	1	1
	9. Reporting of Doses/ Concentrations	Nominal and target chamber concentrations were reported with mean and standard deviations. The analytical method used to measure chamber concentrations (IR spectrometry) was reported and appropriate.	High	1	2	2
	10. Exposure Frequency and Duration	The exposure frequency and duration of exposure were reported and were appropriate for this study type (i.e., acute toxicity).	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	There were minor limitations regarding the concentration spacing. Only one concentration was tested in each of the probe studies (e.g., 2000 ppm or 4000 ppm) and in each study effects were observed on neurological measures.	Medium	2	1	2

Study reference:	Dow Chemical Co (1988). Initial Submission: Evaluation of the Acute Neuropharmacologic Effects of Dichloromethane in Rats (Final Report) with Attachments and Cover Letter Dated 050792 HERO ID: 4214025 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substance. Whole-body chamber exposures were used, rather than nose- or head-only exposures, but this appears to be acceptable for DCM, which was exposed as a vapor and not expected to condense.	High	1	1	1
Test Organism	13. Test Animal Characteristics	Some test animal characteristics (source, species, strain, body weight, and sex) were reported; however, age and health status prior to testing was not reported, so I downgraded the score to medium.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions (target conditions for temperature, humidity, light-dark cycle) were reported and were adequate and the same for the control and exposed populations.	High	1	1	1
	15. Number per Group	The number of animals per group was low in some tests (e.g., with 4000 ppm, there were only two animals/group), but some tests used 8 animals/group.	Medium	2	1	2

Study reference:	Dow Chemical Co (1988). Initial Submission: Evaluation of the Acute Neuropharmacologic Effects of Dichloromethane in Rats (Final Report) with Attachments and Cover Letter Dated 050792 HERO ID: 4214025 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology was reported, but some details of the methodology were unclear due to incomplete reporting. (e.g., COHb measurement).	Medium	2	2	4
	17. Consistency of Outcome Assessment	Details of the outcome assessment protocol were reported, and outcomes were assessed consistently across study groups using the same protocol in all study groups.	High	1	1	1
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported and the study used adequate sampling for the outcomes of interest.	High	1	1	1
	19. Blinding of Assessors		Not Rated	NA	NA	NA
	20. Negative Control Response	The negative control responses were reported for the outcomes of interest and were adequate.	High	1	1	1

Study reference:	Dow Chemical Co (1988). Initial Submission: Evaluation of the Acute Neuropharmacologic Effects of Dichloromethane in Rats (Final Report) with Attachments and Cover Letter Dated 050792 HERO ID: 4214025 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables in test design or procedures were reported; however, DCM is a potential respiratory irritant, but respiratory rate measurement was not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were reported but data on attrition and/or health outcomes unrelated to exposure were not reported for each study group because only substantial differences among groups were noted.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and were appropriate for the datasets.	High	1	1	1
	24. Reporting of Data	Data for exposure-related findings were presented for evaluated outcomes by exposure group. Individual data values were provided in appendices.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**44**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.5172**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

1.2. Aranyi et al 1986, acute/short-term inhalation – immune

Study reference:	Aranyi et al. (1986). The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundamental and Applied Toxicology. 6(4):713-720. HERO ID: 61922 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified by chemical name and SMILES	High	1	2	2
	2. Test Substance Source	Commercial source was identified (B&J laboratories; omitted details include the batch/lot number.	Medium	2	1	2
	3. Test Substance Purity	The test substance purity was not reported, but not expected to be of concern	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	filtered air; a control group was used but lacks some details that are unlikely to have a substantial impact on results.	Medium	2	2	4
	5. Positive Controls	This metric is not rated/applicable for this study type	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study did not report how animals were allocated to study groups	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	The preparation of the test substances for the inhalation chamber was generally described for all substances, but not specific for this test substance. There was no information on the storage of the test substance.	Low	3	1	3

Study reference:	**Aranyi et al. (1986). The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundamental and Applied Toxicology. 6(4):713-720.** **HERO ID: 61922** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Exposures were administered consistently across study groups	High	1	1	1
	9. Reporting of Doses/Concentrations	Reported target and actual test concentrations	High	1	2	2
	10. Exposure Frequency and Duration	Exposure frequency and duration of exposure were identified; a single 3-hour exposure or 3 hours/day for a 5-day exposure is not standard for this study type.	Low	3	1	3
	11. Number of Exposure Groups and Dose Spacing	Only 1 dose tested. The number of exposure concentrations and dose spacing was justified by study authors; "when significant effects were found in single exposures at the TLV level or above exposure, the concentration was reduced stepwise until a no-measurable-effect level was reached for a single exposure; this dose was then used for the 5-day exposure	Low	3	1	3

Study reference:	**Aranyi et al. (1986). The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundamental and Applied Toxicology. 6(4):713-720.** **HERO ID: 61922** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substance; a dynamic whole-body chamber was used for vapors	High	1	1	1
Test Organism	13. Test Animal Characteristics	4-5 wk old Female CD1 mice	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were not sufficiently reported	Low	3	1	3
	15. Number per Group	I7 to 24 mice per treatment	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Incomplete reporting of minor details of the outcome assessment protocol, but unlikely to have a substantial impact on results; few specific details on how the ratio of viable bacterial counts to the radioactive counts and the determination of bactericidal activity were conducted.	Medium	2	2	4
	17. Consistency of Outcome Assessment	See footnote at end of page[1]	High	1	1	1
	18. Sampling Adequacy	See footnote at end of page[1]	High	1	1	1

[1] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Aranyi et al. (1986). The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundamental and Applied Toxicology. 6(4):713-720.** **HERO ID: 61922** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	The study did not report whether assessors were blinded to treatment group, lack of blinding is not expected to have a substantial impact on results.	Not rated	NA	NA	NA
	20. Negative Control Response	See footnote at end of page[1]	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial body weight and respiratory rate were not reported. These deficiencies are likely to have a substantial impact on results	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Data on attrition and/or health outcomes unrelated to exposure for each study group were not reported	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	See footnote at end of page[2]	High	1	1	1
	24. Reporting of Data	The study was designed to determine the effects of inhalation exposure to several chemicals, (including methylene chloride) on susceptibility to bacterial lung infections. Only a single dose was tested for the 5-day exposure.	High	1	2	2

[2] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	Aranyi et al. (1986). The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundamental and Applied Toxicology. 6(4):713-720. HERO ID: 61922 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		Sum of scores:			29	51
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.7586	Overall Score: Nearest *:	1.8
		Overall Quality Level:		Medium		

1.3. Warbrick et al. , 28-day inhalation – immune

Study reference:	**Warbrick et al. (2003). Inhalation exposure to methylene chloride does not induce systemic immunotoxicity in rats. Journal of Toxicology and Environmental Health, Part A: Current Issues, 66(13,13), 1207-1219.** **HERO ID: 732101** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified, but not characterized further	Medium	2	2	4
	2. Test Substance Source	Source was identified: Merck Ltd. (Poole, Dorset, UK)	High	1	1	1
	3. Test Substance Purity	99.9%	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Air alone; Study authors reported using an appropriate concurrent negative control group	High	1	2	2
	5. Positive Controls	Cyclophosphamide; chemical is recommended by the U.S. EPA as a positive control for immunotoxicity studies in which the integrity of antibody production is examined	High	1	1	1
	6. Randomized Allocation	Rats were randomized into groups according to body weight	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	Test substance preparation was reported, but storage conditions were not; deficiencies in reporting not likely to have a substantial effect on results.	Medium	2	1	2

Study reference:	**Warbrick et al. (2003). Inhalation exposure to methylene chloride does not induce systemic immunotoxicity in rats. Journal of Toxicology and Environmental Health, Part A: Current Issues, 66(13,13), 1207-1219.** **HERO ID: 732101** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	See footnote at end of page[3]	High	1	1	1
	9. Reporting of Doses/Concentrations	Exposure was therefore maintained within ± 6.7% of the target of 5000ppm; GC was used to measure chamber test substance and vehicle concentration; overall achieved mean concentration for the study was 5187 + - 347 ppm	High	1	2	2
	10. Exposure Frequency and Duration	6 hours/day, 5 days/week for 28 days	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Only one dose tested, but justified the decision to use a single high dose as a screening study because there have been no indications of immunotoxic effects in a number of animal studies	Medium	2	1	2
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substance	High	1	1	1

[3] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Warbrick et al. (2003). Inhalation exposure to methylene chloride does not induce systemic immunotoxicity in rats. Journal of Toxicology and Environmental Health, Part A: Current Issues, 66(13,13), 1207-1219.** **HERO ID: 732101** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	Young adult (8–12wk old, 154–177 g) male and female Sprague-Dawley (SD) rats	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported	High	1	1	1
	15. Number per Group	8/sex	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcomes of interest	High	1	2	2
	17. Consistency of Outcome Assessment	See footnote at end of page[4]	High	1	1	1
	18. Sampling Adequacy	See footnote at end of page[4]	High	1	1	1
	19. Blinding of Assessors	Outcomes of interest were not subjective measurements	Not Rated	NA	NA	NA
	20. Negative Control Response	The biological responses of the negative control group were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	The respiratory rate was no measured for the inhalation exposure. Methylene chloride is expected to be a respiratory irritant.	Low	3	2	6

[4] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Warbrick et al. (2003). Inhalation exposure to methylene chloride does not induce systemic immunotoxicity in rats. Journal of Toxicology and Environmental Health, Part A: Current Issues, 66(13,13), 1207-1219.** **HERO ID: 732101** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	Data on attrition and/or health outcomes unrelated to exposure for each study group were not reported	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and appropriate for the dataset.	High	1	1	1
	24. Reporting of Data	Data for exposure-related findings were presented for all outcomes by exposure group and sex with quantal presentation of the results and statistics	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**40**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.3333**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

1.1. Shell 1986, 10-day inhalation - rat and mouse - hepatic, respiratory

Study reference:	**Shell Oil, Co (1986). Ten Day Inhalation Toxicity Study to Investigate the Effects on Rat and Mouse Liver and Lung with Methylene Chloride** **HERO ID: 4213825** **STUDY TYPE: New**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified by name.	Medium	2	2	4
	2. Test Substance Source	The source was reported, and measurement of concentration levels were conducted.	Medium	2	1	2
	3. Test Substance Purity	The grade and purity were provided and such that any effects likely due to test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	A concurrent negative control group was included.	High	1	2	2
	5. Positive Controls	Positive controls not required for this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The Latin square method was used for animal allocation (re: obtaining similar body weights/group).	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	The methods and equipment used were described.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	The analytical method used to measure test atmospheres was reported and appropriate.	High	1	2	2

Study reference:	**Shell Oil, Co (1986). Ten Day Inhalation Toxicity Study to Investigate the Effects on Rat and Mouse Liver and Lung with Methylene Chloride** **HERO ID: 4213825** **STUDY TYPE: New**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	The duration and frequency were reported and appropriate.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The concentrations were based on results from lifetime inhalation studies.	High	1	1	1
	12. Exposure Route and Method	The inhalation chamber was appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The species, strain, sex, source, age, and initial body weight were reported. the health status was not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions were reported and the same for the groups.	High	1	1	1
	15. Number per Group	The number of animals per group was sufficient to characterize toxicological effects.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed the outcomes of interest.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcome assessment was carried out consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcome of interest.	High	1	1	1

Study reference:	Shell Oil, Co (1986). Ten Day Inhalation Toxicity Study to Investigate the Effects on Rat and Mouse Liver and Lung with Methylene Chloride HERO ID: 4213825 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	This metric was not applicable to the outcomes in this study.	Not Rated	NA	NA	NA
	20. Negative Control Response	The negative control responses were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	DCM is a respiratory irritant and respiratory rate was not measured.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	No differences were reported or inferred but health outcomes not discussed.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Student's t-test was used for some data, but histopathological and electron microscopic findings were not analyzed.. Data were available to conduct an independent analysis.	Medium	2	1	2
	24. Reporting of Data	Quantal and continuous data were reported for the outcomes of interest. Severity incidences were reported for some endpoints.	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**43**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.4828**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

1.2. General Electric, 1976, 14-day oral rat – mortality, nutrition, metabolic/adult body weight, neurotoxicity/behavior, gastrointestinal, respiratory

Study reference:	General Electric Co (1976b). Dichloromethane Fourteen Day Range-Finding Study in Rats. HERO ID: 4213647 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified definitively (CASRN and name provided).	High	1	2	2
	2. Test Substance Source	The source of the test substance was reported (p. 5), but the chemical description, including source, may not be totally accurate according to p. 5, so there are some uncertainties about the source.	Low	3	1	3
	3. Test Substance Purity	Purity and/or grade were not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	The study authors reported using an appropriate concurrent negative control group (received the vehicle via gavage).	High	1	2	2
	5. Positive Controls	Positive control not indicated by study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study authors did not report how the animals were allocated to study groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	The test substance preparation and storage conditions were not sufficiently reported, and this may have a substantial impact on results.	Low	3	1	3

Study reference:	General Electric Co (1976b). Dichloromethane Fourteen Day Range-Finding Study in Rats. HERO ID: 4213647 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Details of the exposure administration were reported, and exposures were administered consistently across groups.	High	1	1	1
	9. Reporting of Doses/Concentrations	Administered doses were reported without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	Exposure frequency and duration were reported; although administration was only 14 days in this repeated-dose study, the study was designed to be a range-finding study for a longer-duration exposure.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing were considered adequate to address the purpose of the study; however, the selection of dose levels was not justified by the study authors (e.g., basis for selection was not stated).	Medium	2	1	2
	12. Exposure Route and Method	The exposure route and method (oral gavage) were reported and were suited to the test substance.	High	1	1	1

Study reference:	General Electric Co (1976b). Dichloromethane Fourteen Day Range-Finding Study in Rats. HERO ID: 4213647 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Organism	13. Test Animal Characteristics	The test animal species, sex, and starting body weight were reported; however, the source, health status, and age were not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions (e.g., temperature, humidity, light-dark cycle) were not sufficiently reported to evaluate if husbandry was adequate and if differences occurred.	Low	3	1	3
	15. Number per Group	The reported number of animals per study group (5/sex/group) was lower than the typical number used in studies of the same or similar type (i.e., repeated-dose studies).	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	This repeated-dose study only evaluated mortality, general behavior, appearance, body weight, food consumption, and gross pathology, with no additional evaluation of endpoints typically evaluated in studies of similar type (e.g., histopathology); however, it was designed to be a range-finding study.	Medium	2	2	4

Study reference:	General Electric Co (1976b). Dichloromethane Fourteen Day Range-Finding Study in Rats. HERO ID: 4213647 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	17. Consistency of Outcome Assessment	There is insufficient information to evaluate whether outcomes were assessed consistently across study groups.	Low	3	1	3
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported.	High	1	1	1
	19. Blinding of Assessors	Blinding not required	Not Rated	NA	NA	NA
	20. Negative Control Response	The biological responses of the negative control group were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reported differences among the study groups regarding confounding variables.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	Data on attrition or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were not reported, and insufficient data were reported to allow independent analysis (e.g., necropsy results appear to be incompletely reported).	Low	3	1	3

Study reference:	General Electric Co (1976b). Dichloromethane Fourteen Day Range-Finding Study in Rats. HERO ID: 4213647 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Data for exposure-related findings were not shown for each study group (e.g., gross necropsy), but results were described in the text and data were only reported for some outcomes.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**57**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.9655**	**Overall Score: Nearest *:**	**2**
		Overall Quality Level:		**Medium**		

1.3. General Electric 1976, 14-day oral dog – mortality, nutrition, metabolic/body weight, neurotoxicity/behavior, gastrointestinal, respiratory

Study reference:	General Electric Co (1976a). Dichloromethane Fourteen Day Range Finding Study in Dogs. HERO ID: 4213648 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified definitively (CASRN and name).	High	1	2	2
	2. Test Substance Source	The source of the test substance was reported (p. 5), but the chemical description, including source, may not be totally accurate according to p. 5, so there are some uncertainties about the source.	Low	3	1	3
	3. Test Substance Purity	Purity and/or grade were not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	The study authors acknowledged using a concurrent negative control group, but details regarding the negative control group were not reported (e.g., whether also dosed with vehicle) and the lack of details is likely to have a substantial impact on results.	Low	3	2	6
	5. Positive Controls	Positive control not indicated by study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study authors did not report how the animals were allocated to study groups.	Low	3	1	3

Study reference:	General Electric Co (1976a). Dichloromethane Fourteen Day Range Finding Study in Dogs. HERO ID: 4213648 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	7. Preparation and Storage of Test Substance	The test substance preparation and storage conditions were not sufficiently reported, and this may have a substantial impact on results.	Low	3	1	3
	8. Consistency of Exposure Administration	Details of the exposure administration were reported, and exposures were administered consistently across groups.	High	1	1	1
	9. Reporting of Doses/Concentrations	Administered doses were reported without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	Exposure frequency and duration were reported; although administration was only 14 days in this repeated-dose study, the study was designed to be a range-finding study for a longer-duration exposure.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing were considered adequate to address the purpose of the study; however, the selection of dose levels was not justified by the study authors (e.g., basis for selection was not stated).	Medium	2	1	2

Study reference:	General Electric Co (1976a). Dichloromethane Fourteen Day Range Finding Study in Dogs. HERO ID: 4213648 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	The exposure route and method (oral gavage) were reported and were suited to the test substance.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The test animal species, sex, and starting body weight were reported; however, the source, health status, and age were not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions (e.g., temperature, humidity, light-dark cycle) were not sufficiently reported to evaluate if husbandry was adequate and if differences occurred.	Low	3	1	3
	15. Number per Group	The number of animals per study group was insufficient to characterize toxicological effects (1 animal/sex/group). Therefore, results can only be used as support to other studies.	Low	3	1	3

Study reference:	General Electric Co (1976a). Dichloromethane Fourteen Day Range Finding Study in Dogs. HERO ID: 4213648 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	This repeated-dose study only evaluated mortality, general behavior, appearance, body weight, food consumption, and gross pathology, with no additional evaluation of endpoints typically evaluated in studies of similar type (e.g., histopathology); however, it was designed to be a range-finding study.	Medium	2	2	4
	17. Consistency of Outcome Assessment	There is insufficient information to evaluate whether outcomes were assessed consistently across study groups. (e.g., no information on whether evaluations were conducted at same time of day or on the same day of week).	Low	3	1	3
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported.	High	1	1	1
	19. Blinding of Assessors	Blinding not required	Not Rated	NA	NA	NA
	20. Negative Control Response	The biological responses of the negative control group were adequate.	High	1	1	1

Study reference:	General Electric Co (1976a). Dichloromethane Fourteen Day Range Finding Study in Dogs. HERO ID: 4213648 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reported differences among the study groups regarding confounding variables.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	Data on attrition or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	The number of animals per group was not conducive to statistical analysis.	Not Rated	NA	NA	NA
	24. Reporting of Data	Data for exposure-related findings were presented for all outcomes by exposure group and sex.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**28**	**55**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**NA**	**Overall Score: Nearest *:**	**NA**
		Overall Quality Level:		**Low**		
Study Quality Comment:	**The reviewer downgraded this study's overall quality rating. They noted: The study was downgraded to low (from medium) because the number of dogs evaluated per dose for each outcome is too limited to provide confidence in evaluating dose-response results. However, the results of this range-finding study can be consulted, as needed, when considering the body of animal toxicity results. Note: The original calculated score for this study was 2.0. This value is not presented above because the final rating was changed based on professional judgement.**					

1.6.Moser et al 1995, 1 to 14-day oral neurotoxicity study - neurotoxicity/ behavior, mortality, body weight

Study reference:	**Moser, V. C., Cheek, B. M., Macphail, R. C. (1995). A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity Journal of Toxicology and Environmental Health, Part A: Current Issues, 45(2), 173-210.** **HERO ID: 76020** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Identified as analytical grade dichloromethane	High	1	2	2
	2. Test Substance Source	Aldrich Chemical Co; batch no. not reported	Medium	2	1	2
	3. Test Substance Purity	>99%	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent vehicle controls (corn oil)	High	1	2	2
	5. Positive Controls	In some neurobehavioral testing positive controls are needed/suggested. This study did not include a positive control; however, results from 10 different compounds were reported, with at least one compound showing positive effects in each neurofunctional domain tested. This suggests validity of the test.	Medium	2	1	2
	6. Randomized Allocation	Assigned to test groups using random stratification tables based on body weights (nonrandom component).	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	DCM was mixed with corn oil for gavage; storage not reported.	Medium	2	1	2

Study reference:	**Moser, V. C., Cheek, B. M., Macphail, R. C. (1995). A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity Journal of Toxicology and Environmental Health, Part A: Current Issues, 45(2), 173-210.** **HERO ID: 76020** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Consistent across groups; 10 ml/kg dose volume	High	1	1	1
	9. Reporting of Doses/Concentrations	Dose selection based on acute LD50 values. Acute (1 d): 0, 3, 10, 30, or 56% of LD50 (0, 101, 337, 1012, 1889 mg/kg) Subacute (14 d):0, 1, 3, 10 or 30% of LD50 (0, 34, 101, 337, 1012 mg/kg)	High	1	2	2
	10. Exposure Frequency and Duration	1 or 14 d	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	4 exposures plus control	High	1	1	1
	12. Exposure Route and Method	Oral gavage in corn oil	High	1	1	1
Test Organism	13. Test Animal Characteristics	Adult female F344 rats	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Consistent between groups. Adequate reporting of conditions.	High	1	1	1
	15. Number per Group	8/group. Numbers are acceptable but given variability in neurobehavioral endpoints, more animals/group would be ideal.	Medium	2	1	2

Study reference:	Moser, V. C., Cheek, B. M., Macphail, R. C. (1995). A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity Journal of Toxicology and Environmental Health, Part A: Current Issues, 45(2), 173-210. HERO ID: 76020 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	Neurological: FOB and motor activity at several time-points; baseline established prior to exposure Mortality, BW Note: Systemic effects (organ weight, serum chemistry, urinalysis, histopathology) were evaluated in these rats; however, results of systemic analysis reported in separate study (Berman et al. 1995)	High	1	2	2
	17. Consistency of Outcome Assessment	Consistent across study groups	High	1	1	1
	18. Sampling Adequacy	all animals were assessed for relevant outcomes.	High	1	1	1
	19. Blinding of Assessors	All testing was performed blind.	High	1	1	1
	20. Negative Control Response	Control data reported; baseline values similar between groups	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Baseline FOB and motor testing was reported, and results were comparable between groups. Decreased BW of unknown magnitude was reported in the two highest dose groups (steady weight loss).	Medium	2	2	4

Study reference:	**Moser, V. C., Cheek, B. M., Macphail, R. C. (1995). A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity Journal of Toxicology and Environmental Health, Part A: Current Issues, 45(2), 173-210.** **HERO ID: 76020** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	data on attrition and/or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	dose-by-time interaction ANOVA	High	1	1	1
	24. Reporting of Data	Mortality reported in text. Most neurobehavioral findings with significant effects were reported graphically; remaining were reported qualitatively. Body weight loss reported qualitatively.	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**31**	**41**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.3226**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

2. Subchronic Toxicity Studies

2.1. Dow 1961, 90-day dermal study in rabbits - mortality, body weight, neurotoxicity/behavior, skin and connective tissue, hematological, immune, hepatic, renal, gastrointestinal, reproductive, thyroid, cardiovascular

Study reference:	Dow Chemical Co (1961). The Results of Chronic Skin Absorption Studies on Chlorothene and Methylene Chloride with Cover Letter. HERO ID: 4213810 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Technical grade methylene chloride (chemical properties listed)	High	1	2	2
	2. Test Substance Source	Source of material not identified. No batch number or purity (identified as technical grade).	Low	3	1	3
	3. Test Substance Purity	Reported as "technical grade"; % purity not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Concurrent negative control was used	High	1	2	2
	5. Positive Controls	Concurrent positive control (isopropyl alcohol) was used at 15, 100, and 500 mg/kg-d	High	1	1	1
	6. Randomized Allocation	The study did not report how animals were allocated to study groups	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Lack of details re: preparation and storage may have an impact on results if the test substance was allowed to volatilize.	Low	3	1	3

Study reference:	Dow Chemical Co (1961). The Results of Chronic Skin Absorption Studies on Chlorothene and Methylene Chloride with Cover Letter. HERO ID: 4213810 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	In exposure groups, the total daily dose was divided into 4 equal parts that were administer directly onto the shaved skin of animals at 10 am, 12 pm, 2 pm, and 4 pm (5 days/week). Half of the animals had abraded skin (per group). At the end of exposure, the skin was wiped dry. Untreated controls were immobilized in a similar manner (no exposure).	High	1	1	1
	9. Reporting of Doses/Concentrations	0, 50, 100, 200, and 500 mg/kg-day (divided into 4 equal doses). In order to protect against accidental oral exposure, rabbits were restrained during exposure. In order to protect against accidental inhalation exposure, the stocks were situated in exhaust hoods leaving only the heads of the animals exposed to the external atmosphere. Loss of exposure to vaporization was not evaluated but animals were dosed 4 times/day (see metric 10), which would decrease evaporation.	Low	3	2	6

Study reference:	**Dow Chemical Co (1961). The Results of Chronic Skin Absorption Studies on Chlorothene and Methylene Chloride with Cover Letter.** **HERO ID: 4213810** **STUDY TYPE: New**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	90 d, the total daily dose was divided into 4 equal parts that were administer directly onto the shaved skin of animals at 10 am, 12 pm, 2 pm, and 4 pm (5 days/week)	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	3 dose groups plus control.	High	1	1	1
	12. Exposure Route and Method	Dermal exposure under non-occluded conditions. Much smaller doses may have been administered due to vaporization of test material. Administering in 4 parts over 8 hrs may have decreased this, but occluded conditions should have been used.	Low	3	1	3
Test Organism	13. Test Animal Characteristics	young adult male albino rabbits weighing 2-3 kg; source of animals not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Rabbits housed in cages with food available ad libitum (except during 8-hr exposure periods). No additional husbandry conditions reported.	Low	3	1	3
	15. Number per Group	4 males/group	Medium	2	1	2

Study reference:	Dow Chemical Co (1961). The Results of Chronic Skin Absorption Studies on Chlorothene and Methylene Chloride with Cover Letter. HERO ID: 4213810 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	Daily mortality/clinical signs, weighed weekly; hematology assessed at 30, 60, 90 d; histology of skin, brain, heart, lung liver, kidney spleen, stomach, intestine and gonad and weight of brain, lung, heart, liver, stomach, kidney, spleen, gonad, and thyroid evaluated at 30 d (1/group) and 90 d (1/group). Other 2/group maintained for 30d observation.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Consistent across groups	High	1	1	1
	18. Sampling Adequacy	Organ weights and histology only assessed in 1/group at 30 and 90 days.	Unacceptable	4	1	4
	19. Blinding of Assessors	Examined endpoints did not require blinding.	Not Rated	NA	NA	NA
	20. Negative Control Response	Control responses reported.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No exposure-related changes.	High	1	2	2

Study reference:	Dow Chemical Co (1961). The Results of Chronic Skin Absorption Studies on Chlorothene and Methylene Chloride with Cover Letter. HERO ID: 4213810 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	data on attrition and/or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	No statistics reported. Body weights and hematology reported with adequate data for independent analysis, but of low power due to low animal number. Histological and organ weight data cannot be evaluated statistically (only 1/group per sacrifice).	Low	3	1	3
	24. Reporting of Data	Detailed data tables.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**57**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.9000**	**Overall Score: Nearest *:**	**1.9[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of Systematic Review in TSCA Risk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, three of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

2.2. General Electric Co 1976, 90-day oral toxicity in dogs - mortality, body weight, neurotoxicity/behavioral, hematological, immune, ocular and sensory, clinical chemistry, renal, hepatic, cardiovascular, endocrine, gastrointestinal, respiratory, skin and connective tissue, thyroid

Study reference:	General Electric Co (1976c). Dichloromethane Ninety Day Oral Toxicity Study in Dogs HERO ID: 4213649 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Dichloromethane identified by name and chemical structure and mol wt.	High	1	2	2

Study reference:	General Electric Co (1976c). Dichloromethane Ninety Day Oral Toxicity Study in Dogs HERO ID: 4213649 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	2. Test Substance Source	The compound was-received from the General Electric Company, Mount Vernon, Indiana on December 10, 1975. The compound was a clear liquid and was identified as "Dichloromethane* Reagent, A.C.S. CH2C12 FW 84.94 DX835 5509 Matheson Coleman & Bell Manufacturing Chemists". Note from study author: The above description is not totally accurate. The compound was furnished to IR&DC in containers labeled as indicated above but the actual contents were not from the indicated source. The contents were withdrawn on 12/4/75 from a purchased railroad tank - car of methylene chloride purchased from Dow Chemical certified to meet GE plastics Incoming Material Specification PCM-l-Sl. This methylene chloride is typical of that being used currently to produce Lexan® polycarbonate resin in the Mt. Vernon plant.	Medium	2	1	2

Study reference:	General Electric Co (1976c). Dichloromethane Ninety Day Oral Toxicity Study in Dogs HERO ID: 4213649 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	3. Test Substance Purity	Not reported; study authors state "This methylene chloride is typical of that being used currently to produce Lexan® polycarbonate resin in the Mt. Vernon plant."	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Concurrent controls administered 13.33 ml of distilled water/kg-d on the same regimen as treated dogs.	High	1	2	2
	5. Positive Controls	Positive control not required for this type of study	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study did not report how animals were allocated to study groups	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	The compound was dissolved in distilled water at a concentration of 15 mg/ml for gavage administration. Storage not reported (including methods to control volatilization).	Low	3	1	3
	8. Consistency of Exposure Administration	Gavage volume differed between groups (13.33 ml/kg-d for 0 and 200 mg/kg-d; 3.33 ml/kg-d for 50 mg/kg-day; 0.83 ml/kg-d for 12.5 mg/kg-d). But likely to resulted in only minimal differences given that the vehicle is distilled water.	Medium	2	1	2
	9. Reporting of Doses/Concentrations	0, 12.5, 50, or 200 mg/kg-d via gavage	High	1	2	2

Study reference:	General Electric Co (1976c). Dichloromethane Ninety Day Oral Toxicity Study in Dogs HERO ID: 4213649 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	90-d; it is assumed that dogs were dosed 7/days per week, but this is not explicitly stated.	Low	3	1	3
	11. Number of Exposure Groups and Dose Spacing	3 exposure groups plus control; high-dose may not have been high enough (no exposure-related findings).	Low	3	1	3
	12. Exposure Route and Method	gavage	High	1	1	1
Test Organism	13. Test Animal Characteristics	Beagle dogs; 7.9-12.6 kg (male) or 5.4-11.3 kg (female)	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Consistent between groups. Individual housing in temperature and humidity-controlled room. Water available ad libitum. 3000 g of food given per day. Temp and humidity not reported.	Medium	2	1	2
	15. Number per Group	4/sex/group	High	1	1	1

Study reference:	General Electric Co (1976c). Dichloromethane Ninety Day Oral Toxicity Study in Dogs HERO ID: 4213649 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	PECO: Hepatic - clinical chemistry, histo Neurological/Behavior - clinical signs, histo Other: Renal - clinical chemistry, urinalysis, histo Repro - histo Hematological or immunology - hemato, histo Gastrointestinal (histo) Respiratory (histo) Endocrine (histo) Musculoskeletal (histo) Cardiovascular (histo) Thyroid (histo) Ocular and Sensory (histo, ophthalmoscopy) Bd wt, mortality	High	1	2	2
	17. Consistency of Outcome Assessment	Consistent across groups; histology only assessed in control and high-dose (per protocol). Low- and mid-dose histology not evaluated due to lack of effects at high-dose.	High	1	1	1
	18. Sampling Adequacy	4/sex/group	High	1	1	1
	19. Blinding of Assessors	Study endpoints do not require blinding.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control reported; no deviations from standard reported.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Starting BW range reported. No exposure-related changes in BW or food consumption.	High	1	2	2

Study reference:	General Electric Co (1976c). Dichloromethane Ninety Day Oral Toxicity Study in Dogs HERO ID: 4213649 STUDY TYPE: New					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	data on attrition and/or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	No statistics reported by study authors. Data reporting adequate to perform independent statistics.	High	1	1	1
	24. Reporting of Data	Comprehensive data tables.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**43**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.4828**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

2.3. Kirschman et al., 1986, subchronic drinking water -rats and mice - hepatic, hematological and immune, adult body weight, renal, clinical chemistry

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test material identified clearly by name with identified impurities and concentrations.	High	1	2	2
	2. Test Substance Source	Test substance was obtained from a manufacturer.	High	1	1	1
	3. Test Substance Purity	Paper reports that specifications for the test substance to be used in a series of experiments include purity of >99.0%, but descriptions of the test material actually used in the subchronic rat and mouse experiments do not report purity. Food grade DCM was used in the 90-day study without further description. Yet, the study does state that the purity should be greater than that specified in the section discussing the test substance (> 99%). Thus, this omission is not likely to have an impact on the study results.	Medium	2	1	2

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Design	4. Negative and Vehicle Controls	The paper does not specify how the control group was treated, but as the study is a drinking water study it is reasonable to assume that the controls received water without test material.	Medium	2	2	4
	5. Positive Controls	Positive control not required for this type of study	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study did not report how animals were allocated to study groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Study does not report methods for preparation or assessment of stability; these would be critically important for a drinking water study of DCM given its volatility. Although the preparation and storage were not described, the article notes that DCM was analyzed to estimate the doses. There could still be some significant impacts from volatilization depending on how often the authors analyzed DCM in water.	Low	3	1	3

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptabl e, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Details of exposure administration (e.g., ad lib or controlled) were not reported. Given that the authors analyzed for DCM and measured the consumption of water, the lack of details regarding consistency of exposure administration should not result in a result of 'unacceptable' for this study.	Low	3	1	3

Study reference:	Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949. HERO ID: 730551 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Study reports that analytical concentrations were used but does not report these values or the method used to measure them. Water intake and body weight data were not reported, and decreased water consumption and body weights with higher DCM concentrations were noted in both species. Given that the authors analyzed for DCM and measured the consumption of water, the lack of details should not result in a result of 'unacceptable' for this study. Thus, the metric result was changed to 'low.'	Low	3	2	6
	10. Exposure Frequency and Duration	The exposure frequency was not reported, but as a drinking water study is assumed to be 7 days per week. The exposure duration was reported and appropriate for the study type and outcomes of interest.	Medium	2	1	2

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	Three dose groups plus control were tested. The overall dose range (high to low) was 10-fold and the spacing was typical for this type of study. The highest dose did result in some evidence of toxicity.	High	1	1	1
	12. Exposure Route and Method	Drinking water administration appears to have been a poor choice given the observed decrease in water intake (potentially due to palatability) and potential for volatilization of DCM from the drinking water (study did not discuss stability of the test material). Authors did not describe any efforts to mitigate these issues.	Low	3	1	3
Test Organism	13. Test Animal Characteristics	Source, age, health status, and starting body weight were not reported for either species	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were not reported for either species.	Low	3	1	3

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	The number of animals per group was reported (20/sex/group for both rats and mice) and exceeded typical numbers and guideline recommendations for a study of this type.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Methods for outcome assessment were incompletely reported (e.g., missing hematology and clinical chemistry parameters assessed, and missing list of organs weighed and/or examined microscopically)	Low	3	2	6
	17. Consistency of Outcome Assessment	Study did not report how outcome assessment was executed across study groups	Low	3	1	3
	18. Sampling Adequacy	Tabular results show adequacy of sampling for histopathology, but no information on sampling for clinical chemistry, hematology, or organ weights was provided.	Low	3	1	3

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	Does not report blinding of assessors, but outcomes were not subjective. Although histopathology is subjective, conventional practice is that researchers are not blinded unless slides need to be evaluated a second time.	Not Rated	NA	NA	NA
	20. Negative Control Response	inadequate information was available to assess suitability of the control response for any endpoint other than selected histopathology results.	Low	3	1	3
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Study reported decreased drinking water intake in both rats and mice with increasing dose. However, the authors analyzed for DCM and measured the consumption of water; therefore, the lack of details regarding consistency of exposure administration, although of concern, should not be a critical flaw.	Low	3	2	6

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	There were no health outcomes unrelated to exposure in rats, but in mice there were 6 deaths or moribund sacrifices (2 control, 2 low dose, and 2 mid-dose) unrelated to exposure. Although deaths occurred across doses in mice, they did not exceed 10%.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was either not reported or not performed. Histopathology data are reported in sufficient detail to enable statistical analysis, but body weight, hematology, clinical chemistry, and organ weights were not reported quantitatively.	Low	3	1	3
	24. Reporting of Data	Body weight, hematology, clinical chemistry, and organ weights were not reported quantitatively but were described qualitatively. Histopathology results were reported quantitatively.	Low	3	2	6
		Sum of scores:			**29**	**72**

Study reference:	**Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). Review of investigations of dichloromethane metabolism and subchronic oral toxicity as the basis for the design of chronic oral studies in rats and mice Food and Chemical Toxicology, 24(9), 943-949.** **HERO ID: 730551** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptabl e, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:**		**2.4828**	**Overall Score: Nearest *:**	**2.5**
		Overall Quality Level:		**Low**		

3. Chronic Toxicity Studies

3.1. Burek et al 1984, 2-year cancer bioassay - cancer, hepatic, renal

Study reference:	**Burek, J. D.,Nitschke, K. D.,Bell, T. J., Wackerle, D. L., Childs, R. C.,Beyer, J. E.,Dittenber, D. A.,Rampy, L. W., McKenna, M. J. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters Fundamental and Applied Toxicology, 4(1), 30-47.** **HERO ID: 29091** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Test substance was identified by name and chemical formula.	High	1	2	2
	2. Test Substance Source	The source of the test substance was not given; however, analytical verification was accomplished by GC. Manufacturer and lot numbers were given in the unpublished OxyChem (1992) report (4214046).	Medium	2	1	2
	3. Test Substance Purity	Described as technical grade, but analysis by GC indicated purity >99%.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Filtered air controls.	High	1	2	2
	5. Positive Controls	Positive controls not required for this type of study	Not Rated	NA	NA	NA
	6. Randomized Allocation	Computerized randomization procedure.	High	1	1	1

Study reference:	**Burek, J. D.,Nitschke, K. D.,Bell, T. J., Wackerle, D. L., Childs, R. C.,Beyer, J. E.,Dittenber, D. A.,Rampy, L. W., McKenna, M. J. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters Fundamental and Applied Toxicology, 4(1), 30-47.** **HERO ID: 29091** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	7. Preparation and Storage of Test Substance	The equipment and method for vapor generation are not well described; however, there was close agreement between daily nominal and analytical values. The method for vapor generation was described by the unpublished report (OxyChem, 1992; 4214046).	Medium	2	1	2
	8. Consistency of Exposure Administration	See footnote at end of page[5]	High	1	1	1
	9. Reporting of Doses/Concentrations	Range of analytical concentration did not deviate more than 10%.	High	1	2	2
	10. Exposure Frequency and Duration	6 hours/day, 5 days/week, 2-year duration	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Dose response relationships were evident, but unclear if lowest dose was low enough (i.e., liver histopath. changes. at all doses).	Medium	2	1	2
	12. Exposure Route and Method	See footnote at end of page[2]	High	1	1	1
Test Organism	13. Test Animal Characteristics	See footnote at end of page[2]	High	1	2	2

[5] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Burek, J. D.,Nitschke, K. D.,Bell, T. J., Wackerle, D. L., Childs, R. C.,Beyer, J. E.,Dittenber, D. A.,Rampy, L. W., McKenna, M. J. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters Fundamental and Applied Toxicology, 4(1), 30-47.** **HERO ID: 29091** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Adequacy and Consistency of Animal Husbandry Conditions	See footnote at end of page.[6]	High	1	1	1
	15. Number per Group	~95 animals/sex/group	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	See footnote at end of page.[3]	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed similarly across groups.	High	1	1	1
	18. Sampling Adequacy	All dose groups were evaluated for all parameters. Due to deaths in pre-assigned animals to be sampled for various outcomes, different numbers of animals were sometimes taken for sampling.	Medium	2	1	2
	19. Blinding of Assessors	No reference to blinding was made, but all measures were objective. Although histopathology evaluation is not objective, the first evaluation is not traditionally blinded but if additional evaluation of histopathology is needed, reviewers are blinded.	Not rated	NA	NA	NA

[6] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	Burek, J. D.,Nitschke, K. D.,Bell, T. J., Wackerle, D. L., Childs, R. C.,Beyer, J. E.,Dittenber, D. A.,Rampy, L. W., McKenna, M. J. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters Fundamental and Applied Toxicology, 4(1), 30-47. HERO ID: 29091 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	Elevated incidence of histopathology lesions in controls.	Low	3	1	3
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Respiratory rate was not reported; test substance is a respiratory irritant.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Rats had a common viral infection early in the treatment period; salivary gland tumor results may be confounded by this infection. Endpoints other than salivary gland tumors may also be affected.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	See footnote at end of page.[7]	High	1	1	1
	24. Reporting of Data	The data for many outcomes was reported in text. Only selected findings were reported for histopathology. A medium rating is given because data tables are provided in the unpublished study report (OxyChem, 1992; 4214046).	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**43**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.4828**	**Overall Score: Nearest *:**	**1.5**

[7] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Burek, J. D.,Nitschke, K. D.,Bell, T. J., Wackerle, D. L., Childs, R. C.,Beyer, J. E.,Dittenber, D. A.,Rampy, L. W., McKenna, M. J. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters Fundamental and Applied Toxicology, 4(1), 30-47.** **HERO ID: 29091** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptabl e, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		

3.2. Hazleton et al 1983, 2-year oral bioassay - cancer, hepatic

Study reference:	**Hazleton Laboratories (1983). 24-month oncogenicity study of methylene chloride in mice: Final report.** **HERO ID: 29131** **STUDY TYPE: Key** **[See associated reference information at bottom of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Identified by name. CASRN and structure not provided.	Medium	2	2	4
	2. Test Substance Source	Manufacturer and lot no. provided.	High	1	1	1
	3. Test Substance Purity	Purity analyses were conducted every 6 months, but results were reported in an appendix that was NOT included in the pdf.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	2 drinking water control groups	High	1	2	2
	5. Positive Controls	Positive controls are not required for this type of study.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Computerized randomization process.	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage were well described. Pilot study examined stability and homogeneity of test substance in drinking water.	High	1	1	1
	8. Consistency of Exposure Administration	See footnote at end of page.[8]	High	1	1	1

[8] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Hazleton Laboratories (1983). 24-month oncogenicity study of methylene chloride in mice: Final report.** **HERO ID: 29131** **STUDY TYPE: Key** **[See associated reference information at bottom of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Doses were calculated by study authors from analytical measurement of dw concentrations, measured intake and bw values.	High	1	2	2
	10. Exposure Frequency and Duration	24 months is appropriate for cancer bioassay; frequency was not explicitly reported, but 7 days/week is assumed based on reference to observation conducted on Saturday and Sunday.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	Narrow spacing between doses (nominal doses were 0, 60, 125, 185, 250 mg/kg/day); no clear dose-response across groups.	Low	3	1	3
	12. Exposure Route and Method	Drinking water concentrations were measured analytically.	High	1	1	1
Test Organism	13. Test Animal Characteristics	Commonly used mouse strain, obtained from commercial source.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were well-reported and adequate.	High	1	1	1
	15. Number per Group	>50/group and some had 50/group	High	1	1	1

Study reference:	**Hazleton Laboratories (1983). 24-month oncogenicity study of methylene chloride in mice: Final report.** **HERO ID: 29131** **STUDY TYPE: Key** **[See associated reference information at bottom of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	Hematology data were limited to leukocyte count and differential, no clinical chemistry data, no organ weight data.	Low	3	2	6
	17. Consistency of Outcome Assessment	See footnote at end of page.[9]	High	1	1	1
	18. Sampling Adequacy	Outcome evaluated for all animals	High	1	1	1
	19. Blinding of Assessors	No subjective outcomes were reported (initial histopath). By convention, initial histopathological exams not typically blinded.	Not Rated	NA	NA	NA
	20. Negative Control Response	Elevated incidence of liver histopath. lesions in controls. Also, convulsions seen in all groups without identified cause.	Low	3	1	3

[9] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	**Hazleton Laboratories (1983). 24-month oncogenicity study of methylene chloride in mice: Final report.** **HERO ID: 29131** **STUDY TYPE: Key** **[See associated reference information at bottom of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Reported decrease in water consumption in high dose males; however, the pdf does not contain the data tables and the magnitude of the decrease is not reported. Authors calculated actual doses (mg/kg-bw/day) so impact of lower water consumption on results should be minor.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	Convulsions were reported in controls and treated mice. Without an explanation as to cause, it is not clear how the convulsions (or the cause of the convulsions) may have confounded results.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were well-described and appropriate.	High	1	1	1
	24. Reporting of Data	Data tables are missing from the pdf. Results are described in text.	Low	3	2	6
High: >=1 and <1.7 **Medium: >=1.7 and <2.3** **Low: >=2.3 and <=3**		**Sum of scores:**			**29**	**50**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.7241**	**Overall Score: Nearest *:**	**1.7**
		Overall Quality Level:		**Medium**		

Study reference:	**Hazleton Laboratories (1983). 24-month oncogenicity study of methylene chloride in mice: Final report.** **HERO ID: 29131** **STUDY TYPE: Key** **[See associated reference information at bottom of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Associated Reference:	**This study was published as: Serota, DG; Thakur, AK; Ulland, BM; Kirschman, JC; Brown, NM; Coots, RH; Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: II. Mice. Food Chem Toxicol 24: 959-963. (HERO ID: 730593). Information from Serota et al. (1986) was considered during the data quality evaluation of Hazleton et al. (1983).**					

3.3. Nitschke et al., 1988, 2-year bioassay - cancer, mortality, clinical chemistry, hematological, immune, respiratory, cardiovascular, gastrointestinal, ocular, sensory, musculoskeletal/motor function, endocrine, hepatic, reproductive, neurotoxicity/behavior, skin and connective tissue, nutrition and metabolic/ body weight

Study reference:	**Nitschke, K. D., Burek, J. D.,Bell, T. J.,Kociba, R. J.,Rampy, L. W.,McKenna, M. J. (1988). Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats Fundamental and Applied Toxicology, 11(1), 48-59.** **HERO ID: 29244** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified definitively.	High	1	2	2
	2. Test Substance Source	The source of the test substance was reported, including manufacturer and the lot number.	High	1	1	1
	3. Test Substance Purity	The test substance purity (reported as at least 99.5%, as determined by periodic gas chromatography analysis) was such that any observed effects were highly likely to be due to the test substance itself.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	The study authors reported using an appropriate concurrent negative control group.	High	1	2	2
	5. Positive Controls	Positive controls are not required for this type of study	Not Rated	NA	NA	NA
	6. Randomized Allocation	The animals were randomly assigned to groups using a computer-derived randomization process.	High	1	1	1

Study reference:	**Nitschke, K. D., Burek, J. D.,Bell, T. J.,Kociba, R. J.,Rampy, L. W.,McKenna, M. J. (1988). Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats Fundamental and Applied Toxicology, 11(1), 48-59.** **HERO ID: 29244** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation of the test substance was reported, and methods were appropriate. Storage conditions were not reported; however, the test substance was periodically evaluated by gas chromatography and there was no indication of decomposition during the study.	Medium	2	1	2
	8. Consistency of Exposure Administration	Due to a lack of chambers of comparable size, the control animals remained in the animal holding room during each exposure period.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Analytically determined concentrations, based on the mean of daily time-weighted average concentrations, were reported for each group. The methods used to measure the chamber test substance (infrared spectroscopy, 1-2 times/hour) were reported and appropriate.	High	1	2	2

Study reference:	**Nitschke, K. D., Burek, J. D.,Bell, T. J.,Kociba, R. J.,Rampy, L. W.,McKenna, M. J. (1988). Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats Fundamental and Applied Toxicology, 11(1), 48-59.** **HERO ID: 29244** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	The exposure frequency and duration of exposure were reported and appropriate for this study type and the outcomes of interest.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and concentration spacing were justified by the study authors (based on a previous study reporting no NOAEL [Burek et al. 1984] and using concentrations below, above, and intermediate to that resulting in saturation of the mixed function oxidase metabolism of DCM, as discussed on p. 49).	High	1	1	1
	12. Exposure Route and Method	The route and method of exposure were reported and suited to the test substance. The number of air changes per hour was adequate (12/hour).	High	1	1	1
Test Organism	13. Test Animal Characteristics	Starting body weight and health status at the beginning of the study were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions (temperature, humidity, light-dark cycle) were consistent.	High	1	1	1

Study reference:	**Nitschke, K. D., Burek, J. D.,Bell, T. J.,Kociba, R. J.,Rampy, L. W.,McKenna, M. J. (1988). Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats Fundamental and Applied Toxicology, 11(1), 48-59.** **HERO ID: 29244** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	The number of animals per study group was reported and appropriate for the study type and outcome analysis.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed the intended outcomes.	High	1	2	2
	17. Consistency of Outcome Assessment	Details of the outcome assessment protocol were reported, and outcomes were assessed consistently across study groups.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcome of interest.	High	1	1	1
	19. Blinding of Assessors	No evaluations that were considered subjective were conducted and histopathological evaluations were not described as re-evaluation, so I considered this metric N/A.	Not rated	NA	NA	NA
	20. Negative Control Response	The biological responses of the negative control group were adequate.	High	1	1	1

Study reference:	Nitschke, K. D., Burek, J. D.,Bell, T. J.,Kociba, R. J.,Rampy, L. W.,McKenna, M. J. (1988). Methylene chloride: A 2-year inhalation toxicity and oncogenicity study in rats Fundamental and Applied Toxicology, 11(1), 48-59. HERO ID: 29244 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium, Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables in test design or procedures were reported; however, DCM is a potential respiratory irritant but respiratory rate measurement was not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Data on attrition and/or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and appropriate for datasets.	High	1	1	1
	24. Reporting of Data	Data for exposure-related findings were shown for each exposure group.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**39**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.3448**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

3.4. Serota et al., 1986, 2-year oral bioassay in rats - cancer, reproductive, hematological, immune, neurotoxicity/behavioral, renal, hepatic, ocular and sensory, cardiovascular, clinical chemistry, endocrine, gastrointestinal, mortality, musculoskeletal/motor function, body weight, respiratory, skin and connective tissue, thyroid, mortality

Study reference:	Serota, D. G.,Thakur, A. K.,Ulland, B. M.,Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: I. Rats Food and Chemical Toxicology, 24(9), 951-958. HERO ID: 730592 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	food grade dichloromethane	High	1	2	2
	2. Test Substance Source	Diamond Shamrock Industries, with certificate of analysis. Batch no. not reported.	Medium	2	1	2
	3. Test Substance Purity	"Food grade" - percent purity not reported. Analysis at 32, 52, 78 and 104 wk of study confirmed that the DCM sample was stable throughout the study period. A previous study (Kirschman, 1986) was consulted, which has purity information, .	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Two untreated control groups were run concurrently (deionized water only).	High	1	2	2
	5. Positive Controls	Positive controls not necessary for study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Rats were randomly allocated into groups.	High	1	1	1

Study reference:	Serota, D. G.,Thakur, A. K.,Ulland, B. M.,Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: I. Rats Food and Chemical Toxicology, 24(9), 951-958. HERO ID: 730592 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	7. Preparation and Storage of Test Substance	Detailed descriptions of storage and preparation of test substance with periodic testing for stability and accuracy of dosing solutions.	High	1	1	1
	8. Consistency of Exposure Administration	Consistent between groups. Regular testing of water for consistency of exposure solutions.	High	1	1	1
	9. Reporting of Doses/Concentrations	The actual DCM intakes were determined by study authors from measured DCM concentrations in the drinking-water and the actual body weights and water consumption values. Target: 5, 50, 125, 250,and 250(recovery group) mg/kg-d. Measured: 6, 52, 125, 235, and 232 mg/kg-d, respectively (males); 6, 58, 136, 263, and 269 mg/kg-d, respectively (females).	High	1	2	2
	10. Exposure Frequency and Duration	104 wks in main study; 78 wk plus 26-wk recovery in recovery group.	High	1	1	1

Study reference:	**Serota, D. G.,Thakur, A. K.,Ulland, B. M.,Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: I. Rats Food and Chemical Toxicology, 24(9), 951-958.** **HERO ID: 730592** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	4 doses plus control. Dose levels were selected on the basis of findings from subchronic and pharmacokinetic studies of DCM.	High	1	1	1
	12. Exposure Route and Method	Drinking water. There is no discussion of volatility but paper does report that the concentrations were analyzed and demonstrated that they were stable.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	F344 rats (Charles River Breeding Laboratory); ~7 wk old at study initiation; Starting body weight was not reported. Health status is not explicitly stated.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Consistent between groups. Detailed reporting of husbandry conditions.	High	1	1	1
	15. Number per Group	85/sex/group in exposure groups and control group 1 in main study (35/sex/group slated for interim sacrifices, 50/sex/group for terminal sacrifices); 50/sex/group in control group 2; 25/sex/group in recovery group	High	1	1	1

Study reference:	Serota, D. G.,Thakur, A. K.,Ulland, B. M.,Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: I. Rats Food and Chemical Toxicology, 24(9), 951-958. HERO ID: 730592 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	Monitored mortality, clinical signs, body weight, and food/water consumption throughout the study. Comprehensive histopathology, organ weights, hematology, serum chemistry, urinalysis. Ophthalmological evaluation.	High	1	2	2
	17. Consistency of Outcome Assessment	Consistent across groups	High	1	1	1
	18. Sampling Adequacy	Outcome evaluated for all animals which is adequate for this study type	High	1	1	1
	19. Blinding of Assessors	Evaluated endpoints did not require blinding.	Not Rated	NA	NA	NA
	20. Negative Control Response	Control data reported; unexpected findings were not reported.	High	1	1	1

Study reference:	Serota, D. G.,Thakur, A. K.,Ulland, B. M.,Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: I. Rats Food and Chemical Toxicology, 24(9), 951-958. HERO ID: 730592 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial BW not reported; small but statistically significant decreases in BW and water consumption were qualitatively reported for >=125 mg/kg-day groups. Concomitant decreased in food consumption noted for first 13 wks. Based on designation of "small", these are not expected to impact results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	No infections reported. Mortality rates similar, and similar incidental and age-related lesions in all groups (except liver).	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Detailed description of various statistical tests used. Tumor analysis included unadjusted and adjusted for intercurrent mortality.	High	1	1	1

Study reference:	**Serota, D. G.,Thakur, A. K.,Ulland, B. M.,Kirschman, J. C.,Brown, N. M.,Coots, R. H.,Morgareidge, K. (1986). A two-year drinking-water study of dichloromethane in rodents: I. Rats Food and Chemical Toxicology, 24(9), 951-958.** **HERO ID: 730592** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Hepatic nonneoplastic and neoplastic lesions reported quantitatively. Statistically significant changes in body weight, food consumption, drinking water intake, hematology, and clinical chemistry were reported qualitatively. Organ weight findings were considered unrelated to treatment despite occasional dose-dependent findings (reported qualitatively). The remaining results were reported qualitatively (lack of compound-related effects).	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**37**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.2759**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

3.5. Maltoni et al. 1988, oral bioassay (rat, mouse) - cancer

Study reference:	**Maltoni, C.,Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, 534(#issue#), 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified by name, structure, molecular formula and weight.	High	1	2	2
	2. Test Substance Source	The source was identified, but additional details were not reported.	Medium	2	1	2
	3. Test Substance Purity	Purity and composition were reported and such that effects were likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative controls were included	High	1	2	2
	5. Positive Controls	This metric not applicable for this study.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animal allocation was not reported	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Doses administered in olive oil, but preparation and storage conditions were not reported; It is not known whether the method of preparation and storage might have contributed to volatilization.	Low	3	1	3
	8. Consistency of Exposure Administration	Appears to be consistent	Medium	2	1	2

Study reference:	**Maltoni, C.,Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, 534(#issue#), 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Doses and concentrations reported for all experiments.	High	1	2	2
	10. Exposure Frequency and Duration	Data reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Number of exposure groups and spacing (2 groups) were limited regarding the ability to continue the cancer study for the lifetime of the rodents.	Low	3	1	3
	12. Exposure Route and Method	Exposure route was appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The species, strain, sex, and age were reported. Initial body weight and source were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Specifics regarding husbandry were not reported and could not be evaluated.	Low	3	1	3
	15. Number per Group	The numbers of animals for each study were appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Cancer studies are typically conducted for the lifetime of the rodents; because this study had to be terminated at 64 weeks due to mortality, the sensitivity to measure the outcomes of interest is limited.	Low	3	2	6

Study reference:	**Maltoni, C.,Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, 534(#issue#), 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcomes of interest.	High	1	1	1
	19. Blinding of Assessors	This metric is not applicable.	Not Rated	NA	NA	NA
	20. Negative Control Response	The responses appeared to be adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Several parameters were not reported or appeared not to have been measured.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	No data on attrition or health outcomes were reported, but from the data reported, there do not appear to be health effects unrelated to treatment.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical analyses were conducted, but were not described; however, sufficient data were present to conduct independent analysis of outcomes.	Medium	2	1	2

Study reference:	**Maltoni, C.,Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, 534(#issue#), 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Data for tumor outcomes were reported in text and tables. Survival was discussed but quantitative values per dose are not reported, even in the text. It is difficult to interpret the tumor data without details regarding survival.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**55**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.8966**	**Overall Score: Nearest *:**	**1.9**
		Overall Quality Level:		**Medium**		

3.6. Maltoni et al. 1988, inhalation bioassay in rats - cancer

Study reference:	Maltoni, C., Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, Issue No. 534, 352-366. HERO ID: 29235 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	The test substance was identified by name, structure, molecular formula and weight.	High	1	2	2
	2. Test Substance Source	The source was identified, but additional details were not reported.	Medium	2	1	2
	3. Test Substance Purity	Purity and composition were reported and effects were likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative controls were included but unclear if controls were exposed to air.	Medium	2	2	4
	5. Positive Controls	This metric not applicable for this study.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animal allocation was not reported	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Atmosphere generations methods were not reported but concentrations were monitored. It is not known whether the method of preparation and storage might have contributed to volatilization.	Medium	2	1	2
	8. Consistency of Exposure Administration	Unclear, as no details were provided	Low	3	1	3

Study reference:	**Maltoni, C., Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, Issue No. 534, 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Doses and concentrations reported for all experiments.	High	1	2	2
	10. Exposure Frequency and Duration	Data reported but rationale not provided for changes in the inhalation study.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	Only one concentration was used for adults and only one concentration group for offspring (embryos).	Low	3	1	3
	12. Exposure Route and Method	Exposure route was appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The species, strain, sex, and age were reported. Initial body weight and source were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Specifics regarding husbandry were not reported and could not be evaluated.	Low	3	1	3
	15. Number per Group	The numbers of animals were appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Limited information on what outcomes were measured	Low	3	2	6
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for the outcomes of interest.	High	1	1	1

Study reference:	**Maltoni, C., Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, Issue No. 534, 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	This metric is not applicable.	Not Rated	NA	NA	NA
	20. Negative Control Response	The responses appeared to be adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Several parameters were not reported or appeared not to have been measured. DCM is a potential respiratory irritant but respiratory rate measurement was not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	No data on attrition or health outcomes were reported, but from the data reported, there do not appear to be health effects unrelated to treatment.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical analyses were conducted, but were not described; however, sufficient data were present to conduct an independent analysis of outcomes.	Medium	2	1	2

Study reference:	**Maltoni, C., Cotti, G.,Perino, G. (1988). Long-term carcinogenicity bioassays on methylene chloride administered by ingestions to Sprague-Dawley rats and Swiss mice and by inhalation to Sprague-Dawley rats Annals of the New York Academy of Sciences, Issue No. 534, 352-366.** **HERO ID: 29235** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium ,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Data for tumor outcomes were reported in text and tables. Survival was discussed but quantitative values per dose are not reported, even in the text. It is difficult to interpret the tumor data without details regarding survival.	Low	3	2	6
High: >=1 and <1.7 **Medium: >=1.7 and <2.3** **Low: >=2.3 and <=3**		**Sum of scores:**			**29**	**58**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**2.0000**	**Overall Score: Nearest *:**	**2.0**
		Overall Quality Level:		**Medium**		

3.7. NTP, 1986, 2-year inhalation bioassay - cancer

Study reference:	**NTP (1986). NTP Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies) 306, 1-208.** **HERO ID: 732410** **STUDY TYPE: Key** **[See associated reference at bottom of table.]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Name, physiochemical properties, structure, and CASRN were reported.	High	1	2	2
	2. Test Substance Source	Source, lot numbers, and data from identity analyses were reported.	High	1	1	1
	3. Test Substance Purity	Purity such that effects likely due to the test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative control animals were included.	High	1	2	2
	5. Positive Controls	Positive control animals were not required	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals were randomly assigned to groups	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	The equipment and method used to generate the test substance concentrations were recorded.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently across groups	High	1	1	1
	9. Reporting of Doses/Concentrations	Target and analytical concentrations reported for 2-year study, and the method used for measuring concentration was reported and appropriate .	High	1	2	2

Study reference:	NTP (1986). NTP Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies) 306, 1-208. HERO ID: 732410 STUDY TYPE: Key [See associated reference at bottom of table.]					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Exposure duration and frequency were reported and appropriate for a cancer bioassay.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Exposure groups and concentration spacing were adequate to address the purpose of the study.	High	1	1	1
	12. Exposure Route and Method	The test substance was heated in duct before entering chambers; air concentrations continually measured - concentrations are within 90-110% for the majority of time.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	Most test animal characteristics were reported. Health status was assessed but not reported. High level of mononuclear cell leukemia in all male rats but incidence in controls is similar to historical controls.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were reported and were adequate.	High	1	1	1

Study reference:	NTP (1986). NTP Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies) 306, 1-208. HERO ID: 732410 STUDY TYPE: Key [See associated reference at bottom of table.]					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	The number of animals per study group was reported, appropriate for the study type and outcome analysis, and consistent with studies of the same or similar type.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and was sensitive.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently across study groups	High	1	1	1
	18. Sampling Adequacy	Details regarding sampling for the outcome(s) of interest were reported.	High	1	1	1
	19. Blinding of Assessors	Coded slides were re-evaluated by the Pathology Working Group when the original and quality assurance pathologists disagreed. and was conducted in a 'blinded' fashion.	High	1	1	1
	20. Negative Control Response	Negative controls responded appropriately	High	1	1	1

Study reference:	**NTP (1986). NTP Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies) 306, 1-208.** **HERO ID: 732410** **STUDY TYPE: Key** **[See associated reference at bottom of table.]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variables were reported. DCM is a potential respiratory irritant but respiratory rate measurement was not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	An unusually high incidence of mononuclear cell leukemia was seen (all male concentrations and in controls). This is expected to have some impact on results.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were clearly described and appropriate.	High	1	1	1
	24. Reporting of Data	Data were reported for all outcomes.	High	1	2	2
High: >=1 and <1.7 **Medium: >=1.7 and <2.3** **Low: >=2.3 and <=3**		**Sum of scores:**			**30**	**38**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.2667**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		
Associated reference:	**This study was published as: Mennear, JH; McConnell, EE; Huff, JE; Renne, RA; Giddens, E. (1988). Inhalation toxicology and carcinogenesis studies of methylene chloride (dichloromethane) in F344/N rats and B6C3F1 mice. Ann N Y Acad Sci 534: 343-351 (HERO ID: 29240). Information from Mennear et al. (1988) was considered during the data quality evaluation of NTP (1986).**					

3.8. Aiso, 2014, 2-year inhalation bioassay – hepatic and cancer

Study reference:	Aiso et al. (2014). Inhalation carcinogenicity of dichloromethane in rats and mice. Inhalation Toxicology. 26:8, 435-451. HERO ID: 4238148					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Study authors identified the chemical definitely and provided CAS number.	High	1	2	2
	2. Test Substance Source	Test substance source reported, batch/lot number not provided, but each lot of the test substance was analyzed by analytical methods for its purity and stability.	High	1	1	1
	3. Test Substance Purity	Test substance purity reported to be > 99.9%	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent control group exposed to clean air was handled in same manner as test chemical-exposure treated groups.	High	1	2	2
	5. Positive Controls	Positive controls are not typical for this type of study.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals were allocated by stratified randomization procedure into body-weight matched test and control groups.	Medium	2	1	2

Study reference:	Aiso et al. (2014). Inhalation carcinogenicity of dichloromethane in rats and mice. Inhalation Toxicology. 26:8, 435-451. HERO ID: 4238148					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	7. Preparation and Storage of Test Substance	Test substance stored in air tight bottles at room temperature and analyzed for stability; no decomposition products or impurities detected. Vapor generated by bubbling clean air through liquid test substance and diluting to desired concentrations.	High	1	1	1
	8. Consistency of Exposure Administration	Details of exposure administration were reported and exposures were administered consistently across study groups. This included exposure chamber descriptions, time of day of exposures, methods for atmosphere generation, and methods for analyzing chamber concentrations etc.	High	1	1	1
	9. Reporting of Doses/Concentrations	Target and mean (SD) analytical concentrations were reported and SDs and within acceptable range of deviation (SDs were <1% of mean). Concentrations in the chambers monitored at 15 min intervals by GC.	High	1	2	2

Study reference:	Aiso et al. (2014). Inhalation carcinogenicity of dichloromethane in rats and mice. Inhalation Toxicology. 26:8, 435-451. HERO ID: 4238148					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	The study authors reported exposure frequency and duration of exposure appropriate for this study type and/or outcome(s) of interest.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Exposure concentrations selected based on subchronic study conducted by the same laboratory. The number of exposure groups and dose/concentration spacing were justified by study authors and considered adequate to address the purpose of the study.	High	1	1	1
	12. Exposure Route and Method	The route and method of exposure were reported.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	The study authors reported species, strain, sex, health status, age, and starting body weight of the test animals. Test animals were obtained from a commercial source and the animal strain was appropriate for the evaluation of carcinogenesis.	High	1	2	2

Study reference:	Aiso et al. (2014). Inhalation carcinogenicity of dichloromethane in rats and mice. Inhalation Toxicology. 26:8, 435-451. HERO ID: 4238148					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	14. Adequacy and Consistency of Animal Husbandry Conditions	Study authors reported all husbandry conditions for the animals including temperature, humidity, and light-dark cycle.	High	1	1	1
	15. Number per Group	The number of animals per study group was reported which was appropriate for a 2-year cancer study.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology reported. The study was conducted in accordance with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies".	High	1	2	2
	17. Consistency of Outcome Assessment	Study authors provided details of outcome assessment protocol; no inconsistencies were reported.	High	1	1	1
	18. Sampling Adequacy	Except for testicular neoplasms in one male control animal, 1 or 2 male or female animals for thyroid tumors all the animals were evaluated for tumors. However, this is unlikely to impact the interpretation of the data.	High	1	1	1

Study reference:	Aiso et al. (2014). Inhalation carcinogenicity of dichloromethane in rats and mice. Inhalation Toxicology. 26:8, 435-451. HERO ID: 4238148					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	This metric is not applicable for initial histopathology review.	Not Rated	NA	NA	NA
	20. Negative Control Response	The biological responses for the negative controls were reported and were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There was no significant difference in the initial body weight, food or water intake between any study groups of either sex and their respective controls. Although DCM is a potential respiratory irritant, the authors did not report the respiratory rate.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	Authors reported details of animal attrition and health outcomes and did not observe any health effects unrelated to exposure.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Authors clearly described the statistical methods which were appropriate for the dataset analysis.	High	1	1	1
	24. Reporting of Data	Data for exposure-related findings were presented for all outcomes by exposure group and sex, and negative findings were reported qualitatively or quantitatively.	High	1	2	2

Study reference:	Aiso et al. (2014). Inhalation carcinogenicity of dichloromethane in rats and mice. Inhalation Toxicology. 26:8, 435-451. HERO ID: 4238148					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		Sum of scores:			30	33
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.1379	Overall Score: Nearest *:	1.1
		Overall Quality Level:		High		

4. Reproductive/Developmental Studies

4.1. Narotsky and Kavlock 1995, oral developmental study - reproductive, development, neurotoxicity/behavioral, respiratory, body weight, mortality

Study reference:	**Narotsky, M. G.,Kavlock, R. J. (1995). A multidisciplinary approach to toxicological screening: II. Developmental toxicity Journal of Toxicology and Environmental Health, 45(2), 145-171** **HERO ID: 76052** **STUDY TYPE: Key**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Dichloromethane (99.9%)	High	1	2	2
	2. Test Substance Source	Aldrich Chemical Co.; batch no. not reported	Medium	2	1	2
	3. Test Substance Purity	99.9%	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent vehicle control (corn oil)	High	1	2	2
	5. Positive Controls	Positive controls not needed for study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Placed in group using nonbiased procedure that assured a homogenous distribution of body weights among groups. Control for BW introduces nonrandom component.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Mixed with corn oil for gavage. Storage not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Consistent across groups; gavage volume of 1 ml/kg	High	1	1	1
	9. Reporting of Doses/Concentrations	0, 337.5, 450 mg/kg-d	High	1	2	2
	10. Exposure Frequency and Duration	GD 6-19 -Current guidance suggests that organogenesis is from day 5 in rodents, but even suggests that dosing can start even earlier to obtain rets of pre-implantation etc.	Medium	2	1	2

Study reference:	Narotsky, M. G.,Kavlock, R. J. (1995). A multidisciplinary approach to toxicological screening: II. Developmental toxicity Journal of Toxicology and Environmental Health, 45(2), 145-171 HERO ID: 76052 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	2 exposure groups plus control; exposures don't cover a wide range of doses either and thus, not clear whether a dose-response relationship can be demonstrated.	Medium	2	1	2
	12. Exposure Route and Method	gavage in corn oil	High	1	1	1
Test Organism	13. Test Animal Characteristics	Timed-pregnant F344 rats (~90-d-old). Initial BW 150-225g. Obtained from Harlan Sprague Dawley Inc.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Consistent across groups; reported adequately.	High	1	1	1
	15. Number per Group	16-21/group; OECD TG 414 suggests a least 20 pregnant dams per group; thus, lower numbers/group are more for screening purposes.	Medium	2	1	2

Study reference:	Narotsky, M. G.,Kavlock, R. J. (1995). A multidisciplinary approach to toxicological screening: II. Developmental toxicity Journal of Toxicology and Environmental Health, 45(2), 145-171 HERO ID: 76052 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Outcome Assessment	16. Outcome Assessment Methodology	Maternal toxicity: survival, clinical signs, body weight (GD 6, 8, 10, 13, 16, 20) Repro/dev't: resorptions, implants, # live litters, live pups on PND 1 and PND 6, pup weight, gross pup examination; any dead pups were examined for gross malformations and soft-tissue alterations. Usual developmental toxicity studies look at visceral, skeletal and external malformations; this is more of screening level study.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Consistent across groups.	High	1	1	1
	18. Sampling Adequacy	all animals were assessed for relevant outcomes.	High	2	1	2
	19. Blinding of Assessors	Blinding not required for examined endpoints.	Not Rated	NA	NA	NA
	20. Negative Control Response	Control data reported; no deviations from expected noted.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Groups had homogeneous distribution of BW at study initiation. Other confounding variables not identified.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	2 deaths (one in each exposure group) attributed to gavage error but not likely to influence results.	High	1	1	1

Study reference:	Narotsky, M. G.,Kavlock, R. J. (1995). A multidisciplinary approach to toxicological screening: II. Developmental toxicity Journal of Toxicology and Environmental Health, 45(2), 145-171 HERO ID: 76052 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Data Presentation and Analysis	23. Statistical Methods	Dams with one implant excluded from statistical analysis. Pup examination data were not statistically analyzed (considered anecdotal). Other data analyzed using General Linear Models (GLM) procedure.	High	1	1	1
	24. Reporting of Data	Maternal toxicity: Quantitative data for mortality and BW (reported graphically), clinical signs reported qualitatively only Repro/Dev't: Quantitative data for most outcomes (reported graphically or in tables); gross examination of pups reported qualitatively only	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**41**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.4138**	**Overall Score: Nearest *:**	**1.4**
		Overall Quality Level:		**High**		

4.1. General Electric 1976 - combined 1-gen and subchronic oral toxicity study in rats - reproductive, development, hematological, immune, neurotoxicity/behavior, renal, hepatic, ocular, sensory, cardiovascular, endocrine, clinical chemistry, endocrine, gastrointestinal, mortality, musculoskeletal/motor function, body weight, respiratory, thyroid

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Dichloromethane	High	1	2	2

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	2. Test Substance Source	The compound was-received from the General Electric Company, Mount Vernon, Indiana on December 10, 1975. The compound was a clear liquid and was identified as "Dichloromethane* Reagent, A.C.S. CH2C12 FW 84.94 DX835 5509 Matheson Coleman & Bell Manufacturing Chemists". But the study has the following comment: The above description is not totally accurate. The compound was furnished to IR&DC in containers labeled as indicated above but the actual contents were not from the indicated source. The contents were withdrawn on 12/4/75 from a purchased railroad tank - car of methylene chloride purchased from Dow Chemical certified to meet GE plastics Incoming Material Specification PCM-l-Sl. This methylene chloride is typical of that being used currently to produce Lexan® polycarbonate resin in the Mt. Vernon plant.	Medium	2	1	2

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	3. Test Substance Purity	Not reported; study authors state "This methylene chloride is typical of that being used currently to produce Lexan® polycarbonate resin in the Mt. Vernon plant."	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Concurrent negative control group administered distilled water via gavage on the same regimen as treated rats.	High	1	2	2
	5. Positive Controls	Positive control not required for this type of study	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study did not report how animals were allocated to study groups	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	The compound was dissolved in distilled water at a concentration of 15 mg/ml for gavage administration. Storage not reported.	Low	3	1	3
	8. Consistency of Exposure Administration	Gavage volume differed between groups (15 ml/kg-d for 0 and 225 mg/kg-d; 1.67 ml/kg-d for 25 mg/kg-day; 5.0 ml/kg-d for 75 mg/kg-d). The vehicle is distilled water so this difference should not significantly impact results.	Medium	2	1	2
	9. Reporting of Doses/Concentrations	0, 25, 75, or 225 mg/kg-d via gavage	High	1	2	2

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Total exposure: F0 rats 18 weeks; F1 rats 13 weeks. Methods section did not specifically state how long F0 rats were exposed prior to mating, but exposure ended at weaning. Based on Tables 5 and 6 (food consumption in F0 animals), weeks 11-13 were mating. So, F0 rats were exposed 10 weeks prior to mating, for 3 weeks during mating, and through gestation and lactation. It is not stated explicitly in the methods whether the 90-d exposure in F1 rats included 3 wks of nursing or not. Again, based on F1 food consumption table (Table 7) for F1 rats, it appears that the 13-wk F1 exposure was post-weaning (13 wks of F1 food consumption data)	Medium	2	1	2

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	Based on lack of effects at the highest dose this may not have been a high enough exposure to inform toxicity of DCM. The only exposure-related finding reported was a slight, transient decrease in pup body weight on PND 21 at 75 mg/k-d (8%) and 225 mg/kg-d (15%). At study week 0 (assuming post-weaning), F1 body weights at these doses did not differ from control.	Low	3	1	3
	12. Exposure Route and Method	See footnote at end of page[10]	High	1	1	1
Test Organism	13. Test Animal Characteristics	Charles River CD rats, 71-101 g	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions consistent. House individually (except during mating and lactation periods) in wire cages; temperature and humidity-controlled room. Food and water available ad libitum. Temp and humidity not reported.	Medium	2	1	2

[10] Metrics that received a "High" rating met the criteria as discussed in the Applications of Systematic Review for TSCA Risk Evaluation.

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	F0: 10/sex/group; F1: 15/sex/group; For a reproductive toxicity study (OECD TG 415), there should be enough animals for the result to be 20 pregnant animals/group. Using 10 animals/group is more of a screening reproductive toxicity study (e.g., OECD TG 421).	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	Histopathology on a large number of organs/tissues, as well as hematology, biochemistry, urinalysis, body weight, clinical signs were taken.	High	1	2	2
	17. Consistency of Outcome Assessment	Consistent evaluation.	High	1	1	1
	18. Sampling Adequacy	F0 10/group; F1 15/group (10 F1 controls and 10 F1 high-dose for histo; low- and mid-dose groups not evaluated due to lack of high-dose effects - consistent with protocol)	High	1	1	1
	19. Blinding of Assessors	Study endpoints do not require blinding.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses reported; no deviations from standard reported.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Starting BW reported; body weight effects only reported in F1 rats on PND 21 and were minimal.	High	1	2	2

Study reference:	General Electric, Company (1976). Dichloromethane: Reproduction and Ninety-Day Oral Toxicity Study in Rats HERO ID: 730464 STUDY TYPE: Key					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	22. Health Outcomes Unrelated to Exposure	data on attrition and/or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical tests reported for reproductive and developmental endpoints. Statistics not reported for non-reproductive/dev't endpoints; data reporting for survival and body weight adequate for independent statistics. Other endpoints inadequate for statistics (qualitative)	Medium	2	1	2
	24. Reporting of Data	Mortality, Bd wt data, food consumption, and repro/dev't data reported quantitatively. Other endpoints (no exposure-related effects) reported qualitatively. Note that tables of all effects are included in appendices	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**44**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.5172**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

4.1. Raje et al. 1988 – inhalation, dominant lethal – reproductive/developmental

Study reference:	**Raje et al. (1988). Evaluation of in vivo mutagenicity of low dose methylene chloride in mice. Journal of the American College of Toxicology.** **HERO ID: 732088** **STUDY TYPE: Key** **[See accompanying note at end of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Test Substance	1. Test Substance Identity	Identified definitively by chemical name	High	1	2	2
	2. Test Substance Source	Manufacturer was reported without batch/lot no.	Medium	2	1	2
	3. Test Substance Purity	HPLC grade	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Air-exposed controls	High	1	2	2
	5. Positive Controls	Although these are required for evaluating dominant lethal effects, for reproductive/developmental effects it was determined that this is not required	Not rated	NA	NA	NA
	6. Randomized Allocation	The study did not report how animals were allocated to study groups.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	The method and equipment used to generate the test substance as a vapor were reported and appropriate.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently across groups. Only males were exposed.	High	1	1	1
	9. Reporting of Doses/Concentrations	Target concentrations and actual concentrations (mean +-SD) were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Exposure was for 2h/day whereas many inhalation studies are for 6 hrs/day	Medium	2	1	2

Study reference:	**Raje et al. (1988). Evaluation of in vivo mutagenicity of low dose methylene chloride in mice. Journal of the American College of Toxicology.** **HERO ID: 732088** **STUDY TYPE: Key** **[See accompanying note at end of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	11. Number of Exposure Groups and Dose Spacing	There were 3 exposure groups, but the levels were narrowly spaced. (100, 150 and 200 ppm). It is unclear whether the highest dose was high enough. No justification was provided for levels.	Low	3	1	3
	12. Exposure Route and Method	Dynamic whole-body chamber, vapor may condense; air changes not reported.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	Females were not exposed prior to or during mating and gestation	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were reported (e.g., temperature, humidity, light- dark cycle) and were adequate and the same for control and exposed populations.	High	1	1	1
	15. Number per Group	20 males/group	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Only males were dosed. Limited number of parameters were evaluated, including testes histopathology, pregnancy index and uterine examination data. No fetal examinations (external, skeletal, visceral). No measurement of pup wt.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Outcomes were measured consistently across groups	High	1	1	1
	18. Sampling Adequacy	Litter data was provided.	High	1	1	1

Study reference:	**Raje et al. (1988). Evaluation of in vivo mutagenicity of low dose methylene chloride in mice. Journal of the American College of Toxicology.** **HERO ID: 732088** **STUDY TYPE: Key** **[See accompanying note at end of table]**					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	Study endpoints do not require blinding. However, lack of blinding is not expected to have a substantial impact on results; parameters were objective	Not rated	NA	NA	NA
	20. Negative Control Response	Responded as expected	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Respiratory rate was not reported and DCM is expected to be a respiratory irritant.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Data on attrition and/or health outcomes unrelated to exposure were not reported for each study group.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistics were not described; however, text indicate that no statistically significant changes were found.	Low	3	1	3
	24. Reporting of Data	# Post-implantation deaths were not directly reported (reported as % dead/litter). Pre-implantation loss could not be determined because corpora lutea were not measured.	Low	3	2	6
High: >=1 and <1.7 **Medium: >=1.7 and <2.3** **Low: >=2.3 and <=3**		**Sum of scores:**			**29**	**56**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.9310**	**Overall Score: Nearest *:**	**1.9**
		Overall Quality Level:		**Medium**		

Study reference:	Raje et al. (1988). Evaluation of in vivo mutagenicity of low dose methylene chloride in mice. Journal of the American College of Toxicology. HERO ID: 732088 STUDY TYPE: Key [See accompanying note at end of table]					
Domain	**Metric**	**Evaluator's Comment**	**Qualitative Determination [i.e.,High,Medium,Low,Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Although there are some identified deficiencies, this study can be used to consider possible reproductive/developmental effects of methylene chloride						
NOTE: When evaluated as a dominant lethal study (to evaluate the potential for mutagenicity), the study is unacceptable because no positive controls were used						

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Burek, JD; Nitschke, KD; Bell, TJ; Wackerle, DL; Childs, RC; Beyer, JE; Dittenber, DA; Rampy, LW; McKenna, MJ. (1984). Methylene chloride: A two-year inhalation toxicity and oncogenicity study in rats and hamsters. Fundam Appl Toxicol 4: 30-47. http://dx.doi.org/10.1093/toxsci/4.1.30

Dow Chem Co. (1961). THE RESULTS OF CHRONIC SKIN ABSORPTION STUDIES ON CHLOROTHENE AND METHYLENE CHLORIDE WITH COVER LETTER. (OTS: OTS0215228; 8EHQ Num: NA; DCN: 878211128; TSCATS RefID: 20282; CIS: NA).

Dow Chem Co. (1988). INITIAL SUBMISSION: EVALUATION OF THE ACUTE NEUROPHARMACOLOGIC EFFECTS OF DICHLOROMETHANE IN RATS (FINAL REPORT) WITH ATTACHMENTS AND COVER LETTER DATED 050792. (OTS: OTS0537278; 8EHQ Num: 8EHQ-0592-3826; DCN: 88-920002468; TSCATS RefID: 423282; CIS: NA).

General Electric Co. (1976a). Dichloromethane fourteen day range finding study in dogs. (OTS: OTS0205887; 8EHQ Num: NA; DCN: 878210708; TSCATS RefID: 16715; CIS: NA).

General Electric Co. (1976b). DICHLOROMETHANE FOURTEEN DAY RANGE FINDING STUDY IN RATS. (OTS: OTS0205887; 8EHQ Num: NA; DCN: 878210707; TSCATS RefID: 16714; CIS: NA).

General Electric Co. (1976c). DICHLOROMETHANE NINETY DAY ORAL TOXICITY STUDY IN DOGS. (OTS: OTS0205887; 8EHQ Num: NA; DCN: 878210709; TSCATS RefID: 16716; CIS: NA).

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