United States
Environmental Protection Agency

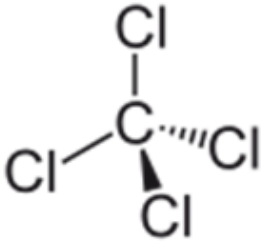
Office of Chemical Safety and
Pollution Prevention

Draft Risk Evaluation for Carbon Tetrachloride

Systematic Review Supplemental File:

Data Quality Evaluation of Epidemiological Studies

CASRN 56-23-5



January 2020

Table Listing

Table 1: **Davis 1934: Evaluation of Acute Toxicity/Poisoning Outcomes**

Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_clinicalobs-Acute Toxicity/Poisoning
HERO ID:	3611

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Low	× 0.4	1.2	Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided.
	Metric 2: Attrition	Medium	× 0.4	0.8	Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described.
	Metric 3: Comparison Group	Low	× 0.2	0.6	No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration.
	Metric 6: Temporality	Low	× 0.4	1.2	This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride.
Domain 3: Outcome Assessment					

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Study Citation: P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type: Davis_CCl4_controlled_inhalation_exposure_clinicalobs-Acute Toxicity/Poisoning
HERO ID: 3611

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Outcomes were outlined throughout the paper and clinical observations were described.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates, besides age, were not collected.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There was no indication of co-exposures being present or measured for during the controlled inhalation exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Low	× 0.25	0.75	The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported.
	Metric 15:	Statistical models	Not Rated	NA	NA	Results were compared to reference values and described qualitatively only.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	

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Study Citation: P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type: Davis_CCl4_controlled_inhalation_exposure_clinicalobs-Acute Toxicity/Poisoning
HERO ID: 3611

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Low		2.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor
† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.
‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 2: **Radican et al. 2008: Evaluation of Cancer Outcomes**

Study Citation:	Radican, L; Blair, A; Stewart, P; Wartenberg, D (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up Journal of Occupational and Environmental Medicine, 50(11), 1306-1319
Data Type:	Hill_Air_Force_Base_CCl4_BreastCancer_Females-Cancer
HERO ID:	699234

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	This study consisted of an extended follow-up of the Hill Air Force Base occupational cohort through 2000. The cohort is composed of former civilian employees, who worked at this aircraft maintenance facility for at least 1 year between January 1, 1952 and December 31, 1956 (n=14,455). The key elements of the study design were reported. Selection into the study was not likely to be biased. The cohort was described in detail in previous publications (Spirtas et al. 1991; Stewart et al. 1991; Blair et al. 1998).
	Metric 2: Attrition	High	× 0.4	0.4	There was no loss of subjects to follow-up reported in the study (as of December 31 2000, 8580 subjects had died and 5875 were still alive); exposure and outcome data were largely complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	Key elements of the study design are reported. Effects levels were adjusted for age, race, and/or sex. The use of an internal comparison group likely reduces the risk of bias relative to the use of an external reference group (e.g., the healthy worker effect).
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	The exposure assessment was conducted by the National Cancer Institute (NCI), using job-exposure matrices, based on information provided by the Air Force. Although exposure misclassification was possible (because individual exposure records were not available), misclassification was likely random and not to appreciably bias the results.
	Metric 5: Exposure levels	Low	× 0.2	0.6	For 21 chemicals (including TCE, Perc, CCl4 and DCM), exposure was classified as yes/no. No quantitative assessment of exposure was conducted.
	Metric 6: Temporality	High	× 0.4	0.4	The study presents the appropriate relationship between exposure and outcome. Outcome was ascertained after information on exposure was obtained. There was a long follow-up period.
Domain 3: Outcome Assessment					

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Study Citation:	Radican, L; Blair, A; Stewart, P; Wartenberg, D (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up Journal of Occupational and Environmental Medicine, 50(11), 1306-1319
Data Type:	Hill_Air_Force_Base_CCl4_BreastCancer_Females-Cancer
HERO ID:	699234

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The outcome was determined from death records from the National Death Index (NDI). It was noted in the study that mortality data can be misleading owing to inaccuracies captured in patient death records.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	A description of measured outcomes is provided in the study report. Effects estimates are provided with confidence limits; number of exposed cases is included.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Adjustments were made for age, race, and gender. However, there was indirect evidence that socioeconomic status (SES) was considerably different among exposed and non-exposed populations. The proportion of non-exposed persons that were salaried was 61% compared to < 1% in the exposed cohort, suggesting a dissimilar SES. This difference may affect the results for some specific cancer types/diseases.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders were assessed using reliable methods (database of employees and NDI). However, other than age, gender, and race, data on other factors (disease history, SES) were not available.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The study evaluated exposure to CCl4 and various other chemicals. Exposures were not mutually exclusive; therefore, it was not possible to evaluate the risk of death from exposure to a singular chemical while controlling for exposure to other chemicals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cohort design and calculation of hazard ratios were appropriate for determining the association between exposure to TCE, Perc, CCl4 and DCM, and all-cause, cancer, and non-cancer mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort was large (adequate for statistical analyses). Despite the relatively large size of the cohort, the number of cases for many causes of death was small to evaluate associations.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis (exposure estimation and statistical modeling) is described in sufficient detail to understand what was done and is conceptually reproducible.

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Study Citation:	Radican, L; Blair, A; Stewart, P; Wartenberg, D (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up Journal of Occupational and Environmental Medicine, 50(11), 1306-1319
Data Type:	Hill_Air_Force_Base_CCl4_BreastCancer_Females-Cancer
HERO ID:	699234

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Medium	× 0.2	0.4	The method and model assumptions used to calculate risk estimates for occupational exposure to TCE, Perc, CCl4 and DCM and all-cause and cause-specific mortality (hazard ratios) are clearly described in the study report.
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure		NA	NA	
	Metric 17: Effect biomarker		NA	NA	
	Metric 18: Method Sensitivity		NA	NA	
	Metric 19: Biomarker stability		NA	NA	
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		1.8	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 3: **Radican et al. 2008: Evaluation of Respiratory Outcomes**

Study Citation:	Radican, L; Blair, A; Stewart, P; Wartenberg, D (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up Journal of Occupational and Environmental Medicine, 50(11), 1306-1319
Data Type:	Hill_Air_Force_Base_CCl4_NonMalignantRespiratoryDisease-Respiratory
HERO ID:	699234

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	This study consisted of an extended follow-up of the Hill Air Force Base occupational cohort through 2000. The cohort is composed of former civilian employees, who worked at this aircraft maintenance facility for at least 1 year between January 1, 1952 and December 31, 1956 (n=14,455). The key elements of the study design were reported. Selection into the study was not likely to be biased. The cohort was described in detail in previous publications (Spirtas et al. 1991; Stewart et al. 1991; Blair et al. 1998).
	Metric 2: Attrition	High	× 0.4	0.4	There was no loss of subjects to follow-up reported in the study (as of December 31 2000, 8580 subjects had died and 5875 were still alive); exposure and outcome data were largely complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	Key elements of the study design are reported. Effects levels were adjusted for age, race, and/or sex. The use of an internal comparison group likely reduces the risk of bias relative to the use of an external reference group (e.g., the healthy worker effect).
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	The exposure assessment was conducted by the National Cancer Institute (NCI), using job-exposure matrices, based on information provided by the Air Force. Although exposure misclassification was possible (because individual exposure records were not available), misclassification was likely random and not to appreciably bias the results.
	Metric 5: Exposure levels	Low	× 0.2	0.6	For 21 chemicals (including TCE, Perc, CCl4 and DCM), exposure was classified as yes/no. No quantitative assessment of exposure was conducted.
	Metric 6: Temporality	High	× 0.4	0.4	The study presents the appropriate relationship between exposure and outcome. Outcome was ascertained after information on exposure was obtained. There was a long follow-up period.
Domain 3: Outcome Assessment					

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Study Citation:	Radican, L; Blair, A; Stewart, P; Wartenberg, D (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up Journal of Occupational and Environmental Medicine, 50(11), 1306-1319
Data Type:	Hill_Air_Force_Base_CCl4_NonMalignantRespiratoryDisease-Respiratory
HERO ID:	699234

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The outcome was determined from death records from the National Death Index (NDI). It was noted in the study that mortality data can be misleading owing to inaccuracies captured in patient death records.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	A description of measured outcomes is provided in the study report. Effects estimates are provided with confidence limits; number of exposed cases is included.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Adjustments were made for age, race, and gender. However, there was indirect evidence that socioeconomic status (SES) was considerably different among exposed and non-exposed populations. The proportion of non-exposed persons that were salaried was 61% compared to < 1% in the exposed cohort, suggesting a dissimilar SES. This difference may affect the results for some specific cancer types/diseases.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders were assessed using reliable methods (database of employees and NDI). However, other than age, gender, and race, data on other factors (disease history, SES) were not available.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The study evaluated exposure to CCl4 and various other chemicals. Exposures were not mutually exclusive; therefore, it was not possible to evaluate the risk of death from exposure to a singular chemical while controlling for exposure to other chemicals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cohort design and calculation of hazard ratios were appropriate for determining the association between exposure to TCE, Perc, CCl4 and DCM, and all-cause, cancer, and non-cancer mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort was large (adequate for statistical analyses). Despite the relatively large size of the cohort, the number of cases for many causes of death was small to evaluate associations.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis (exposure estimation and statistical modeling) is described in sufficient detail to understand what was done and is conceptually reproducible.

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Study Citation:	Radican, L; Blair, A; Stewart, P; Wartenberg, D (2008). Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: Extended follow-up Journal of Occupational and Environmental Medicine, 50(11), 1306-1319
Data Type:	Hill_Air_Force_Base_CCl4_NonMalignantRespiratoryDisease-Respiratory
HERO ID:	699234

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Medium	× 0.2	0.4	The method and model assumptions used to calculate risk estimates for occupational exposure to TCE, Perc, CCl4 and DCM and all-cause and cause-specific mortality (hazard ratios) are clearly described in the study report.
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure		NA	NA	
	Metric 17: Effect biomarker		NA	NA	
	Metric 18: Method Sensitivity		NA	NA	
	Metric 19: Biomarker stability		NA	NA	
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		1.8	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

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where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 4: **Gold et al. 2010: Evaluation of Cancer Outcomes**

Study Citation:	Gold, LS; Stewart, PA; Milliken, K; Purdue, M; Severson, R; Seixas, N; Blair, A; Hartge, P; Davis, S; De Roos, AJ (2010). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents Occupational and Environmental Medicine, 68(6), 391-399
Data Type:	Gold_CCl4_exposed workers_cancer_1-4 yrs-Cancer
HERO ID:	699241

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Study authors note a low participation rate of eligible controls, with individuals in the youngest (35-50) and oldest (65-75) age groups were less likely to participate than those in the middle age group.
	Metric 2:	Attrition	High	× 0.4	0.4	Low attrition for subjects that decided to participate in study. Only one case was excluded because of missing covariate information.
	Metric 3:	Comparison Group	High	× 0.2	0.2	General population controls were selected from a case-control study of non-Hodgkin's lymphoma undertaken at the same time. Controls were identified by random digit dialing with clear inclusion criteria. A table of characteristics was not provided to evaluate similarities, but adjustments were made for age, race, site, gender, and years of education.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Use of a job-exposure matrix in a population based study. Exposure based on participant interview rather than detailed employment history records
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Reports referent group and 3 levels of exposure for cumulative exposure and 10-year lagged cumulative exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Cases were diagnosed between 2000 and 2002 while exposure was assessed from 1941 to time of study enrollment.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases were identified through the review of hospital medical records and records of selected pathology laboratories, oncologists, radiologists and state death certificates.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Effect estimates are reported with a confidence interval. The number of cases and controls are included in a tabular format for date extraction and analysis.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Gold, LS; Stewart, PA; Milliken, K; Purdue, M; Severson, R; Seixas, N; Blair, A; Hartge, P; Davis, S; De Roos, AJ (2010). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents Occupational and Environmental Medicine, 68(6), 391-399
Data Type:	Gold_CCl4_exposed workers_cancer_1-4 yrs-Cancer
HERO ID:	699241

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates gender, age (35-50 years (referent), 51-64 years and 65-74 years), race (only white (referent), any black, any Asian and other), education (less than 12 years (referent), 12-15 years and 16 or more years) and SEER site (Seattle and Detroit).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Potential confounders were considered but method validation not provided. However there is no evidence that the method had poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Exposure to other chlorinated solvents was also assessed with JEM. Study authors note that they report the percentages of control subjects exposed to these chemicals alone and to two of these chemicals and provide an estimate of the association with multiple myeloma for subjects who were exposed to all four (TCE, CCl4, DCM, PERC). But analyses were not adjusted for these exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design chosen was appropriate for the exposure and outcome of interest.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The overall number of cases and controls are adequate to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand what has been done.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	There is sufficient information on how the ORs were calculated.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			~~High~~ ⟶ Medium§		~~1.6~~	
Extracted			Yes			

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Study Citation:	Gold, LS; Stewart, PA; Milliken, K; Purdue, M; Severson, R; Seixas, N; Blair, A; Hartge, P; Davis, S; De Roos, AJ (2010). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents Occupational and Environmental Medicine, 68(6), 391-399
Data Type:	Gold_CCl4_exposed workers_cancer_1-4 yrs-Cancer
HERO ID:	699241

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

§ Evaluator's explanation for rating change: "The number of cases in this subgroup is small (n=4) and caution should be taken when interpreting the findings."

Table 5: **Roberts et al. 2013: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Koenen, K.C., Ascherio, A., Weisskopf, M.G. (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants Environmental Health Perspectives, 121(8), 978-984
Data Type:	Nurses' Health Study II_CCl4_case-control_Autism endpoint-Neurological/Behavior
HERO ID:	1790951

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Data from the Nurses' Health Study II was used. Study reported time frame in which all children (cases and controls) were selected (2005-2008). Children were born in all 50 US states. Exclusion/inclusion criteria is described in the study.
	Metric 2: Attrition	High	× 0.4	0.4	The number of cases/controls included in the study was 329 cases, 22098 controls. Reasons for excluding subjects were clearly detailed. There was minimal loss of subjects reported in results (325 cases/22101 controls)
	Metric 3: Comparison Group	High	× 0.2	0.2	Table 1 shows the demographic characteristics of the cases and controls, which appear to be similar. These include maternal age, year of birth, sex, state of residence, smoking, income, and education information. These were also considered in the analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure was determined based on the location of the mothers beginning in 1989. Children born from 1987-1990 were assigned the geographic location of their mothers in 1989. The nurses address was updated every other year after that and children were assigned based on the closest date. "Hazardous air pollutant (HAP) concentrations were assessed by the U.S. EPA National Air Toxics Assessments in 1990, 1996, 1999, and 2002, which uses an inventory of outdoor sources of air pollution, including both stationary sources (e.g., waste incinerators, small businesses) and mobile sources (e.g., traffic) to estimate average ambient concentrations of pollutants for each census tract based on dispersion models (U.S. EPA 2011)." The erratum states that the authors did not use background exposures when determining the quinitles in 1996, so the quintiles are somewhat different than as reported.

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Study Citation:	Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Koenen, K.C., Ascherio, A., Weisskopf, M.G. (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants Environmental Health Perspectives, 121(8), 978-984
Data Type:	Nurses' Health Study II_CCl4_case-control_Autism endpoint-Neurological/Behavior
HERO ID:	1790951

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Exposure levels ranged from 0.0006-41.9 ug/m3, and divided into 5 quintiles. The range is sufficient to determine a dose-response relationship
	Metric 6:	Temporality	High	× 0.4	0.4	Exposures were measured during time and place of birth from 1987-2002, autism spectrum disorder was first assessed in 2005; therefore, a minimum of 3 years after exposure.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	ASD was reported by the mothers via this question "“Have any of your children been diagnosed with the following diseases?” with autism, Asperger's syndrome, or other ASD listed as separate responses." The ASD diagnoses were validated by telephone administration of the Autism Diagnostic Interview-Revised (ADI-R), to a randomly selected group of 50 monthers from the study.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All measured outcomes were outlined in the methods, and information could be fulling extracted for analysis. Some information was provided in supplemental information.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates were included in the models, including: socioeconomic indicators, smoking, year of birth, maternal age at birth, and air pollution prediction model year.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders were assessed via questionnaires, but there is no indication that the questionnaires were validated
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposure analysis was included in the model: "To investigate further whether one or two pollutants were driving the association between correlated pollutants and ASD, we conducted analyses with diesel, lead, manganese, cadmium, methylene chloride, and nickel—the pollutants most strongly associated with ASD based on tests of highest versus lowest quintile as well as linear trend—in a single model."
Domain 5: Analysis						

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Study Citation:	Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Koenen, K.C., Ascherio, A., Weisskopf, M.G. (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants Environmental Health Perspectives, 121(8), 978-984
Data Type:	Nurses' Health Study II_CCl4_case-control_Autism endpoint-Neurological/Behavior
HERO ID:	1790951

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design was appropriate for assessing the possible association between autism spectrum disorder and exposure to several different compounds. The study design can get at prior exposure to several exposures at once for a specific outcome from a large cohort.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The power was sufficient to detect effects (325 cases and 22101 controls).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The methodology is clearly laid out, and could be reproduced. Methods to calculate the odds ratios and the covariates included were provided. and details were provided on when they were not included.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Statistical methods were appropriate (calculation of ORs, logistic regression models). Linear dose-response was determined by dividing exposures into quintiles and using logistic regression with concentrations entered as a continuous independent variable. Other analysis such as sex, correlation of heavy metals, and covariate analysis were employed.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.5	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High =≥ 1 to < 1.7; Medium =≥ 1.7 to < 2.3; Low =≥ 2.3 to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 6: **Goldman et al. 2012: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Goldman, S.M., Quinlan, P.I., Ross, G.W., Marras, C., Meng, C., Bhudhikanok, G.S., Comyns, K., Korell, M., Chade, A.R., Kasten, M., Priestley, B., Chou, K.L., Fernandez, H.H., Cambi, F., Langston, J.W., Tanner, C.M. (2012). Solvent exposures and Parkinson disease risk in twins Annals of Neurology, 71(6), 776-784
Data Type:	WW2 Twins CCl4 Parkinson's dichotomous pairwise OR-Neurological/Behavior
HERO ID:	2127988

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Key elements of study are reported: participants were selected from the National Academy of Sciences/National Research Council WWII Veteran Twins Registry, an all-male twin cohort. Cases were selected through telephone screening of the entire reachable cohort; concurrently, searches of VA medical databases, the Health Care Financing Administration, and the National Death Index were undertaken to identify other cases. It was stated that age at PD diagnosis or interview was similar between those pairs that completed the interview and those pairs that did not complete the interview. As such, the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2: Attrition	Medium	× 0.4	0.8	Occupational histories were completed by 63.6% of twins with PD and 60.1% of twins without PD leading to a final total of 99 twin pairs. This is moderate exclusion from the analysis sample. Rates of completion were similar between twins with and without PD.
	Metric 3: Comparison Group	High	× 0.2	0.2	In both paired and unpaired analysis, smoking was an included covariate. In unpaired analysis, an age index was also adjusted for. Other important demographic factors in the paired analysis would be highly controlled as the analysis was of twin pairs. The type of twin (monozygotic or dizygotic) was also included as a covariate in the paired analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	This method relies on self-reported occupational histories. There may be some misclassification due recall bias in addition to any bias introduced by accuracy of response for participant proxies.

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Study Citation:	Goldman, S.M., Quinlan, P.I., Ross, G.W., Marras, C., Meng, C., Bhudhikanok, G.S., Comyns, K., Korell, M., Chade, A.R., Kasten, M., Priestley, B., Chou, K.L., Fernandez, H.H., Cambi, F., Langston, J.W., Tanner, C.M. (2012). Solvent exposures and Parkinson disease risk in twins Annals of Neurology, 71(6), 776-784
Data Type:	WW2 Twins CCl4 Parkinson's dichotomous pairwise OR-Neurological/Behavior
HERO ID:	2127988

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	For logistic regression using duration of exposure or cumulative exposure indices, ORs addressed risk associated with a one tertile change in the respective marker of exposure. This represents three or more levels of exposure. For the Ever/Never analysis, only two levels of exposure are used. Ever exposure was defined as exposure to a solvent for at least 2% of work time or 1 hour per week.
	Metric 6:	Temporality	High	× 0.4	0.4	This study investigated occupational exposures beginning at a young age and their association with Parkinson's Disorder later in life. The interval between exposure and outcome measurement is appropriate to measure this association.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases were identified through searches of records in the Department of Veteran's Affairs, the Health Care Financing Administration, and the National Death Index. Participants suspected of having Parkinson's underwent in-person examination with a trained movement disorder specialist. This outcome assessment represents a well-established method. Both neurologists followed standard criteria for PD diagnosis and made their diagnosis by video. There is no mention of blinding during this evaluation., although participants were unaware of study hypotheses.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes mentioned in the abstract, introduction, and methods were presented clearly in the results. ORs are contained in easily extractable tables, including number of participants used in each analysis accompanied by summary measures of exposure in the analyses of cumulative exposure.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	In the paired analysis (paired twins), the conditional logistic regression model included terms for respondent type (monozygotic/dizygotic) and smoking. In the unpaired analysis, respondent type, smoking, and age were all included in the analysis. Models including head injury were stated to be similar to the results shown.

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Study Citation:	Goldman, S.M., Quinlan, P.I., Ross, G.W., Marras, C., Meng, C., Bhudhikanok, G.S., Comyns, K., Korell, M., Chade, A.R., Kasten, M., Priestley, B., Chou, K.L., Fernandez, H.H., Cambi, F., Langston, J.W., Tanner, C.M. (2012). Solvent exposures and Parkinson disease risk in twins Annals of Neurology, 71(6), 776-784
Data Type:	WW2 Twins CCl4 Parkinson's dichotomous pairwise OR-Neurological/Behavior
HERO ID:	2127988

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	In some cases, questionnaires/surveys were completed by proxies such as a spouse or sibling. For several covariates including head injury or smoking, this is not a well-established method, but there was little evidence that the method had poor validity. It should also be noted that results were presented for an analysis excluding twin pairs using proxy respondents. The results of this analysis were in agreement with the main analyses.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures to other solvents was measured in this study. Overall, six different solvents were included in the exposure analysis: TCE, PERC, CCl4, n-hexane, toluene, and xylene. Several analysis strategies were presented to elucidate any effects of co-exposures. Analyses were done for the relationship between PD and exposure to TCE or PERC as well as an analysis of the relationship between exposure to any of the 4 solvents, excluding TCE and PERC.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The retrospective study design is appropriate to investigate long-term or chronic exposure to industrial solvents and development of the neurodegenerative Parkinson's Disease. Appropriate statistical methods (i.e., conditional logistical modeling) were employed to analyze the matched data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There is an adequate number of discordant twin pairs (n=99) for the pairwise analysis and an adequate number of participants in the unpaired analysis (n=126 cases exposed, n=110 controls exposed) to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to reproduce the results if given original data. No apparent issues.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method (logistic regression modeling) of calculating risk is transparent and appropriate. Rationale for variable selection is stated. Model assumptions do not appear to be violated.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	

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Study Citation:	Goldman, S.M., Quinlan, P.I., Ross, G.W., Marras, C., Meng, C., Bhudhikanok, G.S., Comyns, K., Korell, M., Chade, A.R., Kasten, M., Priestley, B., Chou, K.L., Fernandez, H.H., Cambi, F., Langston, J.W., Tanner, C.M. (2012). Solvent exposures and Parkinson disease risk in twins Annals of Neurology, 71(6), 776-784
Data Type:	WW2 Twins CCl4 Parkinson's dichotomous pairwise OR-Neurological/Behavior
HERO ID:	2127988

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 7: **Neta et al. 2012: Evaluation of Cancer Outcomes**

Study Citation:	Neta, G., Stewart, P.A., Rajaraman, P., Hein, M.J., Waters, M.A., Purdue, M.P., Samanic, C., Coble, J.B., Linet, M.S. (2012). Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults Occupational and Environmental Medicine, 69(11), 793-801
Data Type:	CCl4_all_subjects_possibleexp_Glioma-Cancer
HERO ID:	2128240

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	High rating: key elements of study design were reported, and the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2:	Attrition	High	× 0.4	0.4	High participation rates: 92% and 94% for glioma and meningioma cases, respectively. Participation rate among controls was 86%
	Metric 3:	Comparison Group	High	× 0.2	0.2	High rating: cases and controls were similar - controls were patients admitted to the same hospitals as cases for non-malignant conditions with frequency matching by sex, age, race/ethnicity, hospital, and proximity to hospital; differences in baseline characteristics of groups were considered as potential confounding or stratification variables (i.e,. sex and 5-year age groups) and were thereby controlled by statistical analysis
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Low rating: Occupational study population with exposure assessed using in person interviews (i.e., no employment records were utilized). Industrial hygiene experts from examined data collected in the questionnaires, and assessed a level of probability and levels of exposure to groups or classes of solvents as well as certain individual substances.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Medium rating: range and distribution of exposure was sufficient to develop an exposure response estimate; 3 or more levels of exposure were reported
	Metric 6:	Temporality	High	× 0.4	0.4	High rating: temporality is established and the interval between reconstructed exposure and brain tumor risk has an appropriate consideration of relevant exposure windows.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	High rating: ICD-Oncology codes listed; all participating case diagnoses were confirmed by microscopy

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Study Citation:	Neta, G., Stewart, P.A., Rajaraman, P., Hein, M.J., Waters, M.A., Purdue, M.P., Samanic, C., Coble, J.B., Linet, M.S. (2012). Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults Occupational and Environmental Medicine, 69(11), 793-801
Data Type:	CCl4_all_subjects_possibleexp_Glioma-Cancer
HERO ID:	2128240

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	High rating: appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment (i.e., age group (<30, 30–49, 50–69, 70+), race (white vs non-white), sex, hospital site and proximity of residence to the hospital)
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Medium rating: primary confounders (excluding co-exposures) were assessed. The paper did not describe if the computer-based questionnaire used to collect demographic information has been previously validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Medium rating: potential co-pollutant confounding was considered through the adjustment in statistical models, of estimated cumulative occupational exposures to lead, magnetic fields, herbicides and insecticides. In addition, for ever/never analyses for particular solvents, the authors included all other solvents in the model to account for possible confounding by other solvent exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Medium rating: appropriate design (i.e., case control study of chemical exposures in relation to a rare disease), and appropriate statistical methods (i.e., logistic regression analyses) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Medium rating: the number of cases and controls are adequate to detect an effect in the exposed population for the primary analyses of probable/possible solvent exposure vs. unexposed in relation to risk of glioma. The number of exposure cases of meningioma was too small to have the power to conduct stratified analyses or analyses of more detailed exposure metrics.

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Study Citation:	Neta, G., Stewart, P.A., Rajaraman, P., Hein, M.J., Waters, M.A., Purdue, M.P., Samanic, C., Coble, J.B., Linet, M.S. (2012). Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults Occupational and Environmental Medicine, 69(11), 793-801
Data Type:	CCl4_all_subjects_possibleexp_Glioma-Cancer
HERO ID:	2128240

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: logistic regression models were used to generate Odds Ratios. Rationale for variable selection is stated. Model assumptions are met
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.5	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 8: **Ruder et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Ruder, A.M., Yiin, J.H., Waters, M.A., Carreon, T., Hein, M.J., Butler, M.A., Calvert, G.M., Davis-King, K.E., Schulte, P.A., Mandel, J.S., Morton, R.F., Reding, D.J., Rosenman, K.D., Stewart, P.A., Brain Cancer Collaborative Study Group (2013). The Upper Midwest Health Study: Gliomas and occupational exposure to chlorinated solvents Occupational and Environmental Medicine, 70(2), 73-80
Data Type:	Upper Midwest Health Study_CCl4_cumulative_include proxy_glioma-Cancer
HERO ID:	2128307

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Subjects were selected from the same area during the same time frame. Cases were identified through participating medical facilities and neurosurgeon offices. Controls were identified from state driver's license records.91.5% o f cases or their next of kin participated and 70.4% of controls participated. Key elements of the study design are reported..
	Metric 2:	Attrition	High	× 0.4	0.4	Study population consisted of 1175 controls and 798 cases. 97& of the controls (1141/1175) were interviewed and all cases had interviews with 360 being proxy interviews. Some analysis was restricted to cases that were directly interviewed.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were randomly selected and age and sex stratified. There were some differences in the level of education, but this was adjusted for in the analysis. Details comparing cases and controls as well as ineligible and non-participants are detailed in companion publication (Ruder et al. 2006).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Complete occupational history was obtained using a questionnaire modified from the one developed by the National Cancer Institute. Jobs of at least one years duration between the age of 16 and the end of 1992 were included. The questionnaire also asked about specific exposures including solvent and on which jobs and for how many hours a week these exposures occurred. There is potential for cases to have better recall. The probability, intensity, and frequency of exposure in non-farm related jobs was estimated based on occupation, industry, and decade using an annotated appendix of sources of exposure data as well as bibliographic databases of published exposure levels. Complete descriptions of the methods were provided. JEM with complete job history, but based on recalled jobs and some judgement on exposure (although used several cited references).

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Study Citation: Ruder, A.M., Yiin, J.H., Waters, M.A., Carreon, T., Hein, M.J., Butler, M.A., Calvert, G.M., Davis-King, K.E., Schulte, P.A., Mandel, J.S., Morton, R.F., Reding, D.J., Rosenman, K.D., Stewart, P.A., Brain Cancer Collaborative Study Group (2013). The Upper Midwest Health Study: Gliomas and occupational exposure to chlorinated solvents Occupational and Environmental Medicine, 70(2), 73-80

Data Type: Upper Midwest Health Study_CCl4_cumulative_include proxy_glioma-Cancer

HERO ID: 2128307

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Exposure was estimated in cumulative exposure of ppm-h and ppm-years.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established, but it is unclear whether exposures fall within relevant exposure windows for the outcome of interest. Case diagnosis occurred between 1995 and 1997 with job history ending in 1992.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The study focused on histologically confirmed primary intracranial gliomas (ICD-O code 938-948).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Sufficient information was reported. Effect estimates are reported with a confidence interval.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjusted for age group, sex, age, and education.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained via a questionnaire sometimes via proxy.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Although this was occupational exposure, they included people from different jobs at different times and it is unlikely that there would be differential co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Methods are appropriate and appropriate statistical methods were used to address research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study included 798 cases and 1175 controls, which is likely to provide sufficient statistical power. For any given exposure there were more than 100 subjects except when evaluating women only or a subset excluding proxy only. In these cases there were as few as 34 subjects.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Enough information is provided to be reproducible if data were available.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Unconditional logistic regression models were used, which were appropriate for the data and assumptions appear to have been met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	

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Study Citation:	Ruder, A.M., Yiin, J.H., Waters, M.A., Carreon, T., Hein, M.J., Butler, M.A., Calvert, G.M., Davis-King, K.E., Schulte, P.A., Mandel, J.S., Morton, R.F., Reding, D.J., Rosenman, K.D., Stewart, P.A., Brain Cancer Collaborative Study Group (2013). The Upper Midwest Health Study: Gliomas and occupational exposure to chlorinated solvents Occupational and Environmental Medicine, 70(2), 73-80
Data Type:	Upper Midwest Health Study_CCl4_cumulative_include proxy_glioma-Cancer
HERO ID:	2128307

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 9: **Vizcaya et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Vizcaya, D; Christensen, KY; Lavoue, J; Siemiatycki, J (2013). Risk of lung cancer associated with six types of chlorinated solvents: Results from two case-control studies in Montreal, Canada Occupational and Environmental Medicine, 70(2), 81-85
Data Type:	occupational case-control study Montreal (CCl4 any exposure Study II analysis extraction)-Cancer
HERO ID:	2128435

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	This was a population based case-control study in which subjects were restricted to Canadian citizens who were residents in the Montreal metropolitan area. This report did not describe case ascertainment, but cited references (HERO ID 2856585 and 091275) which indicate that histologically confirmed cancer patients from 18 of the largest hospitals were used as cases. Controls were randomly selected frequency matched by age and sex. Participation rates were provided and were slightly higher in the cases.
	Metric 2:	Attrition	Low	× 0.4	1.2	There appears to be a large amount of attrition that was not adequately explained. It is likely that the missing subjects from Table 1 did not have occupations with exposure codes.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases were more likely to be French Canadians than controls. Controls were on average wealthier and had a higher education. Cases were heavier smokers than controls. These were all controlled for in the analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A semi-structured questionnaire was used to obtain details of each job that lasted at least 6 months. A team of industrial chemists and hygienists examined each subject's questionnaire and translated each job into potential exposures from a list of 294 substances without knowledge of the subject's status. Exposure based on collective judgement.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Only two groups were compared and could not be evaluated for trend. Exposed groups were never exposed, ever exposed, or substantial exposure.
	Metric 6:	Temporality	Low	× 0.4	1.2	The temporality of exposure and outcome is uncertain. Although job history was obtained, there is no information provided to determine that the jobs occurred before diagnosis or even if the jobs were prior to diagnosis there is no information provided on how long or how close to the diagnosis the jobs occurred.
Domain 3: Outcome Assessment						

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Study Citation:	Vizcaya, D; Christensen, KY; Lavoue, J; Siemiatycki, J (2013). Risk of lung cancer associated with six types of chlorinated solvents: Results from two case-control studies in Montreal, Canada Occupational and Environmental Medicine, 70(2), 81-85
Data Type:	occupational case-control study Montreal (CCl4 any exposure Study II analysis extraction)-Cancer
HERO ID:	2128435

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases were histologically confirmed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Results were reported in sufficient details. A description of measured outcomes is reported in the methods, abstract, and/or introduction. Effect estimates are reported with a confidence interval and the number of cases/controls are reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Results were adjusted by age, smoking habit, educational attainment, SES, and ethnicity.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained from a questionnaire of unknown reliability and validity. The authors note that "Although it is very difficult to establish the validity of retrospective exposure assessments, we have demonstrated satisfactory levels of reliability and validity in the job histories and in the expert exposure assessments.'
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	It was noted that results were adjusted for exposure to eight known carcinogens. Although there are potential co-exposures for any given job, it is unlikely that they were differential across jobs and within the specific chemicals of interest. Supplemental Table S2 indicated 5 different jobs with exposure to CCl4 making it unlikely that co-exposure was consistent across all 5 jobs in each category.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design and statistical method were appropriate for the research question. A case-control study is the best design to study lung cancers when evaluating many different possible exposures across multiple different jobs. The use of unconditional logistic regression is appropriate for this data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistical power should be sufficient. However, some substantial exposure categories had a small number of subjects.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the unconditional logistic regression analysis used for estimates of odds ratios and the confounders included is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.

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Study Citation:	Vizcaya, D; Christensen, KY; Lavoue, J; Siemiatycki, J (2013). Risk of lung cancer associated with six types of chlorinated solvents: Results from two case-control studies in Montreal, Canada Occupational and Environmental Medicine, 70(2), 81-85
Data Type:	occupational case-control study Montreal (CCl4 any exposure Study II analysis extraction)-Cancer
HERO ID:	2128435

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for calculating the risk estimates (i.e. odds ratios) is transparent and the model assumptions were met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.9	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 10: **Morales-Suárez-Varela et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Morales-Suárez-Varela, MM; Olsen, J; Villeneuve, S; Johansen, P; Kaerlev, L; Llopis-González, A; Wingren, G; Hardell, L; Ahrens, W; Stang, A; Merletti, F; Gorini, G; Aurrekoetxea, JJ; Févotte, J; Cyr, D; Guénel, P (2013). Occupational exposure to chlorinated and petroleum solvents and mycosis fungoides Journal of Occupational and Environmental Medicine, 55(8), 924-931
Data Type:	Case-Control_Occupational_CCl4_MycosisFungoides_OR_aboveMedian_All-Cancer
HERO ID:	2129849

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	140 cases ascertained from requests to hospitals and pathology department, as well as regional/national cancer and pathology registers. Patients from 6 European countries: Denmark, Sweden, France, Germany, Italy, and Spain. Controls from these countries selected from population registries or colon cancer registries. As such, the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Moderate attrition due to patents removed from study due to unconfirmed diagnosis (22) or lack of availability for interview (18); participation rate of 84.75%. Of the eligible controls, 68.2% (3156) were interviewed; only controls within the strata (5 year age + gender) of MF patients used (2846).
	Metric 3:	Comparison Group	High	× 0.2	0.2	Key elements of the study design are reported indicate that that cases and controls were similar (e.g., recruited from the same eligible population with the number of controls described, and eligibility criteria and are recruited within the same time frame. Specifically, 4 controls/case, frequency matched by sex and age (5 years). Population registries and electoral rolls used to select controls in Denmark, Sweden, France, Germany and Italy. Spanish controls from colon cancer patients (no population register).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Interviews with standardized questionnaires to determine occupational history. Next of kin completed interviews for 4 cases and 95 controls. Exposure determined with JEM developed by the French Institute of Health Surveillance using jobs/industries assigned based on interviews by trained coders using international standards.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reports only 2 levels of exposure for CCl4 (exposed/unexposed)

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Study Citation:	Morales-Suárez-Varela, MM; Olsen, J; Villeneuve, S; Johansen, P; Kaerlev, L; Llopis-González, A; Wingren, G; Hardell, L; Ahrens, W; Stang, A; Merletti, F; Gorini, G; Aurrekoetxea, JJ; Févotte, J; Cyr, D; Guénel, P (2013). Occupational exposure to chlorinated and petroleum solvents and mycosis fungoides Journal of Occupational and Environmental Medicine, 55(8), 924-931
Data Type:	Case-Control_Occupational_CCl4_MycosisFungoides_OR_aboveMedian_All-Cancer
HERO ID:	2129849

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established and the interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows. Specifically, the authors considered lag times of 5, 10, or 15 years, which did not make an impact (results not presented).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Clinical and pathological mycosis fungoides (MF) diagnosis from cancer/pathology registers and requests of hospitals, using ICD codes. All diagnosis were reviewed by the same pathologist for adherence to morphological and topographical MF criteria; 22 cases were excluded on this basis.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The results discussed in the introduction/methods were fully provided and extractable. All of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of cases and controls reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Confounders considered in adjusted analysis: age, sex, country, current smoking habit (cigarettes/day), alcohol intake, BMI, and education level.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders were assessed using a less-established method with no reporting of validation against well-established methods. Specifically, covariates were determined from interviews. Next of kin completed interviews for 4 cases and 95 controls.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were not accounted for in this analysis, but no direct evidence that co-exposures differ across cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control design was appropriate for investigating chlorinated solvents and a rare disease such as MF, and appropriate statistical methods (logistic regression) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	100 cases and 2846 controls. Exposed cases relatively low (27 trichloroethylene, 6 perchloroethylene, 9 methylene chloride), but sufficient to detect an effect.

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Study Citation:	Morales-Suárez-Varela, MM; Olsen, J; Villeneuve, S; Johansen, P; Kaerlev, L; Llopis-González, A; Wingren, G; Hardell, L; Ahrens, W; Stang, A; Merletti, F; Gorini, G; Aurrekoetxea, JJ; Févotte, J; Cyr, D; Guénel, P (2013). Occupational exposure to chlorinated and petroleum solvents and mycosis fungoides Journal of Occupational and Environmental Medicine, 55(8), 924-931
Data Type:	Case-Control_Occupational_CCl4_MycosisFungoides_OR_aboveMedian_All-Cancer
HERO ID:	2129849

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The model used for calculating risk estimate (i.e., odds ratios using logistic regression) is fully appropriate. Rationale for covariate selection is not provided, but model assumptions do not appear to be violated.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 11: **Heck et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_CCl4_Neuroblastoma_OR_IQR_2_5km-Cancer
HERO ID:	2225094

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Authors included all cases of neuroblastoma listed in the California Cancer Registry (1990-2007).
	Metric 2:	Attrition	Low	× 0.4	1.2	The study attained a 89% matching rate to California birth certificate (probabilistic linkage program (LinkPlus, Atlanta, GA) and included up to 75 cases and 14,602 controls (depending on the air toxic evaluated as exposure), who lived within 5 km of an air toxics monitor. According to the authors, excluded children (781 cases and 146,763 controls) were more likely to live in a rural county (20% vs. 4%), to have a mother who was White non-Hispanic (35% vs. 26%) and to be born in the US(56% vs. 50%).
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Controls randomly selected from California birth records (no cancer diagnosis before age 6), frequency matched by year of birth; excluded children who had died of other causes prior to age 6. Large number excluded due to missing information on length of gestation. In general, demographic characteristics of cases and controls were similar but there were some differences, for example, in ethnicity (e.g. 40% cases were White non-Hispanic vs 26.1% controls) and neighborhood socio-economic index (e.g. 18.7% of cases vs 29.2% of controls in lowest level).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure based on data from community-based air pollution monitors for participants living within 5 km of an air pollution monitor. For participants born in the period 1998-2007, geocoding based on exact home address, but for those born in 1990-1997, geocoding based on zipcode (potential for exposure misclassification). Additional potential source of bias due to assumption that birth certificate address was consistent throughout the pregnancy.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Exposure-response estimate obtained for several air toxics, including CCl4, Perc and TCE, for interquartile range and in some cases for across quartiles, considering different buffer sizes (5km, 4km, 3km, 2.5 km) around air toxics' monitors.

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Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_CCl4_Neuroblastoma_OR_IQR_2_5km-Cancer
HERO ID:	2225094

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure assessed for full extent of pregnancy and for each trimester. Neuroblastoma has a high incidence in infants, so assessing though 6 years old is appropriate.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Outcome assessed using International Classification of Childhood Cancer, version3 (ICCC-3) code 041 as reported in the California Cancer Registry, but diagnosis was not confirmed. It is not clear if absence of cancer diagnosis in controls was confirmed.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	For CCl4, both OR for IQR at different buffer sizes (2.5km, 3km, 4km, and 5km) and for each quartile (vs. 1st quartile) are reported; however, when reporting results for each quartile it is not clearly stated whether or not these are for the 5km buffer size. For Perc and TCE, OR per interquartile increase reported only for two buffer sizes (2.5km and 5 km) and results for each quartile are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Selection of potential confounders was based on literature review and relationship in sample between demographic and perinatal factors and outcome. Several relevant covariates were considered and retained in final analysis [mother's age, mother's race/ethnicity, birth year, socioeconomic indicator (method of payment for prenatal care)]. However, other potential confounders noted as relevant by the authors in the Introduction section (e.g. birthweight, maternal and paternal alcohol intake and smoking status, paternal occupational exposures) were not evaluated.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Demographic and socio-economic data obtained from birth certificates (mother's age, mother's race/ethnicity, birth year) and US Census data (socio-economic data). SES was assessed through both insurance type and census tract data.

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Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_CCl4_Neuroblastoma_OR_IQR_2_5km-Cancer
HERO ID:	2225094

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures to pollutants were measured but not adjusted for in the regression models. Authors state that, according to cited study (Heck et al., in press), they found that Perc was highly correlated with traffic-related toxics, while other air toxics "were not as strongly correlated with each other." No differences expected between exposure groups.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A case-control study design was used to evaluate the relationship between prenatal exposure to air toxics (CCl4, PERC, TCE) and neuroblastoma (childhood cancer). Logistic regression was used to determine OR for IQR of increase in exposure to each air toxic and, for CCl4, the OR for each quartile relative to the lowest quartile of exposure was also evaluated.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistically significant effects were determined for some air toxics using each respective sample size, but no statistical power was reported. For CCl4, the analysis included 40 cases and 7443 controls, for Perc 67 cases and 12041 controls were included and for TCE 67 cases and 12086 controls were included, for a 5km radius around air pollution monitors.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Detailed description of statistical analysis provided. The covariates adjusted for in the logistic regression explicitly stated for each model. Number of cases/controls used in each analysis presented for 5km and 2.5 km radii.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression appropriately used to determine ORs. Study presents models adjusted just for birth year, or for all confounders that were collected (birth year, maternal age, maternal race/ethnicity, and method of payment - SES). Potential confounders identified from literature and in a previous study (Heck 2009).
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	

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Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_CCl4_Neuroblastoma_OR_IQR_2_5km-Cancer
HERO ID:	2225094

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		2.0	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 12: **Davis 1934: Evaluation of Hematological and Immune Outcomes**

Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_hematology-Hematological and Immune
HERO ID:	3611

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	Low	× 0.4	1.2	Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided.
Metric 2:	Attrition	Medium	× 0.4	0.8	Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described.
Metric 3:	Comparison Group	Low	× 0.2	0.6	No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments.
Metric 5:	Exposure levels	Low	× 0.2	0.6	Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration.
Metric 6:	Temporality	Low	× 0.4	1.2	This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride.
Domain 3: Outcome Assessment					

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Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_hematology-Hematological and Immune
HERO ID:	3611

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Outcomes were outlined throughout the paper and clinical observations were described.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates, besides age, were not collected.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There was no indication of co-exposures being present or measured for during the controlled inhalation exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Low	× 0.25	0.75	The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported.
	Metric 15:	Statistical models	Not Rated	NA	NA	Results were compared to reference values and described qualitatively only.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	

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Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_hematology-Hematological and Immune
HERO ID:	3611

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Low		2.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 13: **Mattei et al. 2014: Evaluation of Cancer Outcomes**

Study Citation:	Mattei, F; Guida, F; Matrat, M; Cenée, S; Cyr, D; Sanchez, M; Radoi, L; Menvielle, G; Jellouli, F; Carton, M; Bara, S; Marrer, E; Luce, D; Stücker, I (2014). Exposure to chlorinated solvents and lung cancer: Results of the ICARE study Occupational and Environmental Medicine, 71(10), 681-689
Data Type:	ICARE cohort (CCl4 women CEI 1)-Cancer
HERO ID:	2799644

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	This is a is French multi-center population-based case-control study conducted from 2001-2007. It included a cancer registry. Case recruitment was performed in collaboration with the French network of cancer registries. Population-based controls were selected by incidence density sampling. All steps of the participation were provided.
	Metric 2: Attrition	Medium	× 0.4	0.8	All attrition was clearly recorded. 10% of eligible cases could not be located. 16% died, and 5% could not be interviewed because of health status. 87% of those remaining agreed to participate. 94% of eligible controls were contacted and 81% agreed to participate. There were a few subjects that were not included in the analysis based on the numbers in the table with out explanation, but this was <10%.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls were selected based on incidence density sampling and were frequency matched to cases by gender and age with further stratification to make SES distribution comparable to the general population living in the departments. Cases were more likely to be current smokers, but this was addressed in the analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Data was collected via a questionnaire. For each job held for at least 1 month, information was collected on the tasks and specific exposures of interest. TCE was the only chlorinated solvent specifically listed and Perc was stated to be the one agent that was self-reported. Chlorinated solvents were assessed using a JEM. For each combination of ISCO and NAF codes, JEM assigned three indices of exposure 1) probability of exposure, 2) intensity of exposure, and 3) frequency of exposure. JEM provided an average level of exposure during a usual work day. Cumulative Exposure Index (CEI) was calculated and transformed into categorical variables. However, it appears that exposure is solely based on self-report and professional judgement.

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Study Citation:	Mattei, F; Guida, F; Matrat, M; Cenée, S; Cyr, D; Sanchez, M; Radoi, L; Menvielle, G; Jellouli, F; Carton, M; Bara, S; Marrer, E; Luce, D; Stücker, I (2014). Exposure to chlorinated solvents and lung cancer: Results of the ICARE study Occupational and Environmental Medicine, 71(10), 681-689
Data Type:	ICARE cohort (CCl4 women CEI 1)-Cancer
HERO ID:	2799644

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Each chemical had at least 3 levels (control + 2 or more CEI levels)
	Metric 6:	Temporality	Low	× 0.4	1.2	The temporality of exposure and outcome is uncertain.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	All cases were histologically confirmed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Sufficient details were provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Confounders adjusted for included age at interview, department, smoking history, number of jobs, and SES. Genders were evaluated separately.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained from a questionnaire without reporting reliability or validity of the questionnaire.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Exposure to asbestos was adjusted for in the analysis. It was noted that exposure to one solvent did not preclude exposure to the others, subjects were categorized in into mutually exclusive exposure groups according to various combinations of specific solvents. Combinations were evaluated separately. However, it appears that there may be too much correlation between exposure to some chemicals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Method is acceptable.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Likely sufficient.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Information was sufficient.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Methods are transparent and assumptions were met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	

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Study Citation:	Mattei, F; Guida, F; Matrat, M; Cenée, S; Cyr, D; Sanchez, M; Radoi, L; Menvielle, G; Jellouli, F; Carton, M; Bara, S; Marrer, E; Luce, D; Stücker, I (2014). Exposure to chlorinated solvents and lung cancer: Results of the ICARE study Occupational and Environmental Medicine, 71(10), 681-689
Data Type:	ICARE cohort (CCl4 women CEI 1)-Cancer
HERO ID:	2799644

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Overall Quality Determination‡		Medium		1.8	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 14: **Garcia et al. 2015: Evaluation of Cancer Outcomes**

Study Citation:	Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14
Data Type:	Cohort_CCl4_CTS_BreastCancer_Q4-Cancer
HERO ID:	3014082

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	High	× 0.4	0.4	California Teachers Study including active and retired female teachers and administrators were enrolled in the California State Teachers Retirement System and completed a questionnaire. Study population was comprised on 5676 women. All participants were included using the same inclusion and exclusion criteria.
Metric 2:	Attrition	High	× 0.4	0.4	Large sample of study population excluded due to women who were not residing in California at baseline, had unknown history of prior cancer, had prior history of invasive or in situ breast cancer, asked to be removed from study after joining, or had an address that couldn't be geocoded. This represents adequate explanation of attrition and is not expected to bias the results.
Metric 3:	Comparison Group	High	× 0.2	0.2	Cases and controls were stated to be similar. Covariates that were different between groups were considered and included as covariates in the final model., including a term for grouped personal risk factors.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	NATA identified and prioritized the air toxicants with respect to their potential population health risks. The first NATA was conducted based on 1996 emissions. EPA models annual ambient HAP concentrations using the Assessment System for Population Exposure Nationwide (ASPEN). This is a well-established method of determining exposure., but may lead to some non-differential exposure misclassification.
Metric 5:	Exposure levels	Medium	× 0.2	0.4	By examining each compound individually, they categorized them into four quantiles of concentration without including exposure from any other compound in the model. Level of exposure adequate. Included four quantiles of exposure, Q1 being no exposure.

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Study Citation:	Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14
Data Type:	Cohort_CCl4_CTS_BreastCancer_Q4-Cancer
HERO ID:	3014082

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Chose to use the 2002 ambient air concentration estimates for this study because that year was approximately the mid-point for the follow up period. Decided against combining multiple years of estimate due to inconsistent methodical approaches and temporal variations in the level of agreement between years of the assessments which could introduce exposure misclassification.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	CTS cohort is followed annually for cancer diagnosis, death, and change of address. Annual linkage between CCR and cohort membership was used to identify incident cancer rates. Defined a case as any woman diagnosed with invasive breast cancer (ICD-03 site codes C500-C509, excluding those with histology codes for 9050-9055, 9140, and 9590-9992) after the date they completed their baseline questionnaire through Dec 31, 2011.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	CCR maintains high standards for data quality and completeness and is estimated to be 99% complete. Ascertained date and cause of death from mortality files as well as reports from relatives.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	All models were stratified by age and adjusted either for race alone or for race and personal risk factors of interest. For each compound, p-values no each non-degenerative quantile HR were adjusted for multiple testing across the ten subsets using False Discovery Rates.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were obtained from the CTS baseline questionnaire. This was self-reported information, but there is no evidence to suggest that it is not a valid method of obtaining covariate information.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	No indication of unbalanced co exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Cohort was appropriate study design. Examined the relationship between risk of breast cancer and numerous compounds of interest. Used two different methods of parameterizing exposure in the models.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Number of subjects for estimated exposure was 5676 women. There were enough subjects to detect effects for some chemicals and for some trends.

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Study Citation:	Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14
Data Type:	Cohort_CCl4_CTS_BreastCancer_Q4-Cancer
HERO ID:	3014082

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Study design and methods can be reproducible with information provided. Provided reasoning on how categories were created for exposure quantiles, why covariates were used. Covariates included in the models are reported explicitly.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Used COX proportional hazard models to estimate hazard rate ratios. Parameterized exposures into quantiles, modeled exposure as a continuous variable, and tested for non-zero slope using a likelihood ratio test.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.5	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 15: **Carton et al. 2017: Evaluation of Cancer Outcomes**

Study Citation:	Carton, M; Barul, C; Menvielle, G; Cyr, D; Sanchez, M; Pilorget, C; Trétarre, B; Stücker, I; Luce, D (2017). Occupational exposure to solvents and risk of head and neck cancer in women: A population-based case-control study in France British Medical Journal Open, 7(1), e012833
Data Type:	ICARE_CCl4_HeadNeckCancer_OR_EverExposure-Cancer
HERO ID:	3480125

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	296 cases of head and neck squamous cell carcinomas and 775 controls were drawn from ICARE, a French population-based case-control study (Luce 2011, HERO ID 1022113). Only women.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Participation rates in initial ICARE study were 82.5% for cases and 80.6% for controls. Restricting to only females with squamous cell carcinomas in areas of interest led to 296 cases and 755 controls.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls selected from general population based on age, geographic region and SES. However, there are statistically significant differences in terms of age, geographic region, SES, smoking and alcohol consumption. These covariates are all considered in the analysis. Cases ~2 years younger than controls, lower SES, and more likely to smoke or drink alcohol.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Employment history from in person interviews and questionnaires. Employment of 1+ month coded by trained coders blinded to status using International Standard Classification of Occupations and the Nomenclature des Activités Françaises. Job-exposure matrix from French Institute of Health Surveillance to predict exposure probability, intensity, and frequency.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Analysis includes dichotomous ever/never exposed, as well as continuous exposure intensity, exposure duration and cumulative exposure indices.
	Metric 6:	Temporality	Low	× 0.4	1.2	Time between potential occupational exposure and diagnosis not stated.
Domain 3: Outcome Assessment						

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Study Citation:	Carton, M; Barul, C; Menvielle, G; Cyr, D; Sanchez, M; Pilorget, C; Trétarre, B; Stücker, I; Luce, D (2017). Occupational exposure to solvents and risk of head and neck cancer in women: A population-based case-control study in France British Medical Journal Open, 7(1), e012833
Data Type:	ICARE_CCl4_HeadNeckCancer_OR_EverExposure-Cancer
HERO ID:	3480125

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases identified from cancer registries in 10 geographical regions of France. Histologically confirmed diagnosis from 2001-2007 in women aged 18-85. ICD-O-3 codes were used to identify squamous cell carcinomas in oral cavity, oropharynx, hypopharynx, oral cavity, and larynx (detailed list of codes in text).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of relevant outcomes (head and neck cancers in women) from the abstract/methods are provided and extractable.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Analyses adjusted for geographical area, age, smoking status, tobacco consumption (pack-years) and alcohol consumption. Interaction terms for smoking and alcohol were also included. SES considered with last occupation and longest occupation, but did not impact ORs and were not presented.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	In person interviews with standardized questionnaire.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Exposures to TCE, Perc, and DCM were strongly correlated. Rather than adjusting for co-exposures, exclusive exposure to individual and combinations of chlorinated solvents were analyzed.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Logistic regression was used appropriately to estimate ORs and CIs.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort contains sufficient participants to detect an effect for TCE, perc, and DCM. Insufficient data for carbon tetrachloride, so it was excluded from analysis beyond an ever/never OR. For analysis involving ever exposure to CCL4, the number of cases and controls is relatively small.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Although the process of creating the regression models was described in detail, adjustments used for covariates were not explicitly stated.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratios and 95% confidence intervals were determined using unconditional logistic regression adjusted for key covariates. Models were transparent and assumptions were met.

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Study Citation:	Carton, M; Barul, C; Menvielle, G; Cyr, D; Sanchez, M; Pilorget, C; Trétarre, B; Stücker, I; Luce, D (2017). Occupational exposure to solvents and risk of head and neck cancer in women: A population-based case-control study in France British Medical Journal Open, 7(1), e012833
Data Type:	ICARE_CCl4_HeadNeckCancer_OR_EverExposure-Cancer
HERO ID:	3480125

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure		NA	NA	
	Metric 17: Effect biomarker		NA	NA	
	Metric 18: Method Sensitivity		NA	NA	
	Metric 19: Biomarker stability		NA	NA	
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		1.8	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 16: **Nelson et al. 2012: Evaluation of Cancer Outcomes**

Study Citation:	Nelson, JS; Burchfiel, CM; Fekedulegn, D; Andrew, ME (2012). Potential risk factors for incident glioblastoma multiforme: The Honolulu Heart Program and Honolulu-Asia Aging Study Journal of Neurooncology, 109(2), 315-321
Data Type:	HHP-HAAS_CCL4_glioblastoma_high occupational-Cancer
HERO ID:	3481852

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Cohort of aging men of Japanese ancestry born between and 1900 and 1919 and between age 45-68 at time of initial examination (1965-1968). Participants identified through WWII selective service records. Of 14,426 men estimated to be Oahu residents, 11,148 were located and 8,006 completed a baseline examination (>70% of target population).
	Metric 2: Attrition	High	× 0.4	0.4	Participants followed through series of six follow-up examinations from 1968-2000, and less than 1% lost to follow-up (5/8,006). Occupational exposure data available for entire cohort based on information collected in first and third examinations.
	Metric 3: Comparison Group	High	× 0.2	0.2	Participants identified through WWII selective service records. All were born between 1900-1919 and were aged 45-68 at time of initial examination (1965-1968). There is no evidence that participants were not similar in health status.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Participants reported present and usual jobs and years worked at these jobs during the first and third examinations. Jobs were coded according to U.S. Bureau of the Census and unique occupation/industry combinations were identified and independently assessed by three industrial hygienists. Likelihood of exposure was assigned by consensus as none, low, medium, and high. An intensity score was calculated using the likelihood of exposure multiplied by number of years worked in usual occupation.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	Exposure levels categorized as none, low or medium, and high, but corresponding numerical levels not presented.
	Metric 6: Temporality	Medium	× 0.4	0.8	Exposure based on responses during first and third examinations (1965-1968 and 1971-1974). GBM developed during the follow-up periods between 1974-1995. However, unclear whether exposures fall within relevant exposure window for outcome.
Domain 3: Outcome Assessment					

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Study Citation:	Nelson, JS; Burchfiel, CM; Fekedulegn, D; Andrew, ME (2012). Potential risk factors for incident glioblastoma multiforme: The Honolulu Heart Program and Honolulu-Asia Aging Study Journal of Neurooncology, 109(2), 315-321
Data Type:	HHP-HAAS_CCL4_glioblastoma_high occupational-Cancer
HERO ID:	3481852

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	All GBM cases were confirmed by histological examination. The source of initial diagnosis was not reported, but is assumed to have come from follow-up examinations, hospital discharge records, and/or death certificates or searches of the National Death Index.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	HR and 95% CI reported for outcome outlined. Number of cases and non-cases also reported for each analysis. All outlined statistical analyses were reported with sufficient detail.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjustment methods not explicitly described, but were made for other risk factors included in the model (age, education, triceps skinfold, sugar consumption, coffee consumption, tea consumption, chest surgery, blood transfusion).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Basic demographic, occupational and socioeconomic data, medical history (chest surgery, blood transfusion, herpes), and lifestyle factors including usual physical activity, smoking habits, alcohol intake, and dietary habits identified from questionnaires completed from the first three examinations (self-reported), but no report of validation. Exposure based on self-report of jobs and classification by independent industrial hygienists. Additional risk factors (e.g., tricep skinfold thickness) were assessed during the first three examinations, but no detailed description of methods provided.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Cases and non-cases were similar in exposure to solvents, pesticides, and metals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design (prospective cohort) and statistical methods (including a multivariate analysis to estimate the hazard ratio associated with exposure to CCl4, using the Cox proportional hazards regression model) were appropriate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Cohort size (8,006) is sufficient to detect an effect, but only 9 cases resulting in low statistical power.

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Study Citation:	Nelson, JS; Burchfiel, CM; Fekedulegn, D; Andrew, ME (2012). Potential risk factors for incident glioblastoma multiforme: The Honolulu Heart Program and Honolulu-Asia Aging Study Journal of Neurooncology, 109(2), 315-321
Data Type:	HHP-HAAS_CCL4_glioblastoma_high occupational-Cancer
HERO ID:	3481852

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Exact logistic regression relating to each potential risk factor was performed to obtain exact p-values which were then used to assess linear trend. Multivariate analysis performed using Cox proportional hazards regression model to estimate hazard ratio.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Model assumptions were described and met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.7	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 17: **Purdue et al. 2016: Evaluation of Cancer Outcomes**

Study Citation:	Purdue, MP; Stewart, PA; Friesen, MC; Colt, JS; Locke, SJ; Hein, MJ; Waters, MA; Graubard, BI; Davis, F; Ruterbusch, J; Schwartz, K; Chow, WH; Rothman, N; Hofmann, JN (2016). Occupational exposure to chlorinated solvents and kidney cancer: A case-control study Occupational and Environmental Medicine, 74(4), 268-274
Data Type:	Case-control study of kidney cancer in workers exposed to chlorinated solvents - CCl4_90% OR-Cancer
HERO ID:	3482059

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Selection factors unlikely to be related to CCl4 exposures
	Metric 2:	Attrition	Medium	× 0.4	0.8	77% participation in cases; 54% participation in controls; rationale was provided.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Age-, gender- and race-matched controls.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Job exposure matrix
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Indicators of probability, frequency and intensity; tertiles for cumulative hours exposed.
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure lagged to account for cancer latency.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases identifies by cancer surveillance system and many histologically confirmed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Odds ratios reported with 95% confidence intervals for kidney cancer and exposure to TCE, CCL4, DCM and Perc
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for age, sex, race, study centre, education level, smoking status, BMI and history of hypertension.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Some covariate information was self-reported (smoking, hypertension, race)
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	TCE exposure did not confound Perc results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control study used to evaluate occupational TCE, Perc, DCM, and CCl4 exposure and kidney cancer.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Between Medium and Unacceptable, Medium is the better characterization. An elevated risk of TCE was detected - it just wasn't stat sig.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Odds ratios calculated with unconditional logistic regression.

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Study Citation:	Purdue, MP; Stewart, PA; Friesen, MC; Colt, JS; Locke, SJ; Hein, MJ; Waters, MA; Graubard, BI; Davis, F; Ruterbusch, J; Schwartz, K; Chow, WH; Rothman, N; Hofmann, JN (2016). Occupational exposure to chlorinated solvents and kidney cancer: A case-control study Occupational and Environmental Medicine, 74(4), 268-274
Data Type:	Case-control study of kidney cancer in workers exposed to chlorinated solvents - CCl4_90% OR-Cancer
HERO ID:	3482059

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Medium	× 0.2	0.4	Adjustments used in determining ORs clearly stated.
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure		NA	NA	
	Metric 17: Effect biomarker		NA	NA	
	Metric 18: Method Sensitivity		NA	NA	
	Metric 19: Biomarker stability		NA	NA	
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		High		1.4	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 18: **Tomenson et al. 1995: Evaluation of Hepatic Outcomes**

Study Citation:	Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type:	No-direct-CCL4-exposure_workers_ALT-hepatotoxicity-Hepatic
HERO ID:	3688717

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Authors reported that the study group consisted of 135 workers, 83% of those eligible for inclusion. These workers were from 3 sites in the northwest of England who had worked on one of the processes with full exposure to carbon tetrachloride. The controls consisted of 276 workers from the same plants but had no risk of exposure to carbon tetrachloride or other hepatotoxic chemicals. It was reported that the study and control groups were well matched for age, height, weight, type of job, and alcohol consumption. The authors did not report the sex of the workers and a table was provided providing evidence that the alcohol consumption was similar between the exposed and control groups, and the ages of both groups were roughly normally distributed, but no evidence on the other covariates was provided.
	Metric 2: Attrition	High	× 0.4	0.4	The authors reported that there were 135 workers in the study group (83% of those eligible for inclusion) and 276 in the control group (77% of the total). The authors stated that a short questionnaire was given to all study and control workers in advance of the study and was used to select eligible participants. The authors stated that the exposed workers had to have potential exposure to carbon tetrachloride either as full-time or on a regular basis. Workers were excluded from the control group if they had worked in or on any of a predefined list of workplaces where there was potential for exposure to carbon tetrachloride over the past 5 years.

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Study Citation: Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type: No-direct-CCL4-exposure_workers_ALT-hepatotoxicity-Hepatic
HERO ID: 3688717

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The authors stated that the study and control groups were well matched for age, height, weight, type of job, and alcohol consumption, however no evidence was provided for this other than a table for alcohol consumption, which was not divided by exposure level (only showed study and controls). In addition, the study group and the controls were from one of the same sites, however the controls were also from an additional site located nearby where carbon tetrachloride was not handled, which may have resulted in some differences between the 2 groups.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposure was estimated based on historical monitoring data for each job category. According to the estimate, study group members were categorized as having high, medium, or low exposure to carbon tetrachloride. Most work groups had historical personal monitoring data and the mean of these results was calculated. For groups of workers where no monitoring data had taken place, categorization was done by judgment of likely exposure from comparison with other groups. This judgment was done by a professional industrial hygienist in association with each plant manager.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	There were 4 exposure categories: mean results of none, low (1 ppm or less), medium (1 - 3 ppm), or high (4 ppm or more) . This distribution of exposure is adequate to determine an exposure-response relationship.
	Metric 6:	Temporality	High	× 0.4	0.4	The outcome assessed, hepatic effects, was based on blood analysis for all workers and controls. The exposure to carbon tetrachloride was assessed based on work history which was obtained from a questionnaire that also contained a question on the length of service in a job exposed to carbon tetrachloride. This information is sufficient to establish a time order for exposure and outcome.
Domain 3: Outcome Assessment						

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Study Citation: Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type: No-direct-CCL4-exposure_workers_ALT-hepatotoxicity-Hepatic
HERO ID: 3688717

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcomes assessed were hepatic enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase, glutamyl transferase, total bile acids, and 5-nucleotidase), that were measured in the blood. These tests are well established and have been used in clinical practice for many years.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	All of the outlined analyses are presented in the results table. There was no adjustment made for covariates., but the authors reported that the controls and workers were well matched for age, height, weight, type of job, and alcohol consumption. However, alcohol consumption could have been a significant factor that affected the results because the study did not evaluate the difference between exposure groups in terms of alcohol consumption.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	The authors stated that the study group and the controls were well matched for age, height, weight, type of job, and alcohol consumption. However, the study was scheduled to start in November 1986 but after a 2 week period of sample collection (about 60 subjects) there was a problem with the availability of controls due to a plant breakdown. It was decided to restart the study in February 1987 and the rest of the samples were taken during a period of about 8 weeks. Therefore, it is possible that the results could be different between the samples taken in November and those in February. The authors analyzed for a synergistic reaction between exposure to carbon tetrachloride and alcohol consumption was examined by including an interaction term between the two factors in the linear model.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	The confounders were assessed based on a questionnaire that was given by one occupational health nursing officer trained for this purpose, but the authors don't report that the questionnaire was validated.

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Study Citation: Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type: No-direct-CCL4-exposure_workers_ALT-hepatotoxicity-Hepatic
HERO ID: 3688717

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The exposure to potential co-exposures was assessed based on the work history of the workers and controls. Workers were excluded from the control group if they had worked in or on any of a predefined list of workplaces were there was exposure to carbon tetrachloride or other known hepatotoxins during the previous 5 years; therefore the potential for exposure to other chemicals appear minimal.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cross-sectional design appears to be appropriate for the question of whether carbon tetrachloride exposure is associated with hepatotoxic effects.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants, 135 workers and 276 controls, appears adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to be understandable and reproducible. The results were presented as the geometric means after logarithmic transformation for each exposure group.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Linear models were fitted to the logarithmically transformed data. The terms in the model included exposure category, age, sampling time, and measure of alcohol consumption.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	Of the biomarkers examined, only ALT is specific to the liver. AST can also be associated with the liver, but it could indicate damage to another organ. Both of these biomarkers measure tissue damage but do not measure functional changes to the liver.
	Metric 18:	Method Sensitivity	Low	× 0.2	0.6	Analytical methods measured biomarkers are adequately reported. No LOQ/LOD reported.
	Metric 19:	Biomarker stability	Low	× 0.2	0.6	On the morning of collection, blood samples were transported to the ICI central toxicology lab for analysis; samples were taken from roughly the same ratio of study and control participants; stability was not stated. To minimize any effect of laboratory variation, blood samples were taken from a roughly constant ratio of study and control group subjects on each day.

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Study Citation:	Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type:	No-direct-CCL4-exposure_workers_ALT-hepatotoxicity-Hepatic
HERO ID:	3688717

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 20:	Sample contamination	Low	× 0.2	0.6	There are no known or measured contamination issues.
	Metric 21:	Method requirements	High	× 0.2	0.2	Instrumentation allows for the biomarker with a high degree of confidence. Biochemical variables measured with Vitatron PA800 analyser or a Kone CD analyser.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 19: **Tomenson et al. 1995: Evaluation of Hematological and Immune Outcomes**

Study Citation:	Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type:	High-CCL4-exposure_workers_hemaglobin-Hematological and Immune
HERO ID:	3688717

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Authors reported that the study group consisted of 135 workers, 83% of those eligible for inclusion. These workers were from 3 sites in the northwest of England who had worked on one of the processes with full exposure to carbon tetrachloride. The controls consisted of 276 workers from the same plants but had no risk of exposure to carbon tetrachloride or other hepatotoxic chemicals. It was reported that the study and control groups were well matched for age, height, weight, type of job, and alcohol consumption. The authors did not report the sex of the workers and a table was provided providing evidence that the alcohol consumption was similar between the exposed and control groups, and the ages of both groups were roughly normally distributed, but no evidence on the other covariates was provided.
	Metric 2: Attrition	High	× 0.4	0.4	The authors reported that there were 135 workers in the study group (83% of those eligible for inclusion) and 276 in the control group (77% of the total). The authors stated that a short questionnaire was given to all study and control workers in advance of the study and was used to select eligible participants. The authors stated that the exposed workers had to have potential exposure to carbon tetrachloride either as full-time or on a regular basis. Workers were excluded from the control group if they had worked in or on any of a predefined list of workplaces where there was potential for exposure to carbon tetrachloride over the past 5 years.

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Study Citation: Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type: High-CCL4-exposure_workers_hemaglobin-Hematological and Immune
HERO ID: 3688717

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The authors stated that the study and control groups were well matched for age, height, weight, type of job, and alcohol consumption, however no evidence was provided for this other than a table for alcohol consumption, which was not divided by exposure level (only showed study and controls). In addition, the study group and the controls were from one of the same sites, however the controls were also from an additional site located nearby where carbon tetrachloride was not handled, which may have resulted in some differences between the 2 groups.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposure was estimated based on historical monitoring data for each job category. According to the estimate, study group members were categorized as having high, medium, or low exposure to carbon tetrachloride. Most work groups had historical personal monitoring data and the mean of these results was calculated. For groups of workers where no monitoring data had taken place, categorization was done by judgment of likely exposure from comparison with other groups. This judgment was done by a professional industrial hygienist in association with each plant manager.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	There were 4 exposure categories: mean results of none, low (1 ppm or less), medium (1 - 3 ppm), or high (4 ppm or more) . This distribution of exposure is adequate to determine an exposure-response relationship.
	Metric 6:	Temporality	High	× 0.4	0.4	The outcome assessed, hepatic effects, was based on blood analysis for all workers and controls. The exposure to carbon tetrachloride was assessed based on work history which was obtained from a questionnaire that also contained a question on the length of service in a job exposed to carbon tetrachloride. This information is sufficient to establish a time order for exposure and outcome.
Domain 3: Outcome Assessment						

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Study Citation:	Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type:	High-CCL4-exposure_workers_hemaglobin-Hematological and Immune
HERO ID:	3688717

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcomes assessed were hepatic enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase, glutamyl transferase, total bile acids, and 5-nucleotidase), that were measured in the blood. These tests are well established and have been used in clinical practice for many years.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	All of the outlined analyses are presented in the results table. There was no adjustment made for covariates., but the authors reported that the controls and workers were well matched for age, height, weight, type of job, and alcohol consumption. However, alcohol consumption could have been a significant factor that affected the results because the study did not evaluate the difference between exposure groups in terms of alcohol consumption.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	The authors stated that the study group and the controls were well matched for age, height, weight, type of job, and alcohol consumption. However, the study was scheduled to start in November 1986 but after a 2 week period of sample collection (about 60 subjects) there was a problem with the availability of controls due to a plant breakdown. It was decided to restart the study in February 1987 and the rest of the samples were taken during a period of about 8 weeks. Therefore, it is possible that the results could be different between the samples taken in November and those in February. The authors analyzed for a synergistic reaction between exposure to carbon tetrachloride and alcohol consumption was examined by including an interaction term between the two factors in the linear model.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	The confounders were assessed based on a questionnaire that was given by one occupational health nursing officer trained for this purpose, but the authors don't report that the questionnaire was validated.

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Study Citation:	Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type:	High-CCL4-exposure_workers_hemaglobin-Hematological and Immune
HERO ID:	3688717

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The exposure to potential co-exposures was assessed based on the work history of the workers and controls. Workers were excluded from the control group if they had worked in or on any of a predefined list of workplaces were there was exposure to carbon tetrachloride or other known hepatotoxins during the previous 5 years; therefore the potential for exposure to other chemicals appear minimal.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cross-sectional design appears to be appropriate for the question of whether carbon tetrachloride exposure is associated with hepatotoxic effects.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants, 135 workers and 276 controls, appears adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to be understandable and reproducible. The results were presented as the geometric means after logarithmic transformation for each exposure group.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Linear models were fitted to the logarithmically transformed data. The terms in the model included exposure category, age, sampling time, and measure of alcohol consumption.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	Of the biomarkers examined, only ALT is specific to the liver. AST can also be associated with the liver, but it could indicate damage to another organ. Both of these biomarkers measure tissue damage but do not measure functional changes to the liver.
	Metric 18:	Method Sensitivity	Low	× 0.2	0.6	Analytical methods measured biomarkers are adequately reported. No LOQ/LOD reported.
	Metric 19:	Biomarker stability	Low	× 0.2	0.6	On the morning of collection, blood samples were transported to the ICI central toxicology lab for analysis; samples were taken from roughly the same ratio of study and control participants; stability was not stated. To minimize any effect of laboratory variation, blood samples were taken from a roughly constant ratio of study and control group subjects on each day.

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Study Citation:	Tomenson JA; Baron CE; O'Sullivan JJ (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occupational and Environmental Medicine, (52), 508-514
Data Type:	High-CCL4-exposure_workers_hemaglobin-Hematological and Immune
HERO ID:	3688717

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 20:	Sample contamination	Low	× 0.2	0.6	There are no known or measured contamination issues.
	Metric 21:	Method requirements	High	× 0.2	0.2	Instrumentation allows for the biomarker with a high degree of confidence. Biochemical variables measured with Vitatron PA800 analyser or a Kone CD analyser.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 20: **Dow Chemical, Co 1992: Evaluation of Cancer Outcomes**

Study Citation:	Dow Chemical Company (1992). Nested case-control study of lung cancer among chemical workers
Data Type:	Occupational_case control_CCl4_lung cancer_High Exposure-Cancer
HERO ID:	4215786

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Any former male employee that had one or more years of service between 1940 and Dec 31, 1980. Cases were those who expired of primary lung cancer prior to Dec 1980. Two controls groups were chosen, deceased (died after the case, not more than 5 years) and living (survived at least as long as the case, but could die later), chosen from all other members of the cohort without cancer. Ages were reported. All men. All control cases were matched for age, race, and year of hire to each case.
	Metric 2:	Attrition	High	× 0.4	0.4	Numbers used in the study were explained in detail. 81.9% completed interviews - 734 subjects
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were matched with cases on race, year of birth (+/- 5) and year of hire.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Employee's Dow work history record served as the starting point for categorizing occupation exposures of interest. Used work area and chemical and physical agent exposure profiles. Chemical and physical agent exposure profiles were developed by a certified industrial hygienist (GHF) for each case and control.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	For carbon tetrachloride a degree of exposure ranking (high, moderate, or low) was assigned to each job. This was based on limited industrial hygiene monitoring data and therefore was not possible to estimate exposure
	Metric 6:	Temporality	Medium	× 0.4	0.8	Interviews conducted in 1984 on all employed >1 year between 1940 and 1980 who were selected for study; onset of disease is estimated to be 3-5 years from exposure. Analysis was also completed with incorporation of a 15 year latency period
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Death certificates and hospital records when available. cases must have bronchus, lung or respiratory system as underlying cause, contributing cause, or as other significant condition
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Ns, ORs, and 95% CIs reported
Domain 4: Potential Counfounding/Variable Control						

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Study Citation: Dow Chemical Company (1992). Nested case-control study of lung cancer among chemical workers
Data Type: Occupational_case control_CCl4_lung cancer_High Exposure-Cancer
HERO ID: 4215786

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for smoking, vitamin A consumption, migration patterns, occupational exposures outside the facility, vitamin supplements, education level. Collected confounding variables by telephone interviews with subject or next of kin; age, race, year of hire, death (+/-5 yr) all considered
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Telephone interview to collect information on participants from participant or next of kin (not as accurate as primary data)
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Attempts were made to adjust for confounding exposures; these were collected from phone interviews (smoking status and duration, vitamin A intake, occupational exposures outside the facility, education level)
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design is appropriate for the population/outcomes studied. f eligible workers who worked at the plant for over 1 year between 1940-1980, those who died of or with respiratory disease were assessed for exposures to chemicals and development of lung cancer
	Metric 13:	Statistical power	Medium	× 0.2	0.4	308 and 616-28 overlapping individuals; exposure determined from job titles and bucketed into high, medium and low exposures. Odds ratios determined for CCl4 exposure with 15 year latency and without regard to year of death as well as across levels of occupational exposure.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Methods are clearly laid out and can be reproduced. Cases and controls were compared with traditional stratification and conditional logistic regression. The observation period for each matched set ended at the time of each death of case.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Statistical methods were not outlined, but indirect evidence shows they are adequate (OR reporting, confounder adjustments)
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	

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Study Citation:	Dow Chemical Company (1992). Nested case-control study of lung cancer among chemical workers
Data Type:	Occupational_case control_CCl4_lung cancer_High Exposure-Cancer
HERO ID:	4215786

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		High		1.5	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 21: **Davis 1934: Evaluation of Renal Outcomes**

Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966					
Data Type:	Davis_CCl4_controlled_inhalation_exposure_renal-Renal					
HERO ID:	3611					
Domain		Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration.
	Metric 6:	Temporality	Low	× 0.4	1.2	This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride.
Domain 3: Outcome Assessment						

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Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_renal-Renal
HERO ID:	3611

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Outcomes were outlined throughout the paper and clinical observations were described.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates, besides age, were not collected.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There was no indication of co-exposures being present or measured for during the controlled inhalation exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Low	× 0.25	0.75	The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported.
	Metric 15:	Statistical models	Not Rated	NA	NA	Results were compared to reference values and described qualitatively only.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	

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Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_renal-Renal
HERO ID:	3611

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Low		2.6	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 22: **Davis 1934: Evaluation of Cardiovascular Outcomes**

Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_BP-Cardiovascular
HERO ID:	3611

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration.
	Metric 6:	Temporality	Low	× 0.4	1.2	This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride.
Domain 3: Outcome Assessment						

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Study Citation: P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type: Davis_CCl4_controlled_inhalation_exposure_BP-Cardiovascular
HERO ID: 3611

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Outcomes were outlined throughout the paper and clinical observations were described.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates, besides age, were not collected.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There was no indication of co-exposures being present or measured for during the controlled inhalation exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Low	× 0.25	0.75	The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported.
	Metric 15:	Statistical models	Not Rated	NA	NA	Results were compared to reference values and described qualitatively only.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	

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Study Citation:	P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966
Data Type:	Davis_CCl4_controlled_inhalation_exposure_BP-Cardiovascular
HERO ID:	3611

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Low		2.6	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 23: **Siemiatycki 1991: Evaluation of Cancer Outcomes**

Study Citation:	Siemiatycki, J (1991). Risk factors for cancer in the workplace
Data Type:	CCL4_worker andy exposure_rectal cancer-Cancer
HERO ID:	157954

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Of 4576 eligible male cases from the Montreal metropolitan area were ascertained between 1979-1985, 3730 completed an interview during this study (initiated in 1979 as a case-control design). Each cancer was coded by the International Classification of Disease for Oncology. Of 541 eligible population male controls, 375 were interviewed and selected from random digit calling, the provincial election of 1981, were noncancer patients hospitalized in the same institutions as those with cancer - a subgroup of control cancer cases unrelated to occupational exposure or with cancer at another site deemed not occupationally relevant was also interviewed.
	Metric 2:	Attrition	High	× 0.4	0.4	81.5% of eligible cases completed interviews. 72% of controls. Nonresponses due to refusal, death, no next of kin found, patient discharged, no valid address, psychiatric cases, no translator, or physician refusal
	Metric 3:	Comparison Group	High	× 0.2	0.2	Population controls, hospital controls and cancer controls (cancer control preferred). Baseline characteristics were collected from participants and adjusted for; cases and controls were similar in that they were selected from Montreal, Canada, between 35-70 years old, male and recruited from 1979-1985.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure determined by questionnaire, no occupational records. Chemist-hygienists interview consultants to better grasp the workings of particular industries, occupations were selected and coded as low medium or high concentrations of exposure to a host of chemicals based on job title
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Any or substantial exposure. was assigned to each job title and patients were assigned to one of the two categories for analysis. Assignments made by a chemist-hygienist.
	Metric 6:	Temporality	Low	× 0.4	1.2	Cases aged 35-70, time since first exposure not estimated; study was initiated in 1979 with exposures occurring before or between 1945-1975.
Domain 3: Outcome Assessment						

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Study Citation: Siemiatycki, J (1991). Risk factors for cancer in the workplace
Data Type: CCL4_worker andy exposure_rectal cancer-Cancer
HERO ID: 157954

Domain		Metric	Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histological or autopsy confirmation of primary tumor site.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	ORs with 90% CIs.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	For each association between occupational exposure and cancer type adjustments were made included age, height, place of birth, and race
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders based on literature and questionnaire data.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Adjustments for other occupational exposure types, smoking, and alcohol intake were made.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This is a case-control study that collected cancer type and lifetime occupational history from cancer patients to determine if occupational history effected cancer risk
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Table 1 (PDF page 61, in text page 142) results, selected for associations where power was adequate (# participants and at least 2% exposure).DCM was included in Table 2 which shows elevated ORs only (irrespective of power to detect excess risk).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Analysis was fully described a Mantel-Haenszel analysis was performed to analyze odds ratios for the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Method was transparent. A Mantel-Haenszel analysis was performed to analyze odds ratios for the data. p-values were computed by the Mantel-Haenszel chi-square test
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.7	
Extracted			Yes			

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Study Citation:	Siemiatycki, J (1991). Risk factors for cancer in the workplace
Data Type:	CCL4_worker andy exposure_rectal cancer-Cancer
HERO ID:	157954

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 24: **Heineman et al. 1994: Evaluation of Cancer Outcomes**

Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_CCl4_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Cases were gathered from death certificates of men who died of brain or other central nervous system tumors during 1978 to 1980 in southern Louisiana and 1979 to 1981 in northern New Jersey and Philadelphia, Pennsylvania. Interviews were conducted with next-of-kin regarding occupational information. A total of 300 cases, which reported a hospital diagnosis of astrocytic brain tumor, was used.
	Metric 2: Attrition	Medium	× 0.4	0.8	Among 483 cases with completed interviews (74% of traced next-to-kin) a hospital diagnosis was reported for 300 individuals. 229 cases had been pathologically confirmed. Of the matched controls 66 were excluded due to a possible association between their cause of death and occupational exposure to CAHs. In logistic regression analysis, omitted 30 subjects with electronics-related jobs.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Controls were frequency matched to cases by age, year of death, cause of death other than brain tumor/ cerebrovascular disease/ homicide/ suicide, and study area. 320 total controls.
Domain 2: Exposure Characterization					

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_CCl4_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Matrices were developed by first identifying the industry and occupation considered to entail potential exposure to each of the CAHs based on data from literature, unpublished industrial hygiene reports and inspection and by personal judgement of the project industrial hygienist. Each industry and occupation was assigned a semi-quantitative estimate of probability and of intensity of exposure to each substance. The matrices were then linked to the work histories of the study subjects. Cumulative exposure indices were calculated for each subject. Judgments regarding exposure made by industrial hygienists were based on work histories provided by next-of-kin, who are likely to provide less accurate information then subjects themselves or workplace records. Poor specificity of some work histories for specific solvents and the interchangeability of solvents for many applications probably reduced the accuracy of exposure assignments.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Cumulative exposure score for each subject was calculated as a weight sum of years in all exposed jobs, with weight based on the square of the intensity of exposure (low=1, medium=2, high=3) assigned to each job. Average intensity was calculated over all exposed jobs for each subjects based on same scores without squaring, weighted by duration of employment in each job. Overall probability of exposure was defined as highest probability score for that substance among their jobs.
	Metric 6:	Temporality	Low	× 0.4	1.2	Each industry and occupation was assigned positive or zero decade indicators for each CAH according to the likely use of the substance during each decade between 1920 and 1980 because the use of CAHs has changed over time. Matrices indicated if the exposure was likely to occur by calendar period and probability and intensity of exposure for each industry and each occupation separately. Latency was considered by lagging exposure by 10 or 20 years.
Domain 3: Outcome Assessment						

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_CCl4_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Death certificates were obtained for 741 men who died of brain or other central nervous system tumors (ICD-9 codes 191, 192, 225, 239.7) during 1978 to 1980 in southern Louisiana and 1979 to 1981 in northern New Jersey and Philadelphia, Pennsylvania.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Recall bias was possible.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for age, study area, employment, and probability of exposure to other chemicals of interest for the logistic regression analysis.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Characterized within methods, study population section. Confounders not assessed by method or instrument- used previous analyses to assess. Cases and controls matched by confounding factors (age, study area). Controlled for employment in electronics-related occupations or industries (which was associated with an excess risk of astrocytic brain tumors in a previous analysis).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposure to electromagnetic fields was not assessed or considered in the analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Used appropriate statistical analyses and study design. Retrospective case-control included matrices on likelihood of a certain chemical to have been used in each industry and occupation by decade and provided probability and intensity of exposure level. Cumulative exposure indices were calculated for subjects.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	300 cases and 320 controls were used in the analysis.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	It would be difficult to reproduce this analysis because of the lack of direct information on exposure to various solvents. Information acquired from next-of-kin was likely less accurate then information from the subjects themselves or from industries that could have provided it.

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_CCl4_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Used maximum likelihood estimates of the OR and 95% CI adjusting for age and study area. Used the statistical significance of linear trends by Mantel (1963). Logistic regression was used to evaluate simultaneously the effects of the CAHs.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		2.1	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 25: **Seidler et al. 2007: Evaluation of Cancer Outcomes**

Study Citation:	Seidler, A; Möhner, M; Berger, J; Mester, B; Deeg, E; Elsner, G; Nieters, A; Becker, N (2007). Solvent exposure and malignant lymphoma: A population-based case-control study in Germany Journal of Occupational Medicine and Toxicology, 2 2
Data Type:	>0, <= 2.3 ppm*yrs CCl4_Total Lymphoma-Cancer-Cancer
HERO ID:	194429

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Key elements of study design were reported including description of study area, recruitment methods, and participation rates. Rationale and study design were previously published and cited (Becker et al., 2004, HERO ID 729470). Complete details were reported in that publication. Reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Medium rating: participation rate among cases and controls was 87.4% and 44.3%, respectively (controls were recruited until 710 were selected), minimal exclusion from the analysis sample and outcome data and exposure were largely complete.
	Metric 3:	Comparison Group	High	× 0.2	0.2	High rating: cases and controls were similar, for each case, a gender, region and age-matched (± 1 year of birth) population control was drawn from the population registration office; differences in baseline characteristics of groups were also considered as potential confounding variables and were thereby controlled by statistical analysis
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	High rating: occupational population, questionnaires administered by trained interviewers that allowed for construction of a job-matrix for entire work history of exposure (i.e., cumulative exposures).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Medium rating: exposure was based on intensity ranging from 0.5 to >100 ppm and frequency ranging from 1 to >30 percent, which were calculated into cumulative ppm x years exposure. These were separated into 3 or more levels of exposure including a no exposure category.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established but it is unclear whether exposure fall within relevant windows for the outcome of interest. A complete occupational history was obtained, but there is no information provided to indicate when exposures occurred in relation to the cancer diagnosis.
Domain 3: Outcome Assessment						

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Study Citation: Seidler, A; Möhner, M; Berger, J; Mester, B; Deeg, E; Elsner, G; Nieters, A; Becker, N (2007). Solvent exposure and malignant lymphoma: A population-based case-control study in Germany Journal of Occupational Medicine and Toxicology, 2 2
Data Type: >0, <= 2.3 ppm*yrs CCl4_Total Lymphoma-Cancer-Cancer
HERO ID: 194429

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Hospital and ambulatory physicians involved in the diagnosis and therapy of malignant lymphoma were asked to identify cases; no assessment of validity (or confirmation) of diagnosis was reported in the paper but could be available in companion publications that were cited. no evidence of differential misclassification.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	High rating: appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment and matching by gender, region and age.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Medium rating: primary confounders (excluding co-exposures) were assessed. The paper notes that trained interviewers administered questionnaires (medical history, lifestyle, occupation) to subjects, did not describe if the questionnaire used to collect information on education, smoking, etc. has been previously validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Medium rating: co-exposures were measured and modeled separately; the authors noted that a high correlation was observed between PCE and TCE (p=0.42). For this reason, it is difficult to disentangle the specific effects of PCE and TCE on risk of lymphoma.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Medium rating: appropriate design (i.e., case control study of solvent exposure in relation to a rare disease), and appropriate statistical methods (i.e., logistic regression analyses) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Medium rating: authors noted that study power might have been insufficient to detect a slightly elevated lymphoma risk among DCM exposed subjects or to detect an increased lymphoma risk among PCE-exposed subjects.

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Study Citation:	Seidler, A; Möhner, M; Berger, J; Mester, B; Deeg, E; Elsner, G; Nieters, A; Becker, N (2007). Solvent exposure and malignant lymphoma: A population-based case-control study in Germany Journal of Occupational Medicine and Toxicology, 2 2
Data Type:	>0, <= 2.3 ppm*yrs CCl4_Total Lymphoma-Cancer-Cancer
HERO ID:	194429

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: logistic regression models were used to generate Odds Ratios. Rationale for variable selection is stated. Model assumptions are met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.5	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High =≥ 1 to < 1.7; Medium =≥ 1.7 to < 2.3; Low =≥ 2.3 to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 26: **Dosemeci et al. 1999: Evaluation of Cancer Outcomes**

Study Citation:	Dosemeci, M; Cocco, P; Chow, WH (1999). Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons American Journal of Industrial Medicine, 36(1), 54-59
Data Type:	renal cancer and occupational CCl4-Cancer
HERO ID:	194813

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Selection was provided in detail and indicates that selection into or out of the study is not likely biased.
	Metric 2:	Attrition	Medium	× 0.4	0.8	There was an overall 86% response rate that did not differ between cases and controls. For the occupational analysis, 438 of the 690 cases and 687 of the 690 controls with complete personal interviews were included. There does not appear to be any missing data for the included 438 cases and 687 controls. However, all cases who died (35%) were excluded from the analysis to avoid using next-of-kin interviews.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	For subjects age 20-64 years, an age- and gender-stratified random sample of white controls was obtained with random digit dialing. For subjects age 65-85 years, an age-and gender-stratified systematic sample of white controls was obtained from the listing of the Health Care Financing Administration. This is a population-based case control study in Minnesota. No information on characteristics were provided for comparing the cases and controls, but they were similar in terms of age, sex, and ethnicity (all were noted to be white).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Occupational history was obtained via interview. Duration of employment in 13 specific occupations/industries and seven jobs with specific exposures were obtained. Occupations and industries were codes based on standard classifications and JEMs were developed by the NCI for nine individual chemicals including Perc, CCl4,TCE, and DCM. Details of the JEM were provided (Dosemeci et al., 1994; Gomez et al., 1994 HERO ID 702154). The JEM is based on probability and intensity scales.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Unclear, but appears to be exposed versus unexposed.
	Metric 6:	Temporality	Low	× 0.4	1.2	The temporality of exposure and outcome is uncertain.
Domain 3: Outcome Assessment						

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Study Citation:	Dosemeci, M; Cocco, P; Chow, WH (1999). Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons American Journal of Industrial Medicine, 36(1), 54-59
Data Type:	renal cancer and occupational CCl4-Cancer
HERO ID:	194813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	RCC were histologically confirmed and identified through the Minnesota Cancer Surveillance System.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All outcomes are reported, but not in a way that would allow for detailed extraction.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Results adjusted for age, gender, smoking, hypertension, use of specific drugs, and BMI. There is not enough information provided to know if SES would be a potential confounder, but considering that controls were randomly selected it is unlikely that this would be a major potential confounder.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was collected via a questionnaire, but validity and reliability were not reported.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	There is no evidence to indicate that there were co-exposures that would appreciably bias the results. Although this was occupational exposure, subjects came from different occupations and areas; therefore, it is unlikely that there would have been differential co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistical power should be sufficient.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis was sufficient to reproduce with access to the analytical data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Methods are transparent.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.9	
Extracted			Yes			

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Study Citation:	Dosemeci, M; Cocco, P; Chow, WH (1999). Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons American Journal of Industrial Medicine, 36(1), 54-59
Data Type:	renal cancer and occupational CCl4-Cancer
HERO ID:	194813

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study

Table 27: **Wang et al. 2009: Evaluation of Cancer Outcomes**

Study Citation:	Wang, R; Zhang, Y; Lan, Q; Holford, TR; Leaderer, B; Zahm, SH; Boyle, P; Dosemeci, M; Rothman, N; Zhu, Y; Qin, Q; Zheng, T (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women American Journal of Epidemiology, 169(2), 176-185
Data Type:	Non Hodgkin Lymphoma_Connecticut women_CCl4-Cancer
HERO ID:	626703

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Authors reported that participants in this study were women ages 21-84 years from Connecticut from 1996 to 2000. The cases were histologically confirmed with non-Hodgkins Lymphoma in Connecticut and had no history of any type of cancer (except nonmelanoma skin cancer). Controls with Connecticut addresses (ages 65 or less) were recruited by random digit dialing or by random selection from Centers for Medicare and Medicaid Services files (ages 65 or older). Cases and controls were matched within 5-year age groups. Both cases and controls held 3-4 jobs during their lifetime but no table was provided comparing covariates in cases vs. controls.
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the NHL cases, 601 out of 832 (72%) completed in person-interviews. Of the controls, the participation rate for those identified via random digit dialing was 69% and it was 47% for those from the Health Care Financing Administration. In-person interviews were completed for 717 controls. Outcome data included information on all 601 cases and 717 controls.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	The participants were from the same population (Connecticut women) and they were matched within 5-years of age. They were adjusted for age, family history of hematopoietic cancers, alcohol consumption, and race.
Domain 2: Exposure Characterization					

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Study Citation:	Wang, R; Zhang, Y; Lan, Q; Holford, TR; Leaderer, B; Zahm, SH; Boyle, P; Dosemeci, M; Rothman, N; Zhu, Y; Qin, Q; Zheng, T (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women American Journal of Epidemiology, 169(2), 176-185
Data Type:	Non Hodgkin Lymphoma_Connecticut women_CCl4-Cancer
HERO ID:	626703

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure was based on the job classification by linking the coded occupational data with a job-exposure matrix updated by industrial hygienists at the NCI. Every occupation and industry was assigned a semi-quantitative estimate of intensity and probability according to a scale of 0-3. Intensity was estimated on the basis of expected exposure level and frequency and exposure probability was the likelihood that a specific substance was used by a worker in a given industry or occupation. The final scores for average exposure intensity and probability were categorized as never exposed (0), low (<3), medium (3-5), and high intensity/probablity (>=6). This method of exposure classification could result in some misclassification of exposure, since the occupational histories were self-reported.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The study used three distributions of exposure: never, low, and medium-high which are sufficient to determine an exposure-response relationship.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Participants provided information on their lifetime occupational history. Exposure within 1 year before diagnosis/interview was excluded from the interview process, however since non-Hodgkins Lymphoma takes many years to develop after exposure, it is unclear if all exposures fell within the relevant window to see the effect.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The study said that cases of Non-Hodgkin Lymphoma were histologically confirmed, but presents no further information on the procedure used to confirm the diagnosis
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The results section presents tables that present the number of cases and controls and the odds ratio and 95% confidence limits for exposure to each solvent at the never, low, and medium-high exposure levels
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	All participants were Connecticut women. ORs for cases and controls were adjusted for age, family history of hematopoietic cancers, alcohol consumption, and race

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Study Citation:	Wang, R; Zhang, Y; Lan, Q; Holford, TR; Leaderer, B; Zahm, SH; Boyle, P; Dosemeci, M; Rothman, N; Zhu, Y; Qin, Q; Zheng, T (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women American Journal of Epidemiology, 169(2), 176-185
Data Type:	Non Hodgkin Lymphoma_Connecticut women_CCl4-Cancer
HERO ID:	626703

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	In-person interviews using a standardized, structured questionnaire were used to collect information on confounders. However, the authors don't report that the questionnaire was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The job histories were divided by potential exposure to 8 specific organic solvents, any organic solvent, or chlorinated solvents in general. However, since the occupational histories were self-reported, there is a possibility of exposure misclassification which could have resulted in non-reporting of co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A case-control study was the appropriate type of study to measure the possible association between occupational exposure and development of Non-Hodgkins Lymphoma and the statistical method used - determination of Odds Ratio was appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	This study consisted of 601 cases and 717 controls which are a sufficient number to detect the effect of non-Hodgkins Lymphoma.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of the statistical methods was sufficient to reproduce the logistic regression models and adjustment factors were included in the footnotes to the tables.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Adjustment factors used in the final model were determined based on logistic regression models and adjustment for other variables, such as level of education, annual family income, tobacco smoking, and medical history of immune-related disease did not result in material changes for the observed associations and were not included in the final model.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	

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Study Citation:	Wang, R; Zhang, Y; Lan, Q; Holford, TR; Leaderer, B; Zahm, SH; Boyle, P; Dosemeci, M; Rothman, N; Zhu, Y; Qin, Q; Zheng, T (2009). Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women American Journal of Epidemiology, 169(2), 176-185
Data Type:	Non Hodgkin Lymphoma_Connecticut women_CCl4-Cancer
HERO ID:	626703

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		1.7	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

† High = 1; Medium = 2; Low = 3; Unacceptable = 4; N/A has no value.

‡ The overall rating is calculated as necessary. EPA may not always provide a comment for a metric that has been categorized as High.

$$\text{Overall rating} = \begin{cases} 4 & \text{if any metric is Unacceptable} \\ \left\lfloor \sum_i (\text{Metric Score}_i \times \text{MWF}_i) \,/\, \sum_j \text{MWF}_j \right\rceil_{0.1} & \text{(round to the nearest tenth) otherwise} \end{cases},$$

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

†† This metric met the criteria for high confidence as expected for this type of study