United States
Environmental Protection Agency

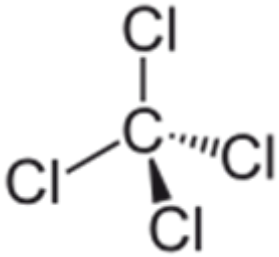
Office of Chemical Safety and
Pollution Prevention

Risk Evaluation for Carbon Tetrachloride

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Animal and In Vitro Studies

CASRN: 56-23-5



January 2020

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1. Acute Toxicity Studies

1.1. Animal toxicity evaluation results of Adams et al 1952 for an acute inhalation toxicity study in rats on mortality outcomes

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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 identified by unambiguous name and contaminants identified.	High	1	2	2
	2. Test Substance Source	Test substance was reportedly a commercial product but specific source was not reported. Infrared absorption spectroscopy used to verify identity and identify contaminants.	Medium	2	1	2
	3. Test Substance Purity	Test substance purity not reported, but paper reports purification of commercial product by redistillation and confirmation of identity by infrared absorption spectroscopy. Minor contaminants were identified at low (? 0.05%) concentrations.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Negative controls not required for acute lethality test	Not Rated	NA	NA	NA
	5. Positive Controls	Positive controls not typical for acute lethality test	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study did not describe method of animal allocation	Low	3	1	3

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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	Method of vapor generation was incompletely reported (equipment not specified; temperature used to achieve vaporization was not reported) but there is no reason to believe there would be an impact on animal exposure, as vapor concentrations were reportedly analyzed regularly and within 10% of nominal.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures at different concentrations were administered for different durations, making it difficult to discern effects of changing duration from effects of changing concentration.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Air concentrations were reported, but it is not clear whether these were nominal or actual concentrations. Analysis of chamber concentrations was by combustion analysis, which is likely an insensitive method.	Low	3	2	6

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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 durations ranged between 0.1 and 12 hours. Acute inhalation lethality tests are typically 4 hours in duration.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	6 exposure groups ranging more than 6-fold (high to low) were used, but the durations of exposure varied by exposure.	Medium	2	1	2
	12. Exposure Route and Method	Dynamic whole body chamber was used for vapor that may condense.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	Test animal species, strain, and source (in-house colony) were reported. Study reports using both sexes but does not indicate which sex was used for each exposure level and duration. Initial health status, age, and body weight were not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions other than the exposure chamber were not reported.	Low	3	1	3
	15. Number per Group	Between 5 and 20 animals were used for each combination of concentration and duration. This is more than required for an acute lethality study	High	1	1	1

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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	Outcome assessment methodology and outcomes assessed were typical for acute lethality study.	High	1	2	2
	17. Consistency of Outcome Assessment	Study reports observing survivors for 2-3 weeks or until full recovery was established. This could lead to inconsistencies in mortality assessment if there are late deaths.	Low	3	1	3
	18. Sampling Adequacy	See footnote at end of page.[1]	High	1	1	1
	19. Blinding of Assessors	Mortality is not subjective outcome.	Not Rated	NA	1	NA
	20. Negative Control Response	Negative controls not required for acute lethality study.	Not Rated	NA	NA	NA
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial body weight, food/water intake, and respiratory rate were not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	See footnote at end of page. [1]	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was not conducted, and an LC50 was not identified. Mortality data enabling independent statistical analysis were reported.	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:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	24. Reporting of Data	Mortality data are reported, but without time to death and not by sex.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**27**	**56**
		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: Varying numbers of animals were exposed to different concentrations for different durations and with varying postexposure observation times. The original calculated score for this study was 2.1. This value is not presented above because the final rating was changed based on professional judgement.**					

1.2. Animal toxicity evaluation results of Adams et al 1952 for an acute inhalation toxicity study in rats on neurological/behavior outcomes

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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 identified by unambiguous name and contaminants identified.	High	1	2	2
	2. Test Substance Source	Test substance was reportedly a commercial product but specific source was not reported. Infrared absorption spectroscopy used to verify identity and identify contaminants.	Medium	2	1	2
	3. Test Substance Purity	Test substance purity not reported, but paper reports purification of commercial product by redistillation and confirmation of identity by infrared absorption spectroscopy. Minor contaminants were identified at low (? 0.05%) concentrations.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Negative controls not required for acute lethality test, but neurotoxicity cannot be assessed without negative controls.	Unacceptable	4	2	8
	5. Positive Controls	Positive controls not typical for acute lethality test	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study did not describe method of animal allocation	Low	3	1	3

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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	Method of vapor generation was incompletely reported (equipment not specified; temperature used to achieve vaporization was not reported) but there is no reason to believe there would be an impact on animal exposure, as vapor concentrations were reportedly analyzed regularly and within 10% of nominal.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures at different concentrations were administered for different durations, making it difficult to discern effects of changing duration from effects of changing concentration.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Air concentrations were reported, but it is not clear whether these were nominal or actual concentrations. Analysis of chamber concentrations was by combustion analysis, which is likely an insensitive method.	Low	3	2	6
	10. Exposure Frequency and Duration	Exposure durations ranged between 0.1 and 12 hours.	High	1	1	1

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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	6 exposure groups ranging more than 6-fold (high to low) were used, but the durations of exposure varied by exposure.	Medium	2	1	2
	12. Exposure Route and Method	Dynamic whole body chamber was used for vapor that may condense.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	Test animal species, strain, and source (in-house colony) were reported. Study reports using both sexes but does not indicate which sex was used for each exposure level and duration. Initial health status, age, and body weight were not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions other than the exposure chamber were not reported.	Low	3	1	3
	15. Number per Group	Between 5 and 20 animals were used for each combination of concentration and duration. This should be adequate for acute toxicity	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Frequency and timing of observation for clinical signs of neurotoxicity was not described.	Low	3	2	6

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	17. Consistency of Outcome Assessment	No information on consistency of clinical observations was provided.	Low	3	1	3
	18. Sampling Adequacy	See footnote at end of page.[1]	High	1	1	1
	19. Blinding of Assessors	Observations for clinical signs may be subjective and blinding was not reported.	Unacceptable	4	1	4
	20. Negative Control Response	Negative controls were not used.	Not Rated	NA	NA	NA
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial body weight, food/water intake, and respiratory rate were not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	See footnote at end of page.[2]	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was not conducted, and data enabling independent statistical analysis were not reported.	Unacceptable	4	1	4
	24. Reporting of Data	Incidences of clinical signs of neurotoxicity were not reported	Unacceptable	4	2	8
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**76**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**2.6207**	**Overall Score: Nearest *:**	**2.6[2]**

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

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

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**Unacceptable[2]**		
Study Quality Comment:	**Footnote 2: Consistent with our *Application of A 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, four of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

1.3. Animal toxicity evaluation results of Bruckner et al 1986 for a study on renal and hepatic outcomes

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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 clearly identified by name (CASRN not provided).	High	1	2	2
	2. Test Substance Source	The source of the test substance (analytical grade CCl4) was reported.	High	1	1	1
	3. Test Substance Purity	The grade, but not the purity of the test substance was reported. Since the test substance was obtained from a manufacturer, it is unlikely that impurities would have a substantial impact on the results.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Appropriate control groups were used. Treated animals were administered CCl4 in corn oil via gavage. Control animals were treated with corn oil only.	High	1	2	2
	5. Positive Controls	A positive control group is not indicated by study type (acute, subacute, and subchronic-duration animal toxicity studies).	Not Rated	NA	NA	NA
	6. Randomized Allocation	The study indicated that rats were randomly divided into groups.	High	1	1	1

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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 study indicated that CCl4 was mixed with corn oil and administered via gavage in a total volume of 1 mL/animal. Test substance stability/storage conditions were not reported, but are not likely to substantially impact the results.	Medium	2	1	2
	8. Consistency of Exposure Administration	Details of exposure administration were reported and exposures were administered consistently across groups (same frequency, same time of day, consistent gavage volumes).	High	1	1	1
	9. Reporting of Doses/Concentrations	Administered doses were reported without ambiguity.	High	1	2	2

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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 were clearly reported. However, minor limitations in the frequency/duration of treatment were identified (acute, subacute, and subchronic durations were not "standard"). Animals treated a single time by gavage were sacrificed 24 hours after exposure (not followed for up to 14 days); animals treated sub-acutely were administered CCl4 on a cycle of 5 days on, 2 days off, 4 days on (with sacrifice after 4 or 11 days), and animals treated for a subchronic duration were administered CCl4 for 12 weeks (less than 90 days).	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	The number of dose groups and dose spacing were justified by the authors and considered adequate to address the purpose of the study (identifying NOAEL and LOAEL levels, with a focus on liver effects).	High	1	1	1

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The test animal species, strain, sex, and starting body weights (within a range) were reported.; the species and strain were appropriate. Animals were obtained from a commercial laboratory. Rats were described as adults (specific age not reported). Health status of the rats was not explicitly specified. These minor limitations are unlikely to substantially impact the study results.	Medium	2	2	4

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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	Some husbandry conditions were specified (i.e. reverse light/dark conditions were reported) . The lack of information on other conditions (i.e. temperature, humidity) are considered minor uncertainties that are unlikely to have a substantial impact on the results (no indication that conditions were different among treated rats and controls).	Medium	2	1	2
	15. Number per Group	The number of animals per study group was reported.. However, only male rats were used; the number of animals used were 5 for acute and sub-acute studies, and 15-16 for the subchronic-duration study (compared to 10/sex/group used for standard 28-day and 90-day repeated-dose studies).	Medium	2	1	2

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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 partially addressed the intended outcomes of interest. Liver and kidney effects were evaluated by examining limited clinical chemistry parameters, organ weights, and/or histopathological effects. Other common clinical chemistry parameters associated with liver and kidney function were not measured.	Medium	2	2	4
	17. Consistency of Outcome Assessment	Outcome assessment protocols were described, and outcomes were assessed consistently across groups.Data for liver lesions were presented quantitatively as means (+/-SD) based on severity scores ranging from 0 to 8.	High	1	1	1

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported, with minor limitations (e.g. number of histology slides evaluated not reported). Numbers of animals evaluated for specific endpoints were generally limited (5-9 males/group, even for the subchronic-duration study).	Medium	2	1	2
	19. Blinding of Assessors	Histopathology slides were coded and examined in a single blind fashion.	High	1	1	1
	20. Negative Control Response	The biological responses of the control group were reported for most endpoints; however, liver histopathology data for control animals subjected to acute and sub-acute treatment were not shown (no effects were reported). Liver weight data were provided in the text for the control and high-dose groups only.	Medium	2	1	2
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reported differences in initial body weights among study groups.	High	1	2	2

Study reference:	**Bruckner, J. V., Mackenzie, W. F., Muralidhara, S., Luthra, R., Kyle, G. M., Acosta, D. (1986). Oral toxicity of carbon tetrachloride: Acute, subacute, and subchronic studies in rats. Fundamental and Applied Toxicology, 6(1), 16-34** **HERO ID: 62379**					
Domain	**Metric**	**Eval 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	See footnote at end of page.[1]	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods		Medium	2	1	2
	24. Reporting of Data	Data were presented by exposure group for most endpoints. Liver histopathology data for the negative control group (acute and subacute studies) are not shown in the data tables. Liver weight data are provided for the control and high-dose groups only.	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**44**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.4667**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

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

1.4. Animal toxicity evaluation results of Hayes et al 1986 for an acute oral lethality study on mortality outcomes

Study reference:	Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463 HERO ID: 194400					
Domain	**Metric**	**Eval 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 identified by unambiguous name	High	1	2	2
	2. Test Substance Source	Test substance source and lot number reported, but certification/analytical verification of identity was not.	Medium	2	1	2
	3. Test Substance Purity	Test substance reported to be HPLC grade and >99% pure.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative control not required for acute lethality study.	Not Rated	NA	NA	NA
	5. Positive Controls	Positive controls not typical for this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study reports randomizing the mice but is not clear regarding the allocation.	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Study reports daily preparation of solution, but does not report storage.	Low	3	1	3
	8. Consistency of Exposure Administration	Only one exposure group tested	Not Rated	4	4	4
	9. Reporting of Doses/Concentrations	Dose reported in mg/kg bw; body weight not reported.	Medium	2	2	4

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	See footnote at end of page.[1]	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Single exposure group is not sufficient to determine LD50	Unacceptable	4	1	4
	12. Exposure Route and Method	See footnote at end of page.[2]	High	1	1	1
Test Organism	13. Test Animal Characteristics	Test animal species, strain, sex, lifestage, and source were reported and appropriate. Initial body weights were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were described and appropriate.	High	1	1	1
	15. Number per Group	10/sex were tested; this is more than adequate for acute lethality	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Duration of post-exposure observation was not reported.	Unacceptable	4	2	8
	17. Consistency of Outcome Assessment	Only one group tested.	Not Rated	NA	NA	NA
	18. Sampling Adequacy	Mortality assessed in all exposed animals.	High	1	1	1
	19. Blinding of Assessors	Mortality is not subjective	Not Rated	NA	NA	NA

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

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	No negative control was used	Not Rated	NA	NA	NA
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Only one group tested	Not Rated	NA	NA	NA
	22. Health Outcomes Unrelated to Exposure	acute lethality test; no other outcomes assessed	Not Rated	NA	NA	NA
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis not possible on single group	Not Rated	NA	NA	NA
	24. Reporting of Data	Mortality data were not reported	Unacceptable	4	2	8
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**24**	**47**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.9583**	**Overall Score: Nearest *:**	**2.0[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of A 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.**					

1.5. Animal toxicity evaluation results of Kronevi et al 1979 for an acute dermal study on liver toxicity, kidney toxicity, and skin morphology outcomes

Study reference:	**T. Kronevi, J. Wahlberg, B. Holmberg (1979). Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs. Environmental Research, 19(1,1), 56-69** **HERO ID: 3684159**					
Domain	**Metric**	**Eval 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 identified as carbon tetrachloride (p.a.).	High	1	2	2
	2. Test Substance Source	Obtained from E. Merck, Darmstadt, Germany. No batch/lot number.	Medium	2	1	2
	3. Test Substance Purity	Not specified, but reported "p.a.", which indicates analytical grade	High	1	1	1
Test Design	4. Negative and Vehicle Controls	No control animals were used. Study authors note that skin morphology in exposed area was compared to skin morphology from unexposed area in the same animal. No comparator for liver or kidney histology.	Unacceptable	4	2	8
	5. Positive Controls		Not Rated	4	4	4
	6. Randomized Allocation	Study authors did not report animal allocation methods.	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Pure solvent was applied, so no preparation was required.	Not Rated	NA	NA	NA
	8. Consistency of Exposure Administration	All animals similarly exposed	High	1	1	1

Study reference:	T. Kronevi, J. Wahlberg, B. Holmberg (1979). Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs. Environmental Research, 19(1,1), 56-69 HERO ID: 3684159					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	1 mL of pure solvent applied within a glass ring with an inside diameter of 20 mm (area 3.1 cm2). At a density of 1.59 g/cm3 = 1.59 g/mL, the administered dose was 1.59 g. Glass ring was covered with glass (occluded conditions).	High	1	2	2
	10. Exposure Frequency and Duration	Exposure was for 15 minutes, 1 hr, 4 hr, or 16 hr	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Only one dose group (pure solvent), but for 4 durations.	Low	3	1	3
	12. Exposure Route and Method	Dermal exposure using a covered glass ring to prevent volatilization or exposure via inhalation or oral routes.	High	1	1	1
Test Organism	13. Test Animal Characteristics	Albino guinea pigs weighting between 440 and 570 g. Source and sex of animals not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	No husbandry conditions were reported, but since this is an acute study this is not likely to have a major impact on study.	Medium	2	1	2

Study reference:	T. Kronevi, J. Wahlberg, B. Holmberg (1979). Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs. Environmental Research, 19(1,1), 56-69 HERO ID: 3684159					
Domain	**Metric**	**Eval 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 were not explicitly reported. Overall number of animals was 20. There were 5 compounds tested, with each compound evaluated for 4 time-points. This implies that only one animal was used per compound per duration.	Unacceptable	4	1	4
Outcome Assessment	16. Outcome Assessment Methodology	Skin biopsy was performed on exposed area and neighboring unexposed animal. Liver and kidney histology were assessed for evaluation of liver and kidney histology.	High	1	2	2
	17. Consistency of Outcome Assessment	See footnote at end of page.[1]	High	1	1	1
	18. Sampling Adequacy	Only one animal per group and no controls, so sampling adequacy is N/A	Not Rated	NA	NA	NA
	19. Blinding of Assessors	Blinding is not required for initial histopathological review.	Not Rated	NA	NA	NA

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

Study reference:	**T. Kronevi, J. Wahlberg, B. Holmberg (1979). Histopathology of skin, liver, and kidney after epicutaneous administration of five industrial solvents to guinea pigs. Environmental Research, 19(1,1), 56-69** **HERO ID: 3684159**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	Skin biopsy results from untreated skin were not reported. No control specimens for liver or kidney histology.	Unacceptable	4	1	4
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Little concern with confounding in acute study design	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	Attrition/infection N/A due to acute study design	Not Rated	NA	NA	NA
Data Presentation and Analysis	23. Statistical Methods	No statistical methods. Only one animal per group, so data insufficient for statistical analysis.	Unacceptable	4	1	4
	24. Reporting of Data	Results 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:**			**30**	**57**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.900**	**Overall Score: Nearest *:**	**1.9[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of A 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.**					

1.6. Animal toxicity evaluation results of Roudabush et al 1965 for an acute dermal toxicity and dermal irritation study on acute toxicity/poisoning and irritation outcomes

Study reference:	**Roudabush, R. L., Terhaar, C. J., Fassett, D. W., Dziuba, S. P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicology and Applied Pharmacology, 7(4), 559-565** **HERO ID: 79743**					
Domain	**Metric**	**Eval 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 clearly identified.	High	1	2	2
	2. Test Substance Source	The manufacturer was reported. The batch lot number for materials was not reported; however, this omission is unlikely to have a substantial impact on result.	Medium	2	1	2
	3. Test Substance Purity	Purity or chemical grade was not reported.; however given other information, purity was not expected to be of concern.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	The use of controls were not discussed in the methodology sections of the report; however, the results table of the dermal irritation tests reported results for distilled water. The standard test guidelines (e.g., OECD) do not require negative controls for acute toxicity studies.	High	1	2	2
	5. Positive Controls	Not 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 for either the acute toxicity nor the irritation studies.	Low	3	1	3

Study reference:	**Roudabush, R. L., Terhaar, C. J., Fassett, D. W., Dziuba, S. P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicology and Applied Pharmacology, 7(4), 559-565** **HERO ID: 79743**					
Domain	**Metric**	**Eval 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 materials were noted to be undiluted. Storage conditions were not reported; however, omission of these details are unlikely to have a substantial impact on results.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposure administration was reported for both studies and were administered consistently across study groups for both species.	High	1	1	1
	9. Reporting of Doses/Concentrations	Study report does not specify the administered dermal doses for the acute toxicity study or the irritation study for either species. The report only states "a minimum of 3 dosages was employed" for the acute dermal toxicity test..	Unacceptable	4	2	8
	10. Exposure Frequency and Duration	The report notes that the procedure followed the protocols described in the Regulations (21 CFR 191.10), which includes details on exposure duration for both the acute dermal toxicity test (24 hours) and the primary irritation test (24 hours and 72 hours).	High	1	1	1

Study reference:	**Roudabush, R. L., Terhaar, C. J., Fassett, D. W., Dziuba, S. P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicology and Applied Pharmacology, 7(4), 559-565** **HERO ID: 79743**					
Domain	**Metric**	**Eval 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	The number of exposure groups was stated as "a minimum of 3 dosages" for the acute dermal toxicity study; the actual number of dose groups and spacing is not reported. The dosing of the irritation study is also not reported.	Unacceptable	4	1	4
	12. Exposure Route and Method	The route and method of exposure was reported and appropriate for the study types	High	1	1	1
Test Organism	13. Test Animal Characteristics	There are deficiencies in the reporting of the test animal characteristics. The strain of guinea pigs and rabbits, sex used for each study, and the starting body weight ranges were reported. There is some uncertainty in the source of white rabbits (reported to be from a "local supplier"). These uncertainties are unlikely to have a substantial impact on results.	Medium	2	2	4

Study reference:	**Roudabush, R. L., Terhaar, C. J., Fassett, D. W., Dziuba, S. P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicology and Applied Pharmacology, 7(4), 559-565** **HERO ID: 79743**					
Domain	**Metric**	**Eval 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	Animal husbandry conditions were not reported. to evaluate if husbandry was adequate and if differences occurred between control and exposed groups..	Low	3	1	3
	15. Number per Group	The reported number of animals per study group for the acute toxicity test was unclear (reported to be "usually" 4 animals/dose group).	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcome(s) of interest.	High	1	2	2
	17. Consistency of Outcome Assessment	There was incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results.	Medium	2	1	2
	18. Sampling Adequacy	Details on outcome assessments sampling were not reported, but is likely that all tested animals were sampled.	Medium	2	1	2
	19. Blinding of Assessors	The study types do not require blinding of assessors.	Not Rated	NA	NA	NA

Study reference:	**Roudabush, R. L., Terhaar, C. J., Fassett, D. W., Dziuba, S. P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicology and Applied Pharmacology, 7(4), 559-565** **HERO ID: 79743**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	The biological response of the negative control group (distilled water) was adequate for the dermal irritation study. There was no reported control used in the acute toxicity test.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no reporting for any possible differences among the study groups that could influence the outcome assessment.; however, the lack of reporting is not likely to have a significant impact on results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	Data for outcomes unrelated to exposure for each study group were not reported, but the lack of reporting is unlikely to influence the study results.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was not well described but would unlikely have a substantial impact on results. The acute toxicity test reported calculating the LD50 using the method of Finney (1952), while the calculation of the primary irritation score were made according to the Regulations (21 CFR 191.11).	Medium	2	1	2

Study reference:	**Roudabush, R. L., Terhaar, C. J., Fassett, D. W., Dziuba, S. P. (1965). Comparative acute effects of some chemicals on the skin of rabbits and guinea pigs. Toxicology and Applied Pharmacology, 7(4), 559-565** **HERO ID: 79743**					
Domain	**Metric**	**Eval 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 reported for most, but not all, outcomes by exposure group. Data was reported for guinea pigs (male only) but was not reported by sex for rabbits, rather the data reported was for males and females combined. There was not presentation of mortality incidence for the acute toxicity study and no description of severity scores for the irritation study (only the primary irritation score was reported). These uncertainties in outcome reporting are unlikely to have substantial impact on results.	Medium	2	2	4
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[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of A 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, one of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

1.7. Animal toxicity evaluation results of Wahlberg et al 1979 for an acute percutaneous toxicity in guinea pig study on mortality and nutrition and metabolic/adult exposure body weight outcomes

Study reference:	J. E. Wahlberg, A. Boman (1979). Comparative percutaneous toxicity of ten industrial solvents in the guinea pig. Scandinavian Journal of Work, Environment and Health, 5(4,4), 345-351 HERO ID: 61688					
Domain	**Metric**	**Eval 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 substances were identified; however, the test substances were lacking characterization details; unlikely to have a substantial impact on results.	Medium	2	2	4
	2. Test Substance Source	The source of the test substances were identified; did not include batch/lot numbers; unlikely to have a substantial impact on results.	Medium	2	1	2
	3. Test Substance Purity	purity or grade of test substances were not reported; possible impurities were not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Distilled water was used as a concurrent control	High	1	2	2
	5. Positive Controls	This metric is not rated/applicable; positive control was not indicated by 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	There were no details of test substance preparation and/or storage conditions reported.	Low	3	1	3

Study reference:	J. E. Wahlberg, A. Boman (1979). Comparative percutaneous toxicity of ten industrial solvents in the guinea pig. Scandinavian Journal of Work, Environment and Health, 5(4,4), 345-351 HERO ID: 61688					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Single application to skin depot (31 cm2) and covered CK: Not 31 cm2. The solvents was administered to a skin depot area 3.1 cm2	High	1	1	1
	9. Reporting of Doses/Concentrations	applied concentrations were reported in ml; mean body weight was reported to estimate an administered dose.	Medium	2	2	4
	10. Exposure Frequency and Duration	single application, covered, and observed for 35 d	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups for CCl4 = 2 and TCE=1; number of exposure groups and spacing were not justified by the author; Doses were considered adequate to address the purpose of the study for changes in body weight for both CCl4 and TCE; however for TCE, it is unclear if the exposure level was adequate to show results relevant to mortality as there were no effects at the single concentration tested.	Medium	2	1	2
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substances	High	1	1	1

Study reference:	J. E. Wahlberg, A. Boman (1979). Comparative percutaneous toxicity of ten industrial solvents in the guinea pig. Scandinavian Journal of Work, Environment and Health, 5(4,4), 345-351 HERO ID: 61688					
Domain	**Metric**	**Eval 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 source, strain, or sex of the test guinea pigs were not reported.	Low	3	2	6
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry conditions were not sufficiently reported to evaluate if husbandry was adequate	Low	3	1	3
	15. Number per Group	20 animals per series	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest; mortality was monitored and body weight was recorded	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	Mortality observations and weight measurements were made for all animals daily except weekends	High	1	1	1
	19. Blinding of Assessors	this metric is not rated/applicable because no subjective outcomes were assessed.	Not Rated	NA	NA	NA

Study reference:	J. E. Wahlberg, A. Boman (1979). Comparative percutaneous toxicity of ten industrial solvents in the guinea pig. Scandinavian Journal of Work, Environment and Health, 5(4,4), 345-351 HERO ID: 61688					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	The biological responses of the negative control group(s) were adequate	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial body weights were reported; there was no reporting of food/water intake; unlikely to have a significant impact on results.	Medium	2	2	4
	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	Noted that an analysis of variance was applied in the statistical calculations, though statistical tests were not specified. P-values (unspecified significance test) were reported for body weight changes. No statistical significance values were reported for mortality	Low	3	1	3
	24. Reporting of Data	Incidence of mortality was reported for both CCl4 and TCE. Body weight changes was reported for TCE, but not CCl4	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**54**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.862**	**Overall Score: Nearest *:**	**1.9**

Study reference:	J. E. Wahlberg, A. Boman (1979). Comparative percutaneous toxicity of ten industrial solvents in the guinea pig. Scandinavian Journal of Work, Environment and Health, 5(4,4), 345-351 HERO ID: 61688					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**Medium**		

2. Short – Term Toxicity Studies

2.1. Animal toxicity evaluation results of Civo et al 1985 for a 4-week inhalation-liver toxicity study on hepatic outcomes

Study reference:	Civo Institute, Tno (1985). Fixed Versus Variable Levels of Exposure in Inhalation Toxicity Testing with Reference to the Workplace Studies with Acetaldehyde and Carbon Tetrachloride. HERO ID: 4215798 (same as 4215910)					
Domain	**Metric**	**Eval 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 identified by name.	High	1	2	2
	2. Test Substance Source	Source was reported incompletely, but the omitted details are unlikely to have a substantial impact on results	Medium	2	1	2
	3. Test Substance Purity	Purity such that effects likely due to test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were used.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Computer randomization used for allocation.	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	Method and equipment of generation was reported.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently.	High	1	1	1
	9. Reporting of Doses/Concentrations	Concentrations were reported.	High	1	2	2
	10. Exposure Frequency and Duration	Frequency and duration were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	the number of groups and concentration spacing were reported and justified.	High	1	1	1

Study reference:	Civo Institute, Tno (1985). Fixed Versus Variable Levels of Exposure in Inhalation Toxicity Testing with Reference to the Workplace Studies with Acetaldehyde and Carbon Tetrachloride. HERO ID: 4215798 (same as 4215910)					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	12. Exposure Route and Method	Exposure route and method were reported and appropriate.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The source, species, strain, sex, and initial body weight were reported. Health status and age were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Husbandry details were reported.	High	1	1	1
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was reported and appropriate.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcomes were assessed consistently.	High	1	1	1
	18. Sampling Adequacy	Sampling was adequate for outcomes of interest.	High	1	1	1
	19. Blinding of Assessors	Blinding not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Respiratory rate was not reported but is not likely to have significant impact on results.	Medium	2	2	4

Study reference:	**Civo Institute, Tno (1985). Fixed Versus Variable Levels of Exposure in Inhalation Toxicity Testing with Reference to the Workplace Studies with Acetaldehyde and Carbon Tetrachloride.** **HERO ID: 4215798 (same as 4215910)**					
Domain	**Metric**	**Eval 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	No health outcomes unrelated to exposure were reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate.	High	1	1	1
	24. Reporting of Data	See footnote at end of page.[1]	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**34**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.172**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

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

2.2. Animal toxicity evaluation results of Hayes et al 1986 for an 14 day oral toxicity test in mice study on mortality, clinical chemistry/biochemical , renal, hepatic, respiratory, hematological and immune, neurological/behavior, and reproductive outcomes

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval 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 identified by unambiguous name	High	1	2	2
	2. Test Substance Source	Test substance source and lot number reported, but certification/analytical verification of identity was not.	Medium	2	1	2
	3. Test Substance Purity	Test substance reported to be HPLC grade and >99% pure.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Both naive and sham-treated control groups were used. Sham-treated controls received vehicle.	High	1	2	2
	5. Positive Controls	Positive controls not typical for this study type.	Not Rated	4	4	4
	6. Randomized Allocation	Study reports randomizing the mice but does not discuss the allocation to groups	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Study reports daily preparation of solution, but does not report storage.	Low	3	1	3
	8. Consistency of Exposure Administration	Administration details are provided, including gavage volume and time of day of administration. No inconsistencies in exposures across groups were noted.	High	1	1	1

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Dose reported in mg/kg bw; body weight not reported.	Medium	2	2	4
	10. Exposure Frequency and Duration	Animals gavaged daily for 14 days	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	3 nonzero doses ranging 4-fold were used. Effects were seen at all doses, so it is not clear that the lowest dose was low enough.	Medium	2	1	2
	12. Exposure Route and Method	See footnote at end of page.[1]	High	1	1	1
Test Organism	13. Test Animal Characteristics	Test animal species, strain, sex, lifestage, and source were reported and appropriate. Initial body weights were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were described and appropriate.	High	1	1	1
	15. Number per Group	20/sex/dose were tested; this is more than adequate.	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:	Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463 HERO ID: 194400					
Domain	**Metric**	**Eval 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	Outcome assessment methodology was described in detail and appropriate. Histopathology was not evaluated, but organ weights, serum chemistry, and hematology were. Food and water intake were not reported. The only neurological and reproductive endpoints assessed were brain and testes weights, respectively.	Medium	2	2	4
	17. Consistency of Outcome Assessment	No inconsistencies in outcome assessment were noted by the authors apart from one gavage death in high dose females.	High	1	1	1
	18. Sampling Adequacy	Mortality, organ weights evaluated in all animals; hematology and serum chemistry evaluated in 5/sex/dose each.	Medium	2	1	2
	19. Blinding of Assessors	No subjective outcomes were evaluated	Not Rated	4	NA	NA
	20. Negative Control Response	Responses of both naive and vehicle controls were reported for all endpoints other than hematology. Responses appeared to be as expected and without excessive variability.	High	1	1	1

Study reference:	Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463 HERO ID: 194400					
Domain	**Metric**	**Eval 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 body weight and food and water intake were not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	The study reports that 20 animals/sex/dose were tested, and that organ weights were evaluated in all animals; however, results are reported for only 10 animals/sex/dose. The study authors do not explain this discrepancy.	Low	3	1	3
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate to the data.	High	1	1	1
	24. Reporting of Data	Mortality, organ weights, and significant clinical chemistry findings were reported; body weight, hematology results, and non-significant clinical chemistry findings were not. The lack of body weight data is problematic for interpretation of relative organ weight changes.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**23**	**55**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.667**	**Overall Score: Nearest *:**	**1.7**

Study reference:	Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463 HERO ID: 194400					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**Medium**		

2.3. Animal toxicity evaluation results of Sun et al 2014 for a study on genomics/metabolomics outcomes

Study reference:	**Sun, J., Schmitt, T., Schnackenberg, L. K., Pence, L., Ando, Y., Greenhaw, J., Yang, X. i, Slavov, S., Davis, K., Salminen, W. F., Mendrick, D. L., Beger, R. D. (2014). Comprehensive analysis of alterations in lipid and bile acid metabolism by carbon tetrachloride using integrated transcriptomics and metabolomics. Metabolomics, 10(6), 1293-1304** **HERO ID: 3487830**					
Domain	**Metric**	**Eval 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	See footnote at end of page.[1]	High	1	2	2
	2. Test Substance Source	Commercial source was identified.	High	1	1	1
	3. Test Substance Purity	Purity not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Vehicle (corn oil) controls were used.	High	1	2	2
	5. Positive Controls	Positive controls were not used for genomic/metabolomics alterations.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals were randomly assigned to each dose group.	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage were not described; however, omission of these details are unlikely to have a substantial impact on results (acute exposure).	Medium	2	1	2
	8. Consistency of Exposure Administration	Gavage volume was not excessive.	High	1	1	1
	9. Reporting of Doses/Concentrations	See footnote at end of page.[1]	High	1	2	2

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

Study reference:	**Sun, J., Schmitt, T., Schnackenberg, L. K., Pence, L., Ando, Y., Greenhaw, J., Yang, X. i, Slavov, S., Davis, K., Salminen, W. F., Mendrick, D. L., Beger, R. D. (2014). Comprehensive analysis of alterations in lipid and bile acid metabolism by carbon tetrachloride using integrated transcriptomics and metabolomics. Metabolomics, 10(6), 1293-1304** **HERO ID: 3487830**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Genomic/metabolic data provide mechanistic understanding for liver effects which occur after acute exposure.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Adequate number of dose groups. Dose spacing justified by previous research.	High	1	1	1
	12. Exposure Route and Method	See footnote at end of page.[1]	High	1	1	1
Test Organism	13. Test Animal Characteristics	FDA colony; species, strain and starting age reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	See footnote at end of page.[1]	High	1	1	1
	15. Number per Group	15/group	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Mechanistic changes related to liver toxicity	High	1	2	2
	17. Consistency of Outcome Assessment	See footnote at end of page.[1]	High	1	1	1
	18. Sampling Adequacy	Summary data for metabolomics and genomics is provided for the high dose group only. Supplemental data tables are available for purchase.	Medium	2	1	2

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

Study reference:	Sun, J., Schmitt, T., Schnackenberg, L. K., Pence, L., Ando, Y., Greenhaw, J., Yang, X. i, Slavov, S., Davis, K., Salminen, W. F., Mendrick, D. L., Beger, R. D. (2014). Comprehensive analysis of alterations in lipid and bile acid metabolism by carbon tetrachloride using integrated transcriptomics and metabolomics. Metabolomics, 10(6), 1293-1304 HERO ID: 3487830					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	Blinding was not reported; however, lack of blinding is not expected to have a substantial impact on results.	Medium	2	1	2
	20. Negative Control Response	Metabolomics changes were reported relative to control.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Lack of reporting of initial body weights and food/water intake is not likely to have a significant impact on results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	See footnote at end of page.[11]	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	See footnote at end of page.[1]	High	1	1	1
	24. Reporting of Data	Summary data is reported in the paper; supplemental data table are available for purchase.	Medium	2	2	4
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**39**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.3**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

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

2.4. Animal toxicity evaluation results of Sun et al 2014 for a study on hepatic outcomes

Study reference:	**Sun, J., Schmitt, T., Schnackenberg, L. K., Pence, L., Ando, Y., Greenhaw, J., Yang, X. i, Slavov, S., Davis, K., Salminen, W. F., Mendrick, D. L., Beger, R. D. (2014). Comprehensive analysis of alterations in lipid and bile acid metabolism by carbon tetrachloride using integrated transcriptomics and metabolomics. Metabolomics, 10(6), 1293-1304** **HERO ID: 3487830**					
Domain	**Metric**	**Eval 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	See footnote at end of page.[1]	High	1	2	2
	2. Test Substance Source	Commercial source was identified.	High	1	1	1
	3. Test Substance Purity	Purity not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Vehicle (corn oil) controls were used.	High	1	2	2
	5. Positive Controls	Positive controls not used for liver toxicity.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals were randomly assigned to each dose group.	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	Preparation and storage were not described; however, omission of these details are unlikely to have a substantial impact on results (acute exposure).	Medium	2	1	2
	8. Consistency of Exposure Administration	Gavage volume was not excessive.	High	1	1	1
	9. Reporting of Doses/Concentrations	See footnote at end of page.[1]	High	1	2	2
	10. Exposure Frequency and Duration	Acute studies are included; liver effects occur after acute exposure.	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:	**Sun, J., Schmitt, T., Schnackenberg, L. K., Pence, L., Ando, Y., Greenhaw, J., Yang, X. i, Slavov, S., Davis, K., Salminen, W. F., Mendrick, D. L., Beger, R. D. (2014). Comprehensive analysis of alterations in lipid and bile acid metabolism by carbon tetrachloride using integrated transcriptomics and metabolomics. Metabolomics, 10(6), 1293-1304** **HERO ID: 3487830**					
Domain	**Metric**	**Eval 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	Two dose groups plus control. High dose chosen to induce mild to moderate adverse effects based on range-finding study. 30 animals received single dose and an additional 15 animals received a total of 3 once daily doses, which should be sufficient for the main purpose of this study (e.g., metabolomics).	High	1	1	1
	12. Exposure Route and Method	See footnote at end of page.[1]	High	1	1	1
Test Organism	13. Test Animal Characteristics	FDA colony; species, strain and starting age reported.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	See footnote at end of page.[1]	High	1	1	1
	15. Number per Group	30 animals received single dose and an additional 15 animals received a total of 3 once daily doses	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Clinical chemistry and liver histopathology.	High	1	2	2
	17. Consistency of Outcome Assessment	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:	**Sun, J., Schmitt, T., Schnackenberg, L. K., Pence, L., Ando, Y., Greenhaw, J., Yang, X. i, Slavov, S., Davis, K., Salminen, W. F., Mendrick, D. L., Beger, R. D. (2014). Comprehensive analysis of alterations in lipid and bile acid metabolism by carbon tetrachloride using integrated transcriptomics and metabolomics. Metabolomics, 10(6), 1293-1304** **HERO ID: 3487830**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	18. Sampling Adequacy	5/group used for clinical chemistry and histopathology.	Medium	2	1	2
	19. Blinding of Assessors	Blinding was not reported; however, lack of blinding is not expected to have a substantial impact on results.	Medium	2	1	2
	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	Lack of reporting of initial body weights and food/water intake is not likely to have a significant impact on results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	See footnote at end of page.[1]	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were well-described.	High	1	1	1
	24. Reporting of Data	See footnote at end of page.[1]	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**37**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.233**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

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

3. Subchronic Toxicity Studies

3.1. Animal toxicity evaluation results of Adams et al 1952 for a subchronic inhalation exposures (46 to 94 days) in rats study on renal, hepatic, nutrition and metabolic/adult exposure body weight, and cardiovascular outcomes

Study reference:	Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66 HERO ID: 62373					
Domain	**Metric**	**Eval 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 identified by unambiguous name and contaminants identified.	High	1	2	2
	2. Test Substance Source	Test substance was reportedly a commercial product but specific source was not reported. Infrared absorption spectroscopy used to verify identity and identify contaminants.	Medium	2	1	2
	3. Test Substance Purity	Test substance purity not reported, but paper reports purification of commercial product by redistillation and confirmation of identity by infrared absorption spectroscopy. Minor contaminants were identified at low (? 0.05%) concentrations.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Both untreated and sham-treated control groups were used.	High	1	2	2
	5. Positive Controls	Positive controls not typical for this study type	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study did not describe method of animal allocation	Low	3	1	3

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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	Method of vapor generation was incompletely reported (equipment not specified; temperature used to achieve vaporization was not reported) but there is no reason to believe there would be an impact on animal exposure, as vapor concentrations were reportedly analyzed regularly and within 10% of nominal.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures at different concentrations were administered for different durations, making it difficult to discern effects of changing duration from effects of changing concentration.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Air concentrations were reported, but it is not clear whether these were nominal or actual concentrations. Analysis of chamber concentrations was by combustion analysis, which is likely an insensitive method.	Low	3	2	6

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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 frequencies ranged between 0.05 and 1 hour per day. This well below the daily duration typically used for subchronic toxicity evaluation.	Unacceptable	4	1	4
	11. Number of Exposure Groups and Dose Spacing	2 exposure concentrations were tested; the low concentration was tested at four different daily exposure durations (0.05 to 1 hr/day)	Medium	2	1	2
	12. Exposure Route and Method	Dynamic whole body chamber was used for vapor that may condense.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	Test animal species, strain, sex, and source (in-house colony) were reported. Study reports choosing animals for the study based on health during pre-exposure observation period. Age and initial body weight were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions other than the exposure chamber were not reported.	Low	3	1	3

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	Group sizes were 5 or 6/sex/group. This is consistent with recommendations for 28 day studies but less than recommended for subchronic studies.	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was described, and outcomes included body weight and weights and histopathology of liver, kidney, lung, and heart.	High	1	2	2
	17. Consistency of Outcome Assessment	No inconsistencies in assessment of these endpoints were reported.	High	1	1	1
	18. Sampling Adequacy	All animals were evaluated for these endpoints.	High	1	1	1
	19. Blinding of Assessors	No subjective outcomes were evaluated.	Not Rated	NA	NA	NA
	20. Negative Control Response	Control responses were not reported.	Unacceptable	4	1	4
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial body weight, food/water intake, and respiratory rate were not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Health outcomes unrelated to exposure were not reported.	High	1	1	1

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval 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	Statistical analysis was conducted and methodology described; the method did not account for multiple comparisons.	Medium	2	1	2
	24. Reporting of Data	All data were reported qualitatively without indication of which control group(s) was compared for statistical analysis.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**32**	**62**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.938**	**Overall Score: Nearest *:**	**1.9[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of A 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, two of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

3.2. Animal toxicity evaluation results of Allis et al 1990 for a 12-week oral study on hepatic, nutrition and metabolic/adult exposure body weight, clinical chemistry/biochemical outcomes

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval 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	High	1	1	1
	3. Test Substance Purity	Test substance purity and grade were not reported and there was no analysis conducted for measurement of impurities, if present.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	A concurrent negative control group was used and was appropriate.	High	1	2	2
	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	The study authors stated that new gavage solutions were used daily and were prepared weekly; however, the procedures for preparing the solutions in vehicle (corn oil) were incompletely reported and storage conditions were not reported. Deficiencies in reporting may have a substantial impact on results.	Low	3	1	3

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval 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 on exposure administration were reported, including consistent dosing volumes, and exposures were administered consistently across study groups in a scientifically sound manner (dose volume of 2 mL/kg was acceptable).	High	1	1	1
	9. Reporting of Doses/Concentrations	The administered doses were reported without ambiguity.	High	1	2	2
	10. Exposure Frequency and Duration	The exposure frequency and duration were reported and were appropriate for the study type and outcomes of interest. In this subchronic study, animals were gavaged 5 days per week for 12 weeks.	High	1	1	1

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval 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	Although two quantitative dose groups (20 and 40 mg/kg/day) were used, there were deficiencies in the dose spacing. Adverse effects, including liver histopathology, clinical chemistry, and reduced body weight gain, were observed at both doses and, in some cases, there were few differences between the two dose groups (e.g., histopathology incidence).	Low	3	1	3
	12. Exposure Route and Method	The route and method of exposure were reported (gavage) and suited to the test substance.	High	1	1	1
Test Organism	13. Test Animal Characteristics	Test animal characteristics were reported (source, species, strain, sex, age, starting body weight); however, health status at the start of the study was not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Most husbandry conditions were reported and were adequate and similar for all groups.	Medium	2	1	2

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	Groups were subdivided for some evaluations, resulting in a lower number of animals per group than is typical. For example, from the 24 animals/dose level, 6 animals each were terminated on respective days 1, 8, 15, and 22 post-exposure for evaluation of hepatic cytochrome P450, serum chemistry, and light microscope histopathology, resulting in only 6 animals/dose group evaluated for these endpoints.	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest, which were primarily effects on the liver.	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

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported and were adequate.	Medium	2	1	2
	19. Blinding of Assessors	No subjective outcomes were reported. Blood samples were assayed commercially and histopathology was not described as a re-evaluation so I scored this metric as not applicable.	Not Rated	NA	NA	NA
	20. Negative Control Response	The negative control response was 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 in initial body weight or food or water intake that could influence the outcome assessment.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	Data on attrition and health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted.	Medium	2	1	2

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval 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	Statistical analyses that were conducted were not described clearly for each endpoint evaluated. Statistical analyses/results were not reported for the hepatic histopathology data (Table 2 of the study report); however, sufficient data were provided to allow an independent analysis. Statistical analysis results were not shown for body weights. Although body weight gain data were provided in a figure (Figure 6), the data were provided without mean values and error bars.	Medium	2	1	2
	24. Reporting of Data	Data for exposure-related findings were presented by exposure group, with quantal and/or continuous presentation, as well as severity scores. Negative findings were reported in the text.	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:		**1.517**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**Medium**		

Study reference:	**Allis, J. W., Ward, T. R., Seely, J. C., Simmons, J. E. (1990). Assessment of hepatic indicators of subchronic carbon tetrachloride injury and recovery in rats. Fundamental and Applied Toxicology, 15(3), 558-570** **HERO ID: 194565**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Study Quality Comment:	**The reviewer downgraded this study's overall quality rating. They noted: I would downgrade the study to medium for the follow reasons: lack of details on test substance purity/grade and lack of details on preparation of test substance and storage, both in the absence of reported measurement of test solutions demonstrating stability of test substance in the prepared solutions during the one week storage period and under the conditions of storage, given potential volatility of CCl4. Note: The original calculated score for this study was 1.5. This value is not presented above because the final rating was changed based on professional judgement.**					

3.3. Animal toxicity evaluation results of Benson et al 1999 for inhalation and drinking water ingestion studies (1, 4 and 12 weeks) on hepatic outcomes

Study reference:	Benson, J. M., Springer, D. L. (1999). Improved risk estimates for carbon tetrachloride. Final report HERO ID: 195107					
Domain	**Metric**	**Eval 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 chemical name.	High	1	2	2
	2. Test Substance Source	No details were provided on them source of the test substance.	Low	3	1	3
	3. Test Substance Purity	Purity was not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Negative air and dw controls.	High	1	2	2
	5. Positive Controls	Positive controls are not generally included in studies of liver toxicity.	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	Inhalation exposure details were provided in the ADME study description (method of vapor generation was described and appropriate).	High	1	1	1
	8. Consistency of Exposure Administration	See footnote at end of page.[1]	High	1	1	1
	9. Reporting of Doses/Concentrations	Actual concentrations were not reported.	Low	3	2	6
	10. Exposure Frequency and Duration	Continuous exposure for dw; 6hour/day 5 days/week, for 1, 4 or 12 weeks.	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:	**Benson, J. M., Springer, D. L. (1999). Improved risk estimates for carbon tetrachloride. Final report** **HERO ID: 195107**					
Domain	**Metric**	**Eval 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	2-3 groups plus control; doses were not justified , but dose response relationships were apparent.	Medium	2	1	2
	12. Exposure Route and Method	Dynamic whole-body chambers.	High	1	1	1
Test Organism	13. Test Animal Characteristics	Rat, mouse and hamster species, strain and age were reported in the ADME study, Obtained from commercial source.	High	1	2	2
	14. Adequacy and Consistency of Animal Husbandry Conditions	Adequate husbandry conditions as described in ADME studies.	High	1	1	1
	15. Number per Group	5-6/group for most endpoints (10/group for serum chemistry at 12 weeks); adequate for statistics.	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	Outcome methods were sensitive for hepatotoxicity (serum chemistry, histopath. and hepatocellular replication).	High	1	2	2
	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
	19. Blinding of Assessors	Blinding was not reported ; however, outcomes were objective.	Medium	2	1	2

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

Study reference:	Benson, J. M., Springer, D. L. (1999). Improved risk estimates for carbon tetrachloride. Final report HERO ID: 195107					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	No incidence of hepatocellular necrosis in controls.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Respiratory rate was not measured; CCl4 is anticipated 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	See footnote at end of page.[1]	High	1	1	1
	24. Reporting of Data	Data were reported for all time points and exposure groups.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**30**	**49**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.633**	**Overall Score: Nearest *:**	**1.6**
		Overall Quality Level:		**High**		

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

3.4. Animal toxicity evaluation results of Condie et al 1986 for a 90-day oral study on mortality, metabolic/adult exposure body weight, hepatic, and clinical chemistry/biochemical outcomes

Study reference:	**Condie, L. W., Laurie, R. D., Mills, T., Robinson, M., Bercz, J. P. (1986). Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. Toxicological Sciences, 7(2), 199-206** **HERO ID: 60712**					
Domain	**Metric**	**Eval 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, including manufacturer and lot number, was reported.	High	1	1	1
	3. Test Substance Purity	The purity was reported (98.2%) and impurities (chloroform, 1.8%) were identified.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	The study authors reported using appropriate concurrent negative control groups (corn oil and Tween-60).	High	1	2	2
	5. Positive Controls	Positive control is not indicated for 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	The study authors did not report preparation and storage conditions, including how often test substance was prepared and under what conditions the test substance was stored. Deficiencies in reporting may have a substantial impact on results.	Low	3	1	3

Study reference:	Condie, L. W., Laurie, R. D., Mills, T., Robinson, M., Bercz, J. P. (1986). Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. Toxicological Sciences, 7(2), 199-206 HERO ID: 60712					
Domain	**Metric**	**Eval 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 exposure administration were reported and exposures were administered consistently across study 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	The exposure frequency and duration of exposure were reported and appropriate for the study type and outcomes of interest.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and spacing were reported and considered adequate for the purpose of the study. Selected concentrations were not justified by the study authors but the selected doses appear acceptable.	High	1	1	1
	12. Exposure Route and Method	The route and method of exposure were reported and these were suited to the test substance.	High	1	1	1

Study reference:	Condie, L. W., Laurie, R. D., Mills, T., Robinson, M., Bercz, J. P. (1986). Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. Toxicological Sciences, 7(2), 199-206 HERO ID: 60712					
Domain	**Metric**	**Eval 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 animal species, strain, and sex were reported; however, age, starting body weight, and health status were not reported. The test species was obtained from a commercial source and was an appropriate model for evaluation of the outcomes of interest. The reporting deficiencies are unlikely to have a substantial impact on results.	Medium	2	2	4
	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	The number of animals per study group was reported and appropriate for the study type.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed the intended outcomes of interest and was sensitive for the outcomes of interest.	High	1	2	2

Study reference:	Condie, L. W., Laurie, R. D., Mills, T., Robinson, M., Bercz, J. P. (1986). Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. Toxicological Sciences, 7(2), 199-206 HERO ID: 60712					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	17. Consistency of Outcome Assessment	The outcome assessment protocol was reported; however, the descriptions of sampling of blood for serum enzymes do not clearly indicate when blood was collected from the animals.	Medium	2	1	2
	18. Sampling Adequacy	Details regarding sampling for the outcomes of interest were reported by the study authors and the study used adequate sampling for the outcomes of interest (e.g., adequate number of animals from each group).	High	1	1	1
	19. Blinding of Assessors	The study did not report evaluation of subjective outcomes except histopathology. According to the criteria, however, this metric is not rated/applicable for initial histopathology review.	Not Rated	NA	NA	NA
	20. Negative Control Response	The negative control response was adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no confounding variables among the study groups that could influence the outcome assessment.	High	1	2	2

Study reference:	Condie, L. W., Laurie, R. D., Mills, T., Robinson, M., Bercz, J. P. (1986). Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. Toxicological Sciences, 7(2), 199-206 HERO ID: 60712					
Domain	**Metric**	**Eval 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 or health outcomes unrelated to exposure were not reported because only substantial differences among groups were noted.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	The statistical methods were clearly described and appropriate for the data set.	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 and/or continuous presentation and description of severity scores.	High	1	2	2
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:		**1.279**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

3.5. Animal toxicity evaluation results of Hayes et al 1986 for a 90-day oral toxicity test in mice study on reproductive, hematological and immune, neurological, renal, hepatic, clinical chemistry/biochemical, mortality, nutrition and metabolic/adult exposure body weight, and respiratory outcomes

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval 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 identified by unambiguous name	High	1	2	2
	2. Test Substance Source	Test substance source and lot number reported, but certification/analytical verification of identity was not.	Medium	2	1	2
	3. Test Substance Purity	Test substance reported to be HPLC grade and >99% pure.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Both naive and sham-treated control groups were used. Sham-treated controls received vehicle.	High	1	2	2
	5. Positive Controls	Positive controls not typical for this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study reports randomizing the mice but does not discuss the allocation to groups	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Study reports daily preparation of solution, but does not report storage.	Medium	2	1	2

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	8. Consistency of Exposure Administration	Administration details are provided, including gavage volume and time of day of administration. No inconsistencies in exposures across groups were noted.	High	1	1	1
	9. Reporting of Doses/Concentrations	Dose reported in mg/kg bw; initial body weight not reported.	Medium	2	2	4
	10. Exposure Frequency and Duration	Animals gavaged daily for 90 days	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	4 nonzero doses ranging 100-fold were used. Effects were seen at all doses, so it is not clear that the lowest dose was low enough.	Medium	2	1	2
	12. Exposure Route and Method	See footnote at end of page.[1]	High	1	1	1
Test Organism	13. Test Animal Characteristics	Test animal species, strain, sex, lifestage, and source were reported and appropriate. Initial body weights were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	All husbandry conditions were described and appropriate.	High	1	1	1
	15. Number per Group	20/sex/dose were tested	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:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval 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	Only liver and kidney were examined microscopically	Medium	2	2	4
	17. Consistency of Outcome Assessment	No inconsistencies in outcome assessment were noted by the authors.	High	1	1	1
	18. Sampling Adequacy	Mortality, body weight, histopathology, and organ weights were reportedly evaluated in all animals; hematology and serum chemistry evaluated in subgroups of 8-10/sex/dose due to low blood volume of mice.	Medium	2	1	2
	19. Blinding of Assessors	Although study reports observing animals for signs of intoxication, no results were reported, so lack of blinding would not be of concern. No other subjective outcomes were evaluated	Not Rated	NA	NA	NA
	20. Negative Control Response	Responses of both naive and vehicle controls were reported for all endpoints other than hematology. Responses appeared to be as expected and without excessive variability.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	Initial body weight and food and water intake were not reported.	Low	3	2	6

Study reference:	**Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463** **HERO ID: 194400**					
Domain	**Metric**	**Eval 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	Study reports that there were no compound-related deaths, but there were several mortalities in the vehicle control and high dose groups (in males) and in vehicle control and all exposure groups (in females); these were presumably gavage errors.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	Statistical methods were reported and appropriate to the data.	High	1	1	1
	24. Reporting of Data	There are unexplained inconsistencies in the numbers of animals exposed and evaluated for histopathology vs the numbers of animals for which histopathology results are reported. Although the authors report that histopathology was evaluated in all control and exposed mice, results are reported for only 10/sex/dose (vs 20/sex/dose exposed and evaluated for organ weights). The authors do not explain this apparent discrepancy.	Low	3	2	6
		Sum of scores:			**29**	**49**

Study reference:	Hayes, J. R., Condie, L. W., Borzelleca, J. F. (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-l mice. Fundamental and Applied Toxicology, 7(3), 454-463 HERO ID: 194400					
Domain	**Metric**	**Eval 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		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		1.690	Overall Score: Nearest *:	1.7
		Overall Quality Level:		High		

3.6. Animal toxicity evaluation results of Nagano et al 2007 for a 13-week inhalation study in rats and mice study on renal, hepatic, hematological and immune, clinical chemistry/biochemical, and body weight outcomes

Study reference:	**Nagano, K., Umeda, Y., Saito, M., Nishizawa, T., Ikawa, N., Arito, H., Yamamoto, S., Fukushima, S. (2007b). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. Journal of Occupational Health, 49(4), 249-259** **HERO ID: 194237**					
Domain	**Metric**	**Eval 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	Analytical-grade CCl4	High	1	2	2
	2. Test Substance Source	source clearly identified..	High	1	1	1
	3. Test Substance Purity	purity specified (98%); each lot analyzed for stability and purity.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	used appropriate concurrent negative control group (clean air) under the same conditions as treated groups.	High	1	2	2
	5. Positive Controls	this metric is not rated/ applicable because a positive control is not indicated by this study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Animals allocated using stratified randomization into weight-matched groups	Medium	2	1	2
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	Details of exposure administration were clearly reported and were consistent across study groups.	High	1	1	1

Study reference:	Nagano, K., Umeda, Y., Saito, M., Nishizawa, T., Ikawa, N., Arito, H., Yamamoto, S., Fukushima, S. (2007b). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. Journal of Occupational Health, 49(4), 249-259 HERO ID: 194237					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Target and analytical concentrations were reported and appropriate.	High	1	2	2
	10. Exposure Frequency and Duration	The exposure frequency and duration of exposure were reported and appropriate.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose/concentration spacing were justified by study authors	High	1	1	1
	12. Exposure Route and Method	The route and method of exposure were reported and were suited to the test substance	High	1	1	1
Test Organism	13. Test Animal Characteristics	The test animal was obtained through the reported commercial source. The test animal species, strain, sex, and age were specified. Starting body weight was not reported, but the authors note that animals were randomized into weight-matched groups. The authors also don't explicitly mention health status of the animals. These omissions are unlikely to have a substantial impact on results.	Medium	2	2	4

Study reference:	Nagano, K., Umeda, Y., Saito, M., Nishizawa, T., Ikawa, N., Arito, H., Yamamoto, S., Fukushima, S. (2007b). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. Journal of Occupational Health, 49(4), 249-259 HERO ID: 194237					
Domain	**Metric**	**Eval 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	All husbandry conditions were reported and adequate. Conditions were the same for control and treated groups.	High	1	1	1
	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 outcomes of interest.	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	Details regarding sampling for the outcomes of interest were reported and adequate. Endpoints were evaluated in an adequate number of animals in each group.	High	1	1	1
	19. Blinding of Assessors	Most outcomes were not subjective; this metric is not rated/applicable for initial histopathology review.	Not Rated	NA	NA	NA

Study reference:	Nagano, K., Umeda, Y., Saito, M., Nishizawa, T., Ikawa, N., Arito, H., Yamamoto, S., Fukushima, S. (2007b). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. Journal of Occupational Health, 49(4), 249-259 HERO ID: 194237					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	20. Negative Control Response	The biological responses of the negative control groups were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There was a lack of reporting of respiratory rates; but this lack of reporting is not likely to have a significant impact on results.	Medium	2	2	4
	22. Health Outcomes Unrelated to Exposure	Data on attrition and health outcome unrelated to exposure for each study group were not reported; the lack of reporting is unlikely to have a substantial impact on results.	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 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:**			**29**	**35**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.207**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

4. Chronic Toxicity Studies

4.1. Animal toxicity evaluation results of Adams et al 1952 for a 6-month inhalation exposures in rats, guinea pigs, rabbits, and monkeys study on renal, hepatic, respiratory, cardiovascular, hematological and immune, nutrition and nutrition and metabolic/adult exposure body weight outcomes

Study reference:	Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66 HERO ID: 62373					
Domain	**Metric**	**Eval 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 identified by unambiguous name and contaminants identified.	High	1	2	2
	2. Test Substance Source	Test substance was reportedly a commercial product but specific source was not reported. Infrared absorption spectroscopy used to verify identity and identify contaminants.	Medium	2	1	2
	3. Test Substance Purity	Test substance purity not reported, but paper reports purification of commercial product by redistillation and confirmation of identity by infrared absorption spectroscopy. Minor contaminants were identified at low (? 0.05%) concentrations.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Both untreated and sham-treated control groups were used.	High	1	2	2
	5. Positive Controls	Positive controls not typical for this study type	Not Rated	NA	NA	NA

Study reference:	Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66 HERO ID: 62373					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	6. Randomized Allocation	Study did not describe method of animal allocation	Low	3	1	3
Exposure Characterization	7. Preparation and Storage of Test Substance	Method of vapor generation was incompletely reported (equipment not specified; temperature used to achieve vaporization was not reported) but there is no reason to believe there would be an impact on animal exposure, as vapor concentrations were reportedly analyzed regularly and within 10% of nominal.	Medium	2	1	2
	8. Consistency of Exposure Administration	Exposures at different concentrations were administered for different durations, making it difficult to discern effects of changing duration from effects of changing concentration.	Low	3	1	3
	9. Reporting of Doses/Concentrations	Air concentrations were reported, but it is not clear whether these were nominal or actual concentrations. Analysis of chamber concentrations was by combustion analysis, which is likely an insensitive method.	Low	3	2	6

Study reference:	Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66 HERO ID: 62373					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Exposures were 7 hr/day, 5 d/week for durations ranging up to about 6 months.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	7 exposure concentrations were tested in rats and guinea pigs, with an overall range of 80-fold. 5 concentrations with a range of 20 fold were tested in rabbits and monkeys. Concentrations were sufficient to identify effect levels.	High	1	1	1
	12. Exposure Route and Method	Dynamic whole body chamber was used for vapor that may condense.	Medium	2	1	2
Test Organism	13. Test Animal Characteristics	Test animal species, strain, sex, and source (in-house colony) were reported. Study reports choosing animals for the study based on health during pre-exposure observation period. Age and initial body weight were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Animal husbandry conditions other than the exposure chamber were not reported.	Low	3	1	3

Study reference:	**Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66** **HERO ID: 62373**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	15. Number per Group	Group sizes were 15/sex for rats, 8/sex for guinea pigs, 2/sex for rabbits, and 2 monkeys.	Medium	2	1	2
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was described, and outcomes included body weight and weights and histopathology of liver, kidney, lung, heart, and spleen. Authors note that limited blood chemistry and hematology endpoints were assessed "in many cases".	High	1	2	2
	17. Consistency of Outcome Assessment	Authors note that limited blood chemistry, liver lipids, and hematology endpoints were assessed "in many cases" but do not specify which groups were evaluated.	Low	3	1	3
	18. Sampling Adequacy	Details regarding outcome sampling were not reported.	Low	3	1	3
	19. Blinding of Assessors	Endpoints were not subjective.	Not Rated	NA	NA	NA
	20. Negative Control Response	Control responses were reported only for body weights and organ weights.	Low	3	1	3

Study reference:	Adams, E. M., Spencer, H. C., Rowe, V. K., McCollister, D. D., Irish, D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Archives of Environmental and Occupational Health, 6(1), 50-66 HERO ID: 62373					
Domain	**Metric**	**Eval 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 body weight, food/water intake, and respiratory rate were not reported.	Low	3	2	6
	22. Health Outcomes Unrelated to Exposure	Health outcomes unrelated to exposure were not reported.	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	Statistical analysis was conducted and methodology described; the method did not account for multiple comparisons.	Medium	2	1	2
	24. Reporting of Data	All data were reported qualitatively without indication of which control group(s) was compared for statistical analysis.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**61**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**2.103**	**Overall Score: Nearest *:**	**2.1**
		Overall Quality Level:		**Low**		
Study Quality Comment:	**The reviewer downgraded this study's overall quality rating. They noted: Limited (predominantly qualitative) reporting of results, varying exposure durations. Note: The original calculated score for this study was 2.1. This value is not presented above because the final rating was changed based on professional judgement.**					

4.2. Animal toxicity evaluation results of DuPont et al 2001 for cancer inhalation-rats (liver), mice (liver, adrenal gland) study on cancer outcomes

Study reference:	DuPont, (2001). Long Term Inhalation Toxicity Studies of Five Chlorinated Hydrocarbons in F344 Rats and BCF1 Mice. Advances in Prevention of Occupational Respiratory Diseases HERO ID: 4215943					
Domain	**Metric**	**Eval 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 identified by name.	Medium	2	2	4
	2. Test Substance Source	Source identified	Medium	2	1	2
	3. Test Substance Purity	Purity reported and such that effects likely due to test substance.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Concurrent negative controls were included.	High	1	2	2
	5. Positive Controls	Positive controls not required.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Study reported that animals were randomly allocated.	High	1	1	1
Exposure Characterization	7. Preparation and Storage of Test Substance	The method and equipment used to generate the vapor were reported.	High	1	1	1
	8. Consistency of Exposure Administration	Exposures were administered consistently	High	1	1	1
	9. Reporting of Doses/Concentrations	Concentrations were reported	High	1	2	2
	10. Exposure Frequency and Duration	Duration and frequency were reported.	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	The number of exposure groups and dose spacing were reported.	High	1	1	1
	12. Exposure Route and Method	Exposure route and method were reported.	High	1	1	1

Study reference:	DuPont, (2001). Long Term Inhalation Toxicity Studies of Five Chlorinated Hydrocarbons in F344 Rats and BCF1 Mice. Advances in Prevention of Occupational Respiratory Diseases HERO ID: 4215943					
Domain	**Metric**	**Eval 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 source, species, strain, sex, and age were reported. Health status and initial body weight were not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	Housing, feed type, and water were reported. No other conditions were reported.	Medium	2	1	2
	15. Number per Group	The number of animals per group was appropriate.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Outcome assessment methodology was reported.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcome assessment was consistent.	High	1	1	1
	18. Sampling Adequacy	All animals were examined for the outcomes of interest	High	1	1	1
	19. Blinding of Assessors	Blinding was not required.	Not Rated	NA	NA	NA
	20. Negative Control Response	Negative control responses were appropriate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	No confounding variable in test design and procedures were reported.	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	No health outcomes unrelated to exposure were reported.	High	1	1	1

Study reference:	DuPont, (2001). Long Term Inhalation Toxicity Studies of Five Chlorinated Hydrocarbons in F344 Rats and BCF1 Mice. Advances in Prevention of Occupational Respiratory Diseases HERO ID: 4215943					
Domain	**Metric**	**Eval 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	Statistical analysis was reported and appropriate for the outcome of interest.	High	1	1	1
	24. Reporting of Data	Data were presented for cancer outcomes. Survival, clinical signs, and body weight were not reported.	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:		**1.276**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

Carbon tetrachloride

4.3. Animal toxicity evaluation results of Nagano et al 2007 for a 2-year bioassay study on cancer, mortality, hepatic, renal, respiratory, endocrine, clinical chemistry/biochemical, and nutrition and metabolic/adult exposure body weight outcomes

Study reference:	Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamato, S., Fukushima, S. (2007a). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhalation Toxicology, 19(13), 1089-1103 HERO ID: 194127					
Domain	**Metric**	**Eval 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; however, the batch/lot number was not reported, although identity was verified by analytical means (gas chromatography) by the study laboratory.	High	1	1	1
	3. Test Substance Purity	The test substance purity and composition were such that any observed effects were highly likely to be due to the test substance itself. The purity was reported as 99.8% and other components were identified with purities provided.	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 control group is not indicated by study type.	Not Rated	NA	NA	NA

Study reference:	Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamato, S., Fukushima, S. (2007a). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhalation Toxicology, 19(13), 1089-1103 HERO ID: 194127					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	6. Randomized Allocation	The study reported that the animals were divided by stratified randomization; however, there were minor limitations in the allocation method due to use of a non-random component (body weight-matched grouping).	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	The test substance preparation methods were reported and appropriate for the test substance. The method and equipment for generating the test substance as a vapor were reported and appropriate. Although not reported, test substance storage conditions were considered appropriate based on observation of stability of the test substance before and after use by gas chromatography and infrared spectrometry analysis.	High	1	1	1
	8. Consistency of Exposure Administration	Details of exposure methods were reported and exposures were administered consistently for the study groups.	High	1	1	1

Study reference:	Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamato, S., Fukushima, S. (2007a). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhalation Toxicology, 19(13), 1089-1103 HERO ID: 194127					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Reporting of Doses/Concentrations	Concentrations were reported without ambiguity. Mean measured concentrations were reported based on chamber concentrations monitored every 15 minutes during the exposures by gas chromatography.	High	1	2	2
	10. Exposure Frequency and Duration	The exposure frequency and duration of exposure were reported and were appropriate for the study type and outcomes of interest.	High	1	1	1

Study reference:	Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamato, S., Fukushima, S. (2007a). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhalation Toxicology, 19(13), 1089-1103 HERO ID: 194127					
Domain	**Metric**	**Eval 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	The number of exposure groups and concentration spacing were justified; however, the highest concentration (125 ppm) resulted in early mortality of most animals. Therefore, there were an insufficient number of animals in this group for statistical analysis of some endpoints, including terminal body weights, organ weights, clinical chemistry, and urinalysis. Two lower concentrations, 5 and 25 ppm, were also included in the study and a sufficient number of animals survived the duration of exposure for statistical analysis on the same endpoints.	Medium	2	1	2
	12. Exposure Route and Method	The route and method of exposure were reported and suited to the test substance.	High	1	1	1
Test Organism	13. Test Animal Characteristics	The test animal source, species, strain, sex, age, and starting body weight were reported; however, health status was not reported.	Medium	2	2	4

Study reference:	Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamato, S., Fukushima, S. (2007a). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhalation Toxicology, 19(13), 1089-1103 HERO ID: 194127					
Domain	**Metric**	**Eval 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	All husbandry conditions were reported, including temperature, humidity, and light-dark cycle, and were adequate and no differences were reported for the test substance-exposed and control groups.	High	1	1	1
	15. Number per Group	The number of animals per study group (50/sex/group) was reported and appropriate for the study type.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed the intended outcomes of interest and was sensitive for the outcomes of interest.	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 using the same protocol.	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

Study reference:	Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamato, S., Fukushima, S. (2007a). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhalation Toxicology, 19(13), 1089-1103 HERO ID: 194127					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	19. Blinding of Assessors	No subjective outcomes were reported so I considered this metric not applicable. Blood samples were analyzed automatically and histopathology was not described as a re-evaluation.	Not Rated	NA	NA	NA
	20. Negative Control Response	The biological responses of the negative control were adequate.	High	1	1	1
Confounding / Variable Control	21. Confounding Variables in Test Design and Procedures	There were no confounding differences among the study groups in initial body weight. Respiratory rate, however, was not reported.	Medium	2	2	4
	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 study groups were noted.	Medium	2	1	2
Data Presentation and Analysis	23. Statistical Methods	The statistical methods were clearly described and appropriate for the data.	High	1	1	1

	24. Reporting of Data	See footnote at end of page.[1]	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**36**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.241**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

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

5. Reproductive/Developmental Toxicity Studies

5.1. Animal toxicity evaluation results of Schwetz et al 1974 for inhalation developmental toxicity study in rats study on growth (early life) and development outcomes

Study reference:	B. A. Schwetz, B. K. J. Leong, P. J. Gehring (1974). Embryo- and Fetotoxcitiy of Inhaled Carbon Tetrachloride 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats. Toxicology and Applied Pharmacology, 28(1,1), 452-464 HERO ID: 62395					
Domain	**Metric**	**Eval 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	Reagent grade CCl4	High	1	2	2
	2. Test Substance Source	Source and lot number were reported. Lot No. 9256, Burdick & Jackson Lab, Inc., Muskegon, Michigan	High	1	1	1
	3. Test Substance Purity	99.9%; listed an unknown component of 0.1%; determined by gas-liquid chromatography	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Control animals for each experiment exposed concurrently to filtered room air	High	1	2	2
	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 method and equipment used to generate the test substance as a vapor was reported and appropriate; storage conditions were not reported	Medium	2	1	2

Study reference:	B. A. Schwetz, B. K. J. Leong, P. J. Gehring (1974). Embryo- and Fetotoxcitiy of Inhaled Carbon Tetrachloride 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats. Toxicology and Applied Pharmacology, 28(1,1), 452-464 HERO ID: 62395					
Domain	**Metric**	**Eval 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 exposure administration were reported and exposures were administered consistently across study groups	High	1	1	1
	9. Reporting of Doses/Concentrations	nominal concentrations were reported and vapor concentration was measured analytically in the chamber and reported.	High	1	2	2
	10. Exposure Frequency and Duration	7 hr/day GD 6-15	High	1	1	1
	11. Number of Exposure Groups and Dose Spacing	Two vapor concentrations tested; one concentration in an initial experiment and the other in a second experiment. Each experiment had its own control group. It is not clear if these experiments were conducted concurrently.	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
Test Organism	13. Test Animal Characteristics	Adult, Sprague Dawley female rats; starting body weight was reported	High	1	2	2

Study reference:	B. A. Schwetz, B. K. J. Leong, P. J. Gehring (1974). Embryo- and Fetotoxcitiy of Inhaled Carbon Tetrachloride 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats. Toxicology and Applied Pharmacology, 28(1,1), 452-464 HERO ID: 62395					
Domain	**Metric**	**Eval 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	Husbandry conditions were reported, but conditions were not specific for temperature, humidity, and light cycle.	Medium	2	1	2
	15. Number per Group	The number of animals per study group was reported, appropriate for the study type	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology addressed or reported the intended outcomes of interest and was sensitive for the outcomes of interest.	High	1	2	2
	17. Consistency of Outcome Assessment	The outcome assessment methodology addressed or reported the intended outcomes of interest	High	1	1	1
	18. Sampling Adequacy	Sampling for the outcomes of interest were adequate; developmental endpoints were evaluated for litters.	High	1	1	1
	19. Blinding of Assessors	Not applicable; initial pathology review; no other subjective outcomes were assessed	Not Rated	NA	NA	NA
	20. Negative Control Response	The biological responses of the negative control group was adequate	High	1	1	1

Carbon tetrachloride

Study reference:	**B. A. Schwetz, B. K. J. Leong, P. J. Gehring (1974). Embryo- and Fetotoxcitiy of Inhaled Carbon Tetrachloride 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats. Toxicology and Applied Pharmacology, 28(1,1), 452-464** **HERO ID: 62395**					
Domain	**Metric**	**Eval 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	The study reported minor differences among the study groups with respect to food consumption of dams; however, there was no effect on the conception rate or number of implantations or size of litters.	Medium	2	2	4
	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 not specified in the methodology section of the paper, but are statistical tests used were specified and clear in the results tables.	Medium	2	1	2
	24. Reporting of Data	Data for exposure-related findings were presented for all outcomes by 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**	**38**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.310**	**Overall Score: Nearest *:**	**1.3**
		Overall Quality Level:		**High**		

5.2. Animal toxicity evaluation results of Narotsky et al 1997

Study reference:	Narotsky, M. G., Pegram, R. A., Kavlock, R. J. (1997). Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. Fundamental and Applied Toxicology, 40(1), 30-36 HERO ID: 194607					
Domain	**Metric**	**Eval 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	See footnote at end of page.[1]	High	1	2	2
	2. Test Substance Source	See footnote at end of page.[1]	High	1	1	1
	3. Test Substance Purity	See footnote at end of page.[1]	High	1	1	1
Test Design	4. Negative and Vehicle Controls	See footnote at end of page.[1]	High	1	2	2
	5. Positive Controls	A positive control group is not required for study type.	Not Rated	NA	NA	NA
	6. Randomized Allocation	Method for allocation "assured a homogeneous distribution of body weights among groups".	Medium	2	1	2
Exposure Characterization	7. Preparation and Storage of Test Substance	Information on stability of dosing formulations is not provided and frequency of preparation is not reported.	Medium	2	1	2
	8. Consistency of Exposure Administration	See footnote at end of page.[1]	High	1	1	1
	9. Reporting of Doses/Concentrations	See footnote at end of page.[1]	High	1	2	2

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

Study reference:	**Narotsky, M. G., Pegram, R. A., Kavlock, R. J. (1997). Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. Fundamental and Applied Toxicology, 40(1), 30-36** **HERO ID: 194607**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Exposure Frequency and Duration	Animals were exposed only on GD 6-15. More complete information on developmental effects of CCl4 could be determined if animals were exposed through the entire gestation period.	Medium	2	1	2
	11. Number of Exposure Groups and Dose Spacing	See footnote at end of page.[1]	High	1	1	1
	12. Exposure Route and Method	See footnote at end of page.[1]	High	1	1	1
Test Organism	13. Test Animal Characteristics	Age of animals was not reported.	Medium	2	2	4
	14. Adequacy and Consistency of Animal Husbandry Conditions	See footnote at end of page.[1]	High	1	1	1
	15. Number per Group	12-13 dams per group	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Main focus of study was full-litter resorption.	High	1	2	2
	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
	19. Blinding of Assessors	Outcomes were not subjective.	Not Rated	NA	NA	NA
	20. Negative Control Response	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:	Narotsky, M. G., Pegram, R. A., Kavlock, R. J. (1997). Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. Fundamental and Applied Toxicology, 40(1), 30-36 HERO ID: 194607					
Domain	**Metric**	**Eval 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	See footnote at end of page.[1]	High	1	2	2
	22. Health Outcomes Unrelated to Exposure	See footnote at end of page.[1]	High	1	1	1
Data Presentation and Analysis	23. Statistical Methods	See footnote at end of page.[1]	High	1	1	1
	24. Reporting of Data	See footnote at end of page.[1]	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**29**	**34**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.172**	**Overall Score: Nearest *:**	**1.2**
		Overall Quality Level:		**High**		

6. In Vitro Studies

6.1. In vitro evaluation results of Araki et al 2004

Study reference:	**Araki, A., Kamigaitao, N., Sasaki, T., Matsushima, T. (2004). Mutagenicity of carbon tetrachloride and chloroform in Salmonella typhimurium TA98, TA100, TA1535, and TA1537, and Escherichia coli WP2uvrA/pKM101 and WP2/pKM101, using a gas exposure method. Environmental and Molecular Mutagenesis, 43(2), 128-133** **HERO ID: 194641**					
Domain	**Metric**	**Eval 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 CASRN.	High	1	2	2
	2. Test Substance Source	The source of the test substance was reported, including manufacturer and batch/lot number.	High	1	1	1
	3. Test Substance Purity	The test substance purity was reported.	High	1	1	1
Test Design	4. Negative and Vehicle Controls	Negative control was reported.	High	1	2	2
	5. Positive Controls	The authors reported testing positive control substances by the pour plate method, but not the gas-phase exposure method.	Medium	2	2	4
	6. Assay procedures	Study authors described the methods and procedures.	High	1	1	1
	7. Standards for tests	Standards for test provided. The QC part of this test criteria may not be applicable.	Not Rated	NA	NA	NA
Exposure Characterization	8. Preparation and Storage of Test Substance	This may not be applicable since the test chemical was purchased from a commercial vendor and can be used with or without storage.	Not Rated	NA	NA	NA
	9. Consistency of Exposure Administration	Authors reported the details of exposure administration.		NA	1	NA

Study reference:	**Araki, A., Kamigaitao, N., Sasaki, T., Matsushima, T. (2004). Mutagenicity of carbon tetrachloride and chloroform in Salmonella typhimurium TA98, TA100, TA1535, and TA1537, and Escherichia coli WP2uvrA/pKM101 and WP2/pKM101, using a gas exposure method. Environmental and Molecular Mutagenesis, 43(2), 128-133** **HERO ID: 194641**					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	10. Reporting of Doses/Concentrations	The exposure doses/concentrations or amounts of test substance were reported.	High	1	2	2
	11. Number of Exposure Groups and Concentration Spacing	Exposure duration was reported.	High	1	2	2
	12. Exposure Route and Method	The number of exposure groups and dose/concentration spacing were justified by study authors.	High	1	1	1
	13. Metabolic Activation	Study authors reported exposures were conducted in the presence and absence of metabolic activation and the type and source, method of preparation.	High	1	1	1
Test Model	14. Test Model	Authors provided descriptive information on the test model.	High	1	2	2
	15. Number per Group	The authors provided details about the tester strains used in this study.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The authors reported the outcome methodology for the study.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcome assessment was consistent.	High	1	1	1

Study reference:	Araki, A., Kamigaitao, N., Sasaki, T., Matsushima, T. (2004). Mutagenicity of carbon tetrachloride and chloroform in Salmonella typhimurium TA98, TA100, TA1535, and TA1537, and Escherichia coli WP2uvrA/pKM101 and WP2/pKM101, using a gas exposure method. Environmental and Molecular Mutagenesis, 43(2), 128-133 HERO ID: 194641					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	18. Sampling Adequacy	Sampling adequacy was reported for the outcome(s) of interest including more data values per dose group from different experiments.	High	1	2	2
	19. Blinding of Assessors	This metric is not applicable.	Not Rated	NA	NA	NA
Confounding / Variable Control	20. Confounding Variables in Test Design and Procedures	No confounding variables identified.	High	1	2	2
	21. Confounding Variables in Outcomes Unrelated to Exposure	Authors did not report any differences in study groups that was not related to chemical exposure.	High	1	1	1
Data Presentation and Analysis	22. Data Analysis	Authors reported statistical analysis of the data.	High	1	1	1
	23. Data Interpretation	Authors followed the two-fold rule for mutagenicity in individual experiments.	High	1	2	2
	24. Cytotoxicity Data	The study authors reported cytotoxicity information.	High	1	1	1
	25. Reporting of Data	Authors reported exposure-related findings as well as data from the negative controls.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**33**	**34**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.030**	**Overall Score: Nearest *:**	**1.0**

Study reference:	Araki, A., Kamigaitao, N., Sasaki, T., Matsushima, T. (2004). Mutagenicity of carbon tetrachloride and chloroform in Salmonella typhimurium TA98, TA100, TA1535, and TA1537, and Escherichia coli WP2uvrA/pKM101 and WP2/pKM101, using a gas exposure method. Environmental and Molecular Mutagenesis, 43(2), 128-133 HERO ID: 194641					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
		Overall Quality Level:		**High**		

6.2. In vitro evaluation results of Garberg et al 1988

Study reference:	Garberg, P., Akerblom, E. L., Bolcsfoldi, G. (1988). Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutation Research, 203(3), 155-176 HERO ID: 7271					
Domain	**Metric**	**Eval 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 clearly identified.	High	1	2	2
	2. Test Substance Source	The source of the test substance reported including manufacturer, but the batch/lot number not provided.	Medium	2	1	2
	3. Test Substance Purity	Although the authors did not report the purity of the chemical, it may be of a minor concern since the chemical is from a standard company.	Medium	2	1	2
Test Design	4. Negative and Vehicle Controls	Test authors report using a concurrent negative control group.	High	1	2	2
	5. Positive Controls	The authors do no report a concurrent positive control group. But it may not be a concern since they have used known genotoxic chemicals in this study.	Not Rated	NA	NA	NA
	6. Assay procedures	Assay procedures were reported in detail.	High	1	1	1
	7. Standards for tests	The QC part of this test criteria may not be applicable.	Not Rated	NA	NA	NA
Exposure Characterization	8. Preparation and Storage of Test Substance	This may not be applicable since the test chemical was purchased from a commercial vendor and can be used with or without storage.	Not Rated	NA	NA	NA

Study reference:	Garberg, P., Akerblom, E. L., Bolcsfoldi, G. (1988). Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutation Research, 203(3), 155-176 HERO ID: 7271					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	9. Consistency of Exposure Administration	Details of exposure administration were reported.	High	1	1	1
	10. Reporting of Doses/Concentrations	Doses/concentrations were reported.	High	1	2	2
	11. Number of Exposure Groups and Concentration Spacing	Exposure duration was reported.	High	1	2	2
	12. Exposure Route and Method	Number of exposure groups and concentration spacing were reported.	High	1	1	1
	13. Metabolic Activation	Tests were done with and without metabolic activation.	High	1	1	1
Test Model	14. Test Model	The authors used a standard genotoxicity test model.	High	1	2	2
	15. Number per Group	The authors reported the number of cells per group.	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	The outcome assessment methodology was reported.	High	1	2	2
	17. Consistency of Outcome Assessment	Outcome assessment was consistent.	High	1	1	1
	18. Sampling Adequacy	Adequate.	High	1	2	2
	19. Blinding of Assessors	This metric is not applicable.	Not Rated	NA	NA	NA

Study reference:	Garberg, P., Akerblom, E. L., Bolcsfoldi, G. (1988). Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutation Research, 203(3), 155-176 HERO ID: 7271					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	20. Confounding Variables in Test Design and Procedures	See footnote at end of page.[1]	High	1	2	2
	21. Confounding Variables in Outcomes Unrelated to Exposure	See footnote at end of page.[1]	High	1	1	1
Data Presentation and Analysis	22. Data Analysis	The authors did not conduct statistical analysis.	Low	3	1	3
	23. Data Interpretation	Data interpretation was consistent.	High	1	2	2
	24. Cytotoxicity Data	Authors reported cytotoxicity data (cell viability).	Unacceptable	4	1	4
	25. Reporting of Data	Data was reported for all doses.	High	1	2	2
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**31**	**38**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.226**	**Overall Score: Nearest *:**	**1.2[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of A 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, one of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

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

6.3. In vitro evaluation results of Imperial et al 1976 for a genotoxicity-bacterial reverse mutation study

Study reference:	Imperial Chemical, Indus (1976). Mutagenicity testing with salmonella typhimurium strains on plates, of gases, liquids and solids for Imperial Chemical Industries Limited with attachments HERO ID: 4213903					
Domain	**Metric**	**Eval 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 identified; CASRN not reported.	Medium	2	2	4
	2. Test Substance Source	Test manufacturer of the substance was reported, but batch/lot number was not reported.	Medium	2	1	2
	3. Test Substance Purity	The purity and grade of the test substance was not reported.	Low	3	1	3
Test Design	4. Negative and Vehicle Controls	Authors reported the use of negative controls.	High	1	2	2
	5. Positive Controls	Authors reported use of positive controls.	High	1	2	2
	6. Assay procedures	Assay procedure was described with limited assay details.	Low	3	1	3
	7. Standards for tests	The QC part of this test criteria may not be applicable.	Not Rated	NA	NA	NA
Exposure Characterization	8. Preparation and Storage of Test Substance	This may not be applicable since the test chemical was purchased from a commercial vendor and can be used with or without storage.	Not Rated	NA	NA	NA
	9. Consistency of Exposure Administration	Although exposure administration information was provided it is incomplete making it less consistent.	Low	3	1	3
	10. Reporting of Doses/Concentrations	Authors reported three doses/concentrations of the test chemical.	High	1	2	2

Study reference:	Imperial Chemical, Indus (1976). Mutagenicity testing with salmonella typhimurium strains on plates, of gases, liquids and solids for Imperial Chemical Industries Limited with attachments HERO ID: 4213903					
Domain	**Metric**	**Eval 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 Concentration Spacing	The exposure duration reported was lower than standard assays.	Low	3	2	6
	12. Exposure Route and Method	Although the number of exposure groups was sufficient, the higher and highest exposure concentrations were highly toxic.	Low	3	1	3
	13. Metabolic Activation	The authors reported the use of metabolic activation, however, the methods lack the details of the protocol.	Low	3	1	3
Test Model	14. Test Model	The authors reported the strain types, their properties and the description of the test model, but provided limited details.	Medium	2	2	4
	15. Number per Group	The authors mentioned the adaptation of a a standard assay method. However, they did not provide details of the number and replicates used per study group.	Unacceptable	4	1	4
Outcome Assessment	16. Outcome Assessment Methodology	The reporting was incomplete and it was unclear whether methods were sensitive for the outcome of interest	Low	3	2	6
	17. Consistency of Outcome Assessment	The authors did not provide specifics about the execution of the study protocol.	Low	3	1	3

Study reference:	Imperial Chemical, Indus (1976). Mutagenicity testing with salmonella typhimurium strains on plates, of gases, liquids and solids for Imperial Chemical Industries Limited with attachments HERO ID: 4213903					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
	18. Sampling Adequacy	Details regarding sampling of outcomes were not fully reported.	Low	3	2	6
	19. Blinding of Assessors	This metric is not applicable for this study.	Not Rated	NA	NA	NA
Confounding / Variable Control	20. Confounding Variables in Test Design and Procedures	Details about the number of organisms used per group were not reported. These deficiencies are likely to have a substantial impact on results.	Low	3	2	6
	21. Confounding Variables in Outcomes Unrelated to Exposure	Data on outcome differences unrelated to exposure were not reported.	Low	3	1	3
Data Presentation and Analysis	22. Data Analysis	Although data is available for calculations, the high toxicity seen at two higher doses might impact the analysis.	Low	3	1	3
	23. Data Interpretation	High toxicity makes the interpretation of data difficult.	Low	3	2	6
	24. Cytotoxicity Data	Although the endpoints of cytotoxicity were defined, the methods of measurements were not fully described or reported.	Low	3	1	3
	25. Reporting of Data	Study authors reported data for all exposure groups.	High	1	2	2
		Sum of scores:			**32**	**75**

Study reference:	**Imperial Chemical, Indus (1976). Mutagenicity testing with salmonella typhimurium strains on plates, of gases, liquids and solids for Imperial Chemical Industries Limited with attachments** **HERO ID: 4213903**					
Domain	**Metric**	**Eval 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		**Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:**		**2.394**	**Overall Score: Nearest *:**	**2.4[1]**
		Overall Quality Level:		**Unacceptable[1]**		
Study Quality Comment:	**Footnote 1: Consistent with our *Application of A 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, one of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.**					

6.4. In vitro evaluation results of Cummings et al 2000

Study reference:	**Cummings, B. S., Lash, L. H. (2000). Metabolism and toxicity of trichloroethylene and S-(1,2-dichlorovinyl)-L-cysteine in freshly isolated human proximal tubular cells. Toxicological Sciences, 53(2), 458-466** **HERO ID: 194686**					
Domain	**Metric**	**Eval 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 identity was clearly stated	High	1	2	2
	2. Test Substance Source	Test substance obtained from Sigma, manufacturer was not reported	High	1	1	1
	3. Test Substance Purity	A purity of 95% was determined by HPLC analysis	High	1	1	1
Test Design	4. Negative and Vehicle Controls	It is assumed that the negative control was solvent alone, but it is not explicitly stated, and it is unclear whether a control, or all samples, were pretreated prior to exposure	Low	3	2	6
	5. Positive Controls	No positive control, not necessary	Not Rated	NA	NA	NA
	6. Assay procedures	Procedures are reported, but some details are unclear. It is not known whether all cells were pre-treated with wither metyrapone or solvent control prior to TCE, or if some cells were treated with TCE only (there is confusion between what is stated in text and what is in the figure)	Medium	2	1	2
	7. Standards for tests	Another study using a similar LDH activity assay as a measure of cytotoxicity was cited.	High	1	1	1

Study reference:	Cummings, B. S., Lash, L. H. (2000). Metabolism and toxicity of trichloroethylene and S-(1,2-dichlorovinyl)-L-cysteine in freshly isolated human proximal tubular cells. Toxicological Sciences, 53(2), 458-466 HERO ID: 194686					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Exposure Characterization	8. Preparation and Storage of Test Substance	Preparation and storage were not reported	Unacceptable	4	1	4
	9. Consistency of Exposure Administration	No signs of inconsistencies were found	High	1	1	1
	10. Reporting of Doses/Concentrations	Dose concentrations were clearly described	High	1	2	2
	11. Number of Exposure Groups and Concentration Spacing	Exposure duration was appropriate for this endpoint	High	1	2	2
	12. Exposure Route and Method	Minimum number required as per PECO (2 dose groups and a negative control)	High	1	1	1
	13. Metabolic Activation	Not applicable to this assay	Not Rated	NA	NA	NA
Test Model	14. Test Model	The test model was appropriate.	High	1	2	2
	15. Number per Group	Two separate samples of hPT cells were isolated from two human patients (n =4) -	High	1	1	1
Outcome Assessment	16. Outcome Assessment Methodology	Methodology was detailed appropriately	High	1	2	2
	17. Consistency of Outcome Assessment	No inconsistencies were apparent.	High	1	1	1
	18. Sampling Adequacy	All of the sample were assayed	High	1	2	2
	19. Blinding of Assessors	Not applicable, endpoints were not subjective	Not Rated	NA	NA	NA

Study reference:	Cummings, B. S., Lash, L. H. (2000). Metabolism and toxicity of trichloroethylene and S-(1,2-dichlorovinyl)-L-cysteine in freshly isolated human proximal tubular cells. Toxicological Sciences, 53(2), 458-466 HERO ID: 194686					
Domain	**Metric**	**Eval Comment**	**Qualitative Determination [i.e., High, Medium, Low, Unacceptable, or Not rated]**	**Metric Score**	**Metric Weighting Factor**	**Weighted Score**
Confounding / Variable Control	20. Confounding Variables in Test Design and Procedures	The numbers (n) of replicates used were appropriate, however, there was a large range in the number of cells per replicate used for the LDH activity assay (0.5 to 10 x 10^6 cells). Ideally the cell numbers should have been standardized, although activity was /mg of protein.	Low	3	2	6
	21. Confounding Variables in Outcomes Unrelated to Exposure	No unrelated exposure outcomes were apparent	High	1	1	1
Data Presentation and Analysis	22. Data Analysis	Statistical analysis was appropriate	High	1	1	1
	23. Data Interpretation	Interpretation was acceptable based on the data reported	High	1	2	2
	24. Cytotoxicity Data	Question does not seem applicable to this study as the main endpoint evaluated was cytotoxicity	Not Rated	NA	NA	NA
	25. Reporting of Data	There is uncertainty about the data reported given the descriptions in the text.	Low	3	2	6
High: >=1 and <1.7 Medium: >=1.7 and <2.3 Low: >=2.3 and <=3		**Sum of scores:**			**31**	**47**
		Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors:		**1.516**	**Overall Score: Nearest *:**	**1.5**
		Overall Quality Level:		**High**		

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