United States
Environmental Protection Agency

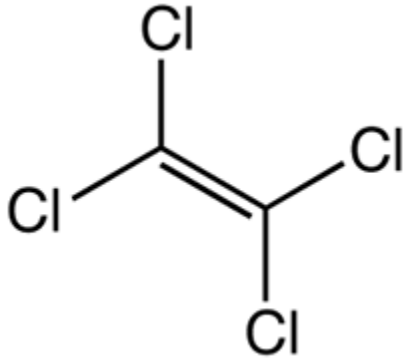
Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for Perchloroethylene

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Studies

CASRN: 127-18-4



December 2020

EPA's Office of Pollution Prevention and Toxics (OPPT) developed data quality criteria for epidemiological studies. The first version of the criteria was documented in the Application of Systematic Review in TSCA Risk Evaluations document (EPA Document #740-P1-8001). The initial criteria were updated after considering EPA/OPPT's practical experience and comments from the public. This systematic review supplemental document describes the updated data quality criteria for epidemiological studies that EPA/OPPT intends to apply for the TSCA risk evaluations. Refer to Appendix H of the Application of Systematic Review in TSCA Risk Evaluations document for details about the data quality evaluation tool.

Table Listing

Table 1: **Stewart et al. 1970: Evaluation of Acute Toxicity/Poisoning Outcomes**

Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	3141

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Sixteen healthy male subjects were recruited from laboratory personnel, ranging in age from 24 to 64 years of age. For repeated exposures, male subjects were aged 36 to 64 years. Participants were noted to be healthy for the previous 6 years. Further details on selection are not provided.
	Metric 2: Attrition	Medium	× 0.4	0.8	Only five of the sixteen recruited subjects were included in the repeated exposure group. The reason for the use of this sub-sample was not described. However, in the repeated exposure experiment, all five subjects were followed for each exposure period.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	A control group was not utilized in this study design. The study authors state that they were unable to confine the same participants in a control exposure scenario, but no other information is provided. Subjects clinical chemistry, and urinalysis results were compared to reference values obtained 1 hour prior to exposure. Cognitive function test were preformed throughout exposure, and results were compared to references (source not clear).
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Purity of the test material was reported (99.6 percent) and the inhalation chamber was adequately described. The mean, standard deviation, and range of exposure over each exposure period was reported. Concentrations of perchloroethylene in the exposure chamber were determined using both infrared spectroscopy and gas chromatography with a hydrogen flame detector (GC-FID).
	Metric 5: Exposure levels	Low	× 0.2	0.6	Only one level of exposure was used for this study. There was no concurrent control and subjects could only be compared to data from prior examinations and reference values for clinical chemistry endpoints.

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	3141

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Each subject in the repeated exposure study had been followed for six years prior to the study. It is assumed this was performed as routine occupational medical examinations and screenings. Samples were taken just prior to exposure, and effects were measured after exposure, establishing temporality between exposure and effects.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	A physical examination was performed prior to each exposure period. A pre-exposure blood sample was collected and clinical chemistry endpoints were measured. Each subject also provided urine for urinalysis. During exposure, subjective measures and measures of cognitive function (Crawford manual dexterity, Flannagan coordination, arithmetic, and inspection tests, and a modified Romberg test) were collected each hour. There was no control group, so investigators and participants would not have been blinded to exposure. This represents a mixture of methods with high validity (clinical chemistry/urinalysis) and methods with uncertain validity and a concern for lack of blinding (cognitive and subjective measures).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All outcomes outlined in the abstract, introduction, and methods were described either quantitatively or qualitatively in the results. Most figures and tables include standard error or standard deviation.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates were not included in the analysis. All subjects were adult males. The subjects are described to be of the same occupation and BMI was addressed by qualitatively comparing expired concentrations of perchloroethylene and subject BMI.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Age, sex, BMI, and occupational title were all presumably obtained by physical examination and employment records.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Inhalation chambers were monitored by IR and GC-FLD. There was no indication of co-exposures.
Domain 5: Analysis						

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Study Citation: R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type: perchloroethylene_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID: 3141

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study utilized a controlled inhalation exposure to perchloroethylene. No concurrent control group was employed and participants clinical chemistry and cognitive function results were compared to reference values.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sixteen subjects were included in the single exposure experiment while five subjects were utilized in the repeated exposure experiment. All five subjects were adult males. This represents a small sample size and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Results are presented with number of subjects, ranges and means. Analysis are well described and could be reproduced given original data.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Results were compared to reference values and described qualitatively only. So no analysis was provided. Only toxicokinetic data (elimination of perchloroethylene via exhalation) was provided in a quantitative manner.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene was measured in expired air from exposed subjects, collected in Saran bags or glass pipettes. This is a direct measurement of perchloroethylene in expired air.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	The limit of detection is not reported, however, reported data indicate that concentrations were above the limit of detection in all subjects for the duration of follow-up (16 days post exposure).
	Metric 19:	Biomarker stability	High	NA	NA	Sample storage was described. Samples collected in glass pipettes were analyzed within 16 hours and samples from Saran bags were analyzed within 2 hours of collection. There was no reported loss of samples.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	There was no documentation in regard to sample contamination.
	Metric 21:	Method requirements	Low	× 0.2	0.6	Samples from Saran bags were analyzed using infrared spectroscopy and samples from glass pipettes were analyzed using gas chromatography (assumed to be GC-FID).
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary for samples of breath.

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Data Type:	perchloroethylene_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	3141

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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 2: **Stewart et al. 1977: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type:	ControlledExposure_Perc_Behavior_NeurologicalEffects-Neurological/Behavior
HERO ID:	58215

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Volunteer subjects were recruited from the general population via a college newsletter and deemed medically, physical, and neurologically healthy prior to the start of the experiment. Most subjects (9/12) were under 30. Of those over 30, only one completed the study. While the subject composition is expected for a controlled exposure study. All participant were Caucasian. The population is not representative of the general population.
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the 12 participants in the study, 3 withdrew midway through the study and one was added 2 days into the 55 day study. Both male subjects over 30 withdrew from the study. There was no indication that withdrawal was associated with health effects related to the study.
	Metric 3: Comparison Group	High	× 0.2	0.2	Subjects underwent health evaluations prior to enrollment and completed behavioral and neurological analysis at a controlled dose of 0 ppm, thus serving as their own controls.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	In this controlled exposure study, subjects were exposed to perc via inhalation at levels of 0, 25 or 100 ppm for 5.5 hours/day to simulate occupational exposure in dry cleaning and industrial degreasing operation environments. Exposure occurred in a series of sealed rooms and perc levels were measured continuously via infrared spectrometry and gas chromatography with a flame ionization detector.

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Study Citation: R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type: ControlledExposure_Perc_Behavior_NeurologicalEffects-Neurological/Behavior
HERO ID: 58215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The highest exposure level (100 ppm) was the Occupational Safety and Health Agency (OSHA) standard and expected to rapidly equilibrate. Subject exercised moderately during exposure to simulate changes in inhalation rates that may mimic occupational exposures. Subjects were exposed for 5.5 hrs/day 1-2 days/week, with exposures sometimes occurring on consecutive days. Perchloroethylene levels were determined in blood and breath and indicate an exposure gradient. Baseline values were provided, but blood and breath levels were not evaluated for every instance of 0 ppm exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Behavioral and neurological evaluations were conducted throughout exposure. Test were conducted within 5-10 minutes of the start and end of each exposure window.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The following behavioral and neurological tests were conducted during exposure within the controlled exposure chamber: Michigan eye-hand coordination, rotary pursuit, Flanagan coordination, saccade eye velocity, dual-attention tasks, and Lorr-McNair mood evaluation test. Electroencephalograms were taken during exposure. Clinical symptoms were evaluated (headache, fatigue, nausea). There were some equipment malfunctions throughout the study, which were generally resolved within a few days. These evaluations were conducted using standardized and explicit protocols and were used to evaluate a range of outcomes.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Authors report that testing occurred in double-blind mode, indicating both subjects and assessors were blinded to exposure status. It was noted that subjects could smell the perchloroethylene at the high exposure level (100ppm) but not the low exposure level (25 ppm).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	The analysis was not adjusted for any covariates. The disproportionate withdrawal of older subjects indicates that age could be an important covariate, which was not accounted for in the analysis.

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Study Citation:	R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type:	ControlledExposure_Perc_Behavior_NeurologicalEffects-Neurological/Behavior
HERO ID:	58215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Subjects completed a health questionnaire and extensive physical examinations prior to exposure, which indicated the selected subjects were healthy. Details on demographic parameters (socioeconomic status, race) are not provided, but age and sex were reported.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The study was designed to probe interactions of perc with diazepam and ethanol. Subjects were exposed to perc via inhalation either alone or concurrently with dosages of diazepam (0, 6, 10 mg/day) or vodka (0.0, 0.75, 1.5 ml/kg body weight). Controls of perc only exposure were also used, which were the exclusive focus of this study quality evaluation.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The controlled exposure study evaluates behavioral and neurological outcomes in a small group of 12 subjects with known perc exposure of 0, 25 or 100 ppm. The design is appropriate for the assessment of behavioral and neurological effects associated with acute exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The statistical power was not explicitly stated. Although there were a low number of subjects, each exposure level was evaluated in groups of 4-6 subjects 6-9 times. Results were presented with a statement on statistical significance.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Analysis are reported with great detail and data is reported by session and subject with means and standard deviations.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Appropriate analysis was conducted for each endpoint, including regression models and analysis of variance.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene was determined in blood and breath of subjects. In this controlled exposure study, the biomarkers of exposure served as a confirmation of exposure, rather than the primary methods of determining exposure levels.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarkers of effect were assessed.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	IR spectrometry was used to determine perchloroethylene, which was identified in all exposed subjects.

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Study Citation:	R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type:	ControlledExposure_Perc_Behavior_NeurologicalEffects-Neurological/Behavior
HERO ID:	58215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Biomarker stability	Low	× 0.2	0.6	Storage and stability information not provided.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	Documentation of steps to prevent sample contamination are not provided, but there is no indication of contamination.
	Metric 21:	Method requirements	Low	× 0.2	0.6	Perchloroethylene was quantified with GC/FID, which has known interferants.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary for these matrices (blood/breath).
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: **NIOSH 1985: Evaluation of Cancer Outcomes**

Study Citation:	NIOSH (National Institute for Occupational Safety and Health) (1985). Abstract of retrospective cohort mortality study of dry cleaner workers using perchloroethylene with cover letter dated 011486 & EPA acknowledgement letter dated 103085
Data Type:	Union cohort (perc, <10 years latency) SMR all cancer-Cancer
HERO ID:	4214476

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	The study provided most key elements of the study design including the selection process, description of the study areas, and inclusion/exclusion criteria. Participation rates were not reported, but are not likely to be an issue as union records and governmental databases were used to obtain information.
	Metric 2:	Attrition	Medium	× 0.4	0.8	There was less than moderate subject loss to follow up. Although the number of exclusions were not reported nor the beginning number of eligible participants, the reasons for exclusion were well-documented.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Results stratified by age, sex, and race and choice of reference population is reported.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Time weighted average and peak exposures to Perc were determined by collecting personal air samples for a sample of facilities. Some or complete solvent history for each worker was acceptable inclusion criteria for the analysis, so complete history was not known for some subjects.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	4 year-range latency groups and 4 year-range exposure groups were used in the analysis; but this was based solely on years of employment and did not incorporate the personal air samples that were reported in the study.
	Metric 6:	Temporality	High	× 0.4	0.4	Latency time for cancer was taken into account.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes were assessed using well-established methods. Death certificates were obtained from the State Vital Statistics Offices, and the underlying cause of death was coded by a trained nosologist according to the Revision of the ICD codes in effect at the time of death.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Number of observed and expected deaths and SMRs were reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	NIOSH (National Institute for Occupational Safety and Health) (1985). Abstract of retrospective cohort mortality study of dry cleaner workers using perchloroethylene with cover letter dated 011486 & EPA acknowledgement letter dated 103085
Data Type:	Union cohort (perc, <10 years latency) SMR all cancer-Cancer
HERO ID:	4214476

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Most results are stratified by age, sex, and color (white vs. non-white).
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	For race and age, when union records were incomplete, info (including demographic) was obtained from the Social Security Administration.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	It was assumed that petroleum solvents were used during time periods of unknown solvent use; however, in an effort to restrict an analysis to a cohort of workers exposed to Perc with no confouding exposure to stoddard solvents, analyses were conducted on a sub-cohort of workers who were employed only in facilities where Perc was the primary solvent.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study uses an appropriate statistical method to address the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants is adequate to detect an effect in the exposed population. The final exposed population included 1690 workers who contributed a total of 42,267 person-years to the analysis.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data and included the calculation of person-years and calculation of standardized mortality ratios.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for calculating the SMRs was 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‡			High		1.5	
Extracted			Yes			

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Study Citation:	NIOSH (National Institute for Occupational Safety and Health) (1985). Abstract of retrospective cohort mortality study of dry cleaner workers using perchloroethylene with cover letter dated 011486 & EPA acknowledgement letter dated 103085
Data Type:	Union cohort (perc, <10 years latency) SMR all cancer-Cancer
HERO ID:	4214476

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 4: **Azimi et al. 2017: Evaluation of Genotoxicity Outcomes**

Study Citation:	M. Azimi, M. R. Bahrami, V. Rezaei Hachesu, J. Zavar Reza, H. Mihanpour, M. J. Zare Sakhvidi, M. Mostaghaci (2017). Primary DNA Damage in Dry Cleaners with Perchlorethylene Exposure International Journal of Occupational and Environmental Medicine, 8(4,4), 224-231
Data Type:	PCE_exposed workers_DNA damage in leukocytes-Other (please specify below)
HERO ID:	5926276

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	The selection criteria for exposed participants and controls were reported. THe referent population was drawn from Yazd city and it is inferred but not specified that the exposed subjects were as well. Methods of participant recruitment/selection were not reported (apart from exclusion criteria).
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of individuals were not reported at important stages of study . Reasons were not provided for non-participation at each stage
	Metric 3:	Comparison Group	Low	× 0.2	0.6	The referent population was drawn from Yazd city and it is inferred but not specified that the exposed subjects were as well. Methods of participant recruitment/selection were not reported (except exclusion criteria). Referent subjects were matched on age, sex, and smoking status. Descriptive characteristics were reported only for the matching parameters (age, sex, smoking status).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was assessed based solely on employment and employment duration at dry cleaners.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reports 2 levels of exposure (e.g., exposed/unexposed))
	Metric 6:	Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure and outcome and the exposure window was appropriate; exposed subjects had worked for a median duration of 8 years (IQR of 1 to 13.5 years).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Blood samples collected at same time of day for all participants; the number of work (exposed) days prior to sampling was not reported. Outcome assessment (comet assay) was described fully and scoring was performed by a single researcher blinded to sample status. Scoring criteria were cited to another publication.

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Study Citation:	M. Azimi, M. R. Bahrami, V. Rezaei Hachesu, J. Zavar Reza, H. Mihanpour, M. J. Zare Sakhvidi, M. Mostaghaci (2017). Primary DNA Damage in Dry Cleaners with Perchlorethylene Exposure International Journal of Occupational and Environmental Medicine, 8(4,4), 224-231
Data Type:	PCE_exposed workers_DNA damage in leukocytes-Other (please specify below)
HERO ID:	5926276

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Summary data (mean, range, SD were reported for tail length, % DNA in tail, tail moment, olive tail moment) for exposed and controls after stratification by sex or smoking status.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Sex and smoking status were considered using stratification. Study authors evaluated correlations protective behavior covariates (PPE, ventilation, etc.) but did not consider potential coexposures to other dry cleaning chemicals, medications, or alcohol.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were evaluated by questionnaire. Study authors did not report whether the questionnaire was validated but there was no indication that the method had poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	It is inferred that primary chemical used in the dry cleaners was perc, but potential co-exposures in these facilities were not considered in the analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	Study design was appropriate and an appropriate statistical method was used to analyze the results.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	Sample size was calculated based on previous data on tail length effect size and power calculation. "The minimum sample size in each group for a power of 80% and a two-sided significance level of 0.05 was 31"
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data
	Metric 15:	Statistical models	Not Rated	NA	NA	Statistical models were not used.
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:	M. Azimi, M. R. Bahrami, V. Rezaei Hachesu, J. Zavar Reza, H. Mihanpour, M. J. Zare Sakhvidi, M. Mostaghaci (2017). Primary DNA Damage in Dry Cleaners with Perchlorethylene Exposure International Journal of Occupational and Environmental Medicine, 8(4,4), 224-231
Data Type:	PCE_exposed workers_DNA damage in leukocytes-Other (please specify below)
HERO ID:	5926276

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		2.2	
Extracted		No			

⋆ 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 5: **Stewart et al. 1977: Evaluation of Acute Toxicity/Poisoning Outcomes**

Study Citation:	R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type:	ControlledExposure_Perc_AcuteEffects-Acute Toxicity/Poisoning
HERO ID:	58215

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Volunteer subjects were recruited from the general population via a college newsletter and deemed medically, physical, and neurologically healthy prior to the start of the experiment. Most subjects (9/12) were under 30. Of those over 30, only one completed the study. While the subject composition is expected for a controlled exposure study. All participant were Caucasian. The population is not representative of the general population.
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the 12 participants in the study, 3 withdrew midway through the study and one was added 2 days into the 55 day study. Both male subjects over 30 withdrew from the study. There was no indication that withdrawal was associated with health effects related to the study.
	Metric 3: Comparison Group	High	× 0.2	0.2	Subjects underwent health evaluations prior to enrollment and completed behavioral and neurological analysis at a controlled dose of 0 ppm, thus serving as their own controls.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	In this controlled exposure study, subjects were exposed to perc via inhalation at levels of 0, 25 or 100 ppm for 5.5 hours/day to simulate occupational exposure in dry cleaning and industrial degreasing operation environments. Exposure occurred in a series of sealed rooms and perc levels were measured continuously via infrared spectrometry and gas chromatography with a flame ionization detector.

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Study Citation: R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type: ControlledExposure_Perc_AcuteEffects-Acute Toxicity/Poisoning
HERO ID: 58215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The highest exposure level (100 ppm) was the Occupational Safety and Health Agency (OSHA) standard and expected to rapidly equilibrate. Subject exercised moderately during exposure to simulate changes in inhalation rates that may mimic occupational exposures. Subjects were exposed for 5.5 hrs/day 1-2 days/week, with exposures sometimes occurring on consecutive days. Perchloroethylene levels were determined in blood and breath and indicate an exposure gradient. Baseline values were provided, but blood and breath levels were not evaluated for every instance of 0 ppm exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Behavioral and neurological evaluations were conducted throughout exposure. Test were conducted within 5-10 minutes of the start and end of each exposure window.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The following behavioral and neurological tests were conducted during exposure within the controlled exposure chamber: Michigan eye-hand coordination, rotary pursuit, Flanagan coordination, saccade eye velocity, dual-attention tasks, and Lorr-McNair mood evaluation test. Electroencephalograms were taken during exposure. Clinical symptoms were evaluated (headache, fatigue, nausea). There were some equipment malfunctions throughout the study, which were generally resolved within a few days. These evaluations were conducted using standardized and explicit protocols and were used to evaluate a range of outcomes.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Authors report that testing occurred in double-blind mode, indicating both subjects and assessors were blinded to exposure status. It was noted that subjects could smell the perchloroethylene at the high exposure level (100ppm) but not the low exposure level (25 ppm).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	The analysis was not adjusted for any covariates. The disproportionate withdrawal of older subjects indicates that age could be an important covariate, which was not accounted for in the analysis.

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Study Citation:	R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type:	ControlledExposure_Perc_AcuteEffects-Acute Toxicity/Poisoning
HERO ID:	58215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Subjects completed a health questionnaire and extensive physical examinations prior to exposure, which indicated the selected subjects were healthy. Details on demographic parameters (socioeconomic status, race) are not provided, but age and sex were reported.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The study was designed to probe interactions of perc with diazepam and ethanol. Subjects were exposed to perc via inhalation either alone or concurrently with dosages of diazepam (0, 6, 10 mg/day) or vodka (0.0, 0.75, 1.5 ml/kg body weight). Controls of perc only exposure were also used, which were the exclusive focus of this study quality evaluation.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The controlled exposure study evaluates behavioral and neurological outcomes in a small group of 12 subjects with known perc exposure of 0, 25 or 100 ppm. The design is appropriate for the assessment of behavioral and neurological effects associated with acute exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The statistical power was not explicitly stated. Although there were a low number of subjects, each exposure level was evaluated in groups of 4-6 subjects 6-9 times. Results were presented with a statement on statistical significance.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Analysis are reported with great detail and data is reported by session and subject with means and standard deviations.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Appropriate analysis was conducted for each endpoint, including regression models and analysis of variance.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene was determined in blood and breath of subjects. In this controlled exposure study, the biomarkers of exposure served as a confirmation of exposure, rather than the primary methods of determining exposure levels.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarkers of effect were assessed.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	IR spectrometry was used to determine perchloroethylene, which was identified in all exposed subjects.

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Study Citation:	R. D. Stewart, C. L. Hake, A. Wu, J. Kalbfleisch, P. E. Newton, S. K. Marlow, M. Vucicevic-Salama (1977). Effects of perchloroethylene/drug interaction on behavior and neurological function
Data Type:	ControlledExposure_Perc_AcuteEffects-Acute Toxicity/Poisoning
HERO ID:	58215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Biomarker stability	Low	× 0.2	0.6	Storage and stability information not provided.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	Documentation of steps to prevent sample contamination are not provided, but there is no indication of contamination.
	Metric 21:	Method requirements	Low	× 0.2	0.6	Perchloroethylene was quantified with GC/FID, which has known interferants.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary for these matrices (blood/breath).
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 6: **Ikeda et al. 1980: Evaluation of Genotoxicity Outcomes**

Study Citation:	M. Ikeda, A. Koizumi, T. Watanabe, A. Endo, K. Sato (1980). Cytogenetic and cytokinetic investigations on lymphocytes from workers occupationally exposed to tetrachloroethylene Toxicology Letters, 5(3-4,3-4), 251-256
Data Type:	Perc_exposed workers_CA and SCE-Other (please specify below)
HERO ID:	58236

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Key elements of the study design and information on the population (e.g., setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) are not reported. Exposed subjects described only as factory workers in degreasing and "support" departments, and the control group was not described at all.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of individuals were not reported at important stages of study (e.g., numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	Concurrent controls were indicated and included males and females, but were not further characterized.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Workroom air concentrations were measured using Kitagawa detection tubes. No further details (timing, area vs breathing zone, etc.) were provided.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Control and high and lower exposures.
	Metric 6:	Temporality	Low	× 0.4	1.2	The temporality of exposure and outcome is uncertain. It is not clear whether blood samples were obtained immediately following exposure. In addition, the employment duration in the high exposed group ranged from 2 years to 18 years (among 6 subjects).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Outcomes (CAs, SCEs) were assessed using well-established methods, but few details of the methods were provided (cited to another publication).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	CAs were reported as % and SCE were reported as mean +/- SD for all groups.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	M. Ikeda, A. Koizumi, T. Watanabe, A. Endo, K. Sato (1980). Cytogenetic and cytokinetic investigations on lymphocytes from workers occupationally exposed to tetrachloroethylene Toxicology Letters, 5(3-4,3-4), 251-256
Data Type:	Perc_exposed workers_CA and SCE-Other (please specify below)
HERO ID:	58236

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Unacceptable	× 1	1	The sex distribution varied between high and control groups (high exposure was 5 males and 1 female, controls 6 males and 5 females). No information on smoking/tobacco use among subjects was provided.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates were not assessed.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	Co-exposures were not assessed or discussed.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	The study design was appropriate and statistical analysis was adequate.
	Metric 13:	Statistical power	Unacceptable	× 0.25	0.06	The number of participants per group was very low (11 controls, 4 low exposure, and 6 high exposure) and probably insufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	The description of the analysis is sufficient to understand what was done and to be reproducible with access to the raw data.
	Metric 15:	Statistical models	Not Rated	NA	NA	Statistical models were not used.
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‡			Unacceptable⋆⋆		2.7	
Extracted			No			

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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: **Mutti et al. 1992: Evaluation of Renal Outcomes**

Study Citation:	Mutti, A; Alinovi, R; Bergamaschi, E; Biagini, C; Cavazzini, S; Franchini, I; Lauwerys, RR; Bernard, AM; Roels, H; Gelpi, E; Rosello, J; Ramis, I; Price, RG; Taylor, SA; de Broe, M; Nuyts, GD; Stolte, H; Fels, LM; Herbort, C (1992). Nephropathies and exposure to perchloroethylene in dry-cleaners The Lancet, 330(8813), 189-193
Data Type:	Perc-nephrotoxicity markers-Renal
HERO ID:	58348

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Almost no information is provided on how the subjects were selected. No method of recruitment was provided. Limited information provided on setting (i.e., dry cleaning shops) and exclusion criteria.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of individuals were not reported at important stages of study (e.g., numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). It is only noted that there were 50 exposed and 50 unexposed subjects
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Controls were matched by sex and age. Other baseline characteristics were similar, but there were some slight differences. These differences are not likely enough to significantly bias the results.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposed subjects worked in a dry-cleaning shop. Controls were blood donors. Exposure was measured in the blood and air of workers, but only a single level was provided with no JEM, this level was also not used in the analysis. Levels in the workers and air were measured using gas chromatography with mass selective detector with levels ranging from trace amounts to 85 ppm. Median PCE in air was 14.8 ppm and in blood was 143 ug/L. No blood levels were measured in the controls. Therefore, exposure for analysis is based only on working in a dry-cleaning shop or not.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Only exposed and unexposed.
	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. Exposed subjects were noted to have worked in a dry-cleaning shop and exposed to Perc for 10 years on average. However, there is no information provided on when the exposure stopped or how long it would take to effect the renal biomarkers.

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Study Citation: Mutti, A; Alinovi, R; Bergamaschi, E; Biagini, C; Cavazzini, S; Franchini, I; Lauwerys, RR; Bernard, AM; Roels, H; Gelpi, E; Rosello, J; Ramis, I; Price, RG; Taylor, SA; de Broe, M; Nuyts, GD; Stolte, H; Fels, LM; Herbort, C (1992). Nephropathies and exposure to perchloroethylene in dry-cleaners The Lancet, 330(8813), 189-193

Data Type: Perc-nephrotoxicity markers-Renal

HERO ID: 58348

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Methods appear to be standard methods with citations, but it is unclear if these are the gold standards. There was no mention of standard kit assays being used. However, methods are acceptable.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All information is provided in sufficient detail.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Subjects were matched by age and sex. Subjects were similar in characteristics reported including height, weight, BMI, and smoking status. There were more controls who drank alcohol, but the amount consumed was not that different. Exposed subjects had more drug consumption. The study authors did not consider there to be a distinguishable difference. It is not clear if SES would be a potential confounder as it isn't clear where the blood donors were obtained or if SES would be a confounder for the biomarkers measured.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	A standardized questionnaire (not stated to be validate) was used.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Although there is potential for exposure to other chemicals in dry cleaning, Perc is likely the highest exposure and there is no evidence that exposure to other chemicals would have occurred at a similar rate in the exposed subjects.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	Appropriate design (i.e., cross-sectional design for assessment of renal disease in relation to perc exposure) and statistical methods (i.e., comparisons between group means were based on the t test for independent samples, correlations among variables assessed by Pearson's coefficients) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	There were 50 exposed and 50 unexposed. This was enough for the outcome measured and statistical results were obtained.
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	Description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.

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Study Citation:	Mutti, A; Alinovi, R; Bergamaschi, E; Biagini, C; Cavazzini, S; Franchini, I; Lauwerys, RR; Bernard, AM; Roels, H; Gelpi, E; Rosello, J; Ramis, I; Price, RG; Taylor, SA; de Broe, M; Nuyts, GD; Stolte, H; Fels, LM; Herbort, C (1992). Nephropathies and exposure to perchloroethylene in dry-cleaners The Lancet, 330(8813), 189-193
Data Type:	Perc-nephrotoxicity markers-Renal
HERO ID:	58348

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Not Rated	NA	NA	No risk estimates were derived. Mean values were compared using t-tests and frequency of abnormal results.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.143	0.29	Perc levels were measured in the blood with gas chromatography with a mass selective detector. LODs were not provided.
	Metric 17:	Effect biomarker	High	× 0.143	0.14	Biomarkers are generally accepted as being related to kidney function and indicate key events in AOP. As noted by the authors 'The biochemical and immunochemical abnormalities suggested diffuse structural and functional changes within the kidney'.
	Metric 18:	Method Sensitivity	Low	× 0.143	0.43	No LOD was provided.
	Metric 19:	Biomarker stability	Medium	× 0.143	0.29	Limited information on storage history (just that it was stored at -20 degrees C), and no information on stability.
	Metric 20:	Sample contamination	Medium	× 0.143	0.29	There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable.
	Metric 21:	Method requirements	Medium	× 0.143	0.29	Instrumentation was employed that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (i.e., Perc levels were measured in the blood with gas chromatography with a mass selective detector; renal biomarkers measured with cited assay methods).
	Metric 22:	Matrix adjustment	Medium	× 0.143	0.29	Applicable for the biomarker under consideration, however, the study only provides results using one method (no matrix adjustment is discussed).
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 =≥ 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 8: **Olsen et al. 1990: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyronen, P., Taskinen, H., Lindbohm, M. L., Heinonen, O. P., Brandt, L., Kolstad, H., Halvorsen, B. A., Egenaes, J. (1990). Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia Scandinavian Journal of Work, Environment and Health, 16(3,3), 163-168
Data Type:	Perc_exposed_workers_Reproductive&Developmental Endpoints-Growth (early life) and Development
HERO ID:	63821

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Most key elements of the study design were reported and the information provided indicates that selection/participation was not likely biased. The study indicated that there was no indication that there was a difference in risk in nonparticipating plants. In the Kyyrönnen et al. (1989) study, cases were pregnancies among dry cleaning/laundry workers in Finland employed for at least 3 months from 1973-1983 (and matched to controls). Numbers of participants at various stages of the study and inclusion/exclusion criteria were reported. The study population for the Olsen et al. (1990) study consisted of pregnancies among dry cleaning and/or laundry workers in Finland, Sweden, Norway, and Denmark, who had worked for at least 1 month during the same time period. Information pertaining to the participation rate, inclusion/exclusion criteria, and participant selection (Denmark) or case ascertainment (other countries) were provided; however, there were small differences in study design based on data that were available for each country. More information pertaining to each population was cited to additional references. It is not possible to determine the degree of overlap between Finland populations used in the two studies.
	Metric 2: Attrition	Medium	× 0.4	0.8	There was moderate subject loss during the study; however, reasons for these exclusions from analyses were reported. From the initial number of selected cases and controls in the Kyyrönnen et al. (1989) study, subjects were excluded based on absent questionnaire responses and/or due to individual matching (controls with a missing case were removed). Reasons for exclusion cited in the Olsen et al. (1990) study included women that could not be located, absent questionnaire responses, missing information (such as timing of pregnancy), and/or missing referents or cases from a matched set.

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Study Citation:	Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyronen, P., Taskinen, H., Lindbohm, M. L., Heinonen, O. P., Brandt, L., Kolstad, H., Halvorsen, B. A., Egenaes, J. (1990). Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia Scandinavian Journal of Work, Environment and Health, 16(3,3), 163-168
Data Type:	Perc_exposed_workers_Reproductive&Developmental Endpoints-Growth (early life) and Development
HERO ID:	63821

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 3:	Comparison Group	High	× 0.2	0.2	Both studies employed nested case-control design within cohorts of laundry and dry-cleaning workers. The Kyyrönnen et al. (1989) study indicated that age-matched controls were selected for each case from women who had given birth to a healthy child (nearest available matching of age with tolerance of +/- 2 years) from the same time period. The study authors indicated that the source population from which cases and controls were used was homogeneous. For the Olsen et al. (1990) study, referents were matched to each case by mother's age (+/- 2 years), year of pregnancy, and parity (except for the Finnish population).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Kyyrönnen et al. (1989) indicated that questionnaires included requests for information about general work tasks and exposure to PCE (and other chemicals) specific to the the first 3 months of pregnancy. Blood perc levels (i.e., biomonitoring data) were available for 7 of the study subjects (4 cases and 3 controls). The study authors indicated that measurements of blood PCE agreed with self-reports of exposure (despite not all cases having elevated blood PCE levels). For Olsen et al. (1990), data on exposure during pregnancy were collected using a questionnaire in Finland, by interview in Sweden and Denmark, and obtained from employers in Norway. The study indicated that exposure assessment was based mainly on recollection of exposure during the first trimester (spontaneous abortion) or later in the pregnancy (reproduction failures in relation to birth). Exposure classification (low, high) for the cohorts in Sweden, Denmark, and Norway was performed by an industrial hygienist blinded to outcome. For the Finnish population, exposure was assessed by the researchers based on reported work history and exposure frequency. Other than blood PCE measurements for a few study participants (Kyyrönnen et al. 1989), no quantitative estimates of exposure were provided in either study.

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Study Citation:	Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyronen, P., Taskinen, H., Lindbohm, M. L., Heinonen, O. P., Brandt, L., Kolstad, H., Halvorsen, B. A., Egenaes, J. (1990). Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia Scandinavian Journal of Work, Environment and Health, 16(3,3), 163-168
Data Type:	Perc_exposed_workers_Reproductive&Developmental Endpoints-Growth (early life) and Development
HERO ID:	63821

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Although these authors did report 3 exposure levels (no exposure, low, and high), the analyses by Kyyrönnen et al. (1989) used only high vs no PCE exposure, or any vs no exposure (i.e., two exposure groups). The study conducted by Olsen et al. (1990) evaluated 3 exposure groups (i.e., no exposure, low exposure, and high exposure).
	Metric 6:	Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure and outcome. Exposures to perc during the first trimester of pregnancy were evaluated, and outcomes related to those pregnancies (including spontaneous abortion, still birth, low birth weight, and malformations) were evaluated.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcome data were objectively measured (i.e., obtained from registries, and confirmed by the study subjects). The Kyyrönnen et al. (1989) study indicated that pregnancy outcomes were obtained (using diagnostic codes) from the nationwide Hospital Discharge Register and supplemented with information on patients treated in clinics and the Finnish Register for Congenital Malformations. In the Olsen et al. (1990) study, data related to pregnancy outcomes were taken entirely from national computerized registers (birth and hospital registers to avoid selection bias).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	In both studies, a description of measured outcomes (i.e., spontaneous abortion, still birth, low birth weight, and/or congenital malformations) is reported, and effect estimates (odds ratios) are reported with 95% confidence intervals. The analyses performed by Olsen et al. (1990) clearly reported numbers of cases/controls used for each analysis (see Tables 3, 4, and 5).
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyronen, P., Taskinen, H., Lindbohm, M. L., Heinonen, O. P., Brandt, L., Kolstad, H., Halvorsen, B. A., Egenaes, J. (1990). Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia Scandinavian Journal of Work, Environment and Health, 16(3,3), 163-168
Data Type:	Perc_exposed_workers_Reproductive&Developmental Endpoints-Growth (early life) and Development
HERO ID:	63821

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	In both studies, controls were matched to cases by age (+/- 2 years) and by sex (by virtue of pregnancy). The Kyyrönnen et al. (1989) study indicated that controls and cases were drawn from a relatively homogeneous source population (with respect to socioeconomic status). In this study, use of other solvents, heavy lifting at work, and use of alcohol were considered as covariates. Olsen et al. (1990) calculated ORs adjusted for parity and smoking (all cohorts) and drinking (Swedish and Finnish cohorts). The study indicated that controlling for confounding due to lifestyle factors was only possible to a limited extent, but an effect on results was unlikely because women had similar work habits and socioeconomic status and there was no indication that cases and controls differed in essential life-style factors.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Potential confounders were assessed using reliable methodology (e.g., questionnaires and/or registry information).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	In the Kyyrönnen et al. (1989) study, exposures to other solvents were evaluated separately (Tables 3 and 6); adjusted effects of PCE exposure on spontaneous abortion were shown in Table 4. In the Olsen et al. (1990) study, no specific methods were reported to control for co-exposures. The study indicated that PCE was predominantly used (with fluorocarbons becoming increasingly common in the late 1980s) and that exposures were assessed considering information available about PCE measurements in the workplace, and information from employers.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen for these studies (nested case-control) was appropriate to assess the association between PCE exposure and pregnancy outcomes, and used appropriate methods to address the question (logistic regression analyses).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls were 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 understand what has been done and to be conceptually reproducible with access to the analytic data.

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Study Citation:	Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyronen, P., Taskinen, H., Lindbohm, M. L., Heinonen, O. P., Brandt, L., Kolstad, H., Halvorsen, B. A., Egenaes, J. (1990). Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia Scandinavian Journal of Work, Environment and Health, 16(3,3), 163-168
Data Type:	Perc_exposed_workers_Reproductive&Developmental Endpoints-Growth (early life) and Development
HERO ID:	63821

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The statistical models were described fully and selection of variables was reported.
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			No			

⋆ 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: **Seiji et al. 1990: Evaluation of Genotoxicity Outcomes**

Study Citation:	K. Seiji, C. Jin, T. Watanabe, H. Nakatsuka, M. Ikeda (1990). Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene, or tetrachloroethylene, with reference to smoking habits International Archives of Occupational and Environmental Health, 62(2,2), 171-176
Data Type:	Perc_exposed workers_SCE in peripheral lymphocytes-Other (please specify below)
HERO ID:	75419

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Key elements of the study design and information on the population (e.g., setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection) were not reported. Previous studies were cited that may contain these details (Liu et al., 1988).
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of individuals were not reported at important stages of study (e.g., numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	There is only indirect evidence (e.g., stated by the authors without providing a description of methods) that groups are similar (matched by sex age, smoking habit and place of residence).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposure was assessed at the end of the work shift (TWA breathing zone concentrations for each worker were directly measured during an 8 h shift by a diffusive technique).
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Analysis used 2 levels of exposure (e.g., exposed/unexposed); exposure concentration data were reported as geometric mean and 75th percentile for exposed.
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is appropriate; blood taken at the end of the work shift, and exposed workers had been working on average 40.9 to 41.9 months prior to sampling.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome (SCE) was assessed using well established methods and the methods described in detail.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	A description of measured outcomes is reported in the methods, abstract, and/or introduction. Effect estimates are reported as mean +/- SD for all groups.

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Study Citation:	K. Seiji, C. Jin, T. Watanabe, H. Nakatsuka, M. Ikeda (1990). Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene, or tetrachloroethylene, with reference to smoking habits International Archives of Occupational and Environmental Health, 62(2,2), 171-176
Data Type:	Perc_exposed workers_SCE in peripheral lymphocytes-Other (please specify below)
HERO ID:	75419

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	SCE analyses were stratified by sex and smoking habit.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	The methods for covariate characterization are not described, but may be described in publications cited in the methods section.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential coexposures for each group of workers were not considered or characterized.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	Study design was appropriate and statistical analysis was adequate.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	The number of participants was adequate to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	The description of the analysis is sufficient to understand what was done and to be reproducible with access to the raw data.
	Metric 15:	Statistical models	Not Rated	NA	NA	Risk estimates were not 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‡			Medium		1.8	
Extracted			No			

⋆ 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 10: **Pesch et al. 2000: Evaluation of Cancer Outcomes**

Study Citation:	Pesch, B; Haerting, J; Ranft, U; Klimpel, A; Oelschlägel, B; Schill, W (2000). Occupational risk factors for renal cell carcinoma: Agent-specific results from a case-control study in Germany International Journal of Epidemiology, 29(6), 1014-1024
Data Type:	Case-control study of renal cell cancer excess risk-Perc females medium exp.-Cancer
HERO ID:	85973

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Setting, response rate, inclusion and exclusion criteria, methods of case ascertainment and control matching were described and found acceptable.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Response rates were 88% for cases and 71% for controls.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were frequency-matched to cases (1 case to 4 controls) by geographical region, sex and age (5-year age group). Differences between case and control age distribution were said to be a result of sharing the control group with older cancer cases.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure categories estimated by JEM and JETM were based on job titles and job tasks from questionnaires and interviews (not employment records). Specified chemical agent exposures were estimated based on probability and intensity of exposure associated with the job titles and task.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Medium, high or substantial exposure ratings were used.
	Metric 6:	Temporality	Medium	× 0.4	0.8	88.5% of RCC cases were interviewed in the first 2 months after diagnosis. Temporality of exposure is established, but it is unclear whether exposures fall within relevant exposure windows for the outcome of interest.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Diagnosis was confirmed histologically (95%) and sonography (5%).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	ORs with CIs were used and appropriate.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for age, study center and smoking.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Assessed by valid and reliable questionnaires.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Other chemical agent worker exposures were not appropriating adjusted for which could result in biased exposure-outcome association.
Domain 5: Analysis						

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Study Citation:	Pesch, B; Haerting, J; Ranft, U; Klimpel, A; Oelschlägel, B; Schill, W (2000). Occupational risk factors for renal cell carcinoma: Agent-specific results from a case-control study in Germany International Journal of Epidemiology, 29(6), 1014-1024
Data Type:	Case-control study of renal cell cancer excess risk-Perc females medium exp.-Cancer
HERO ID:	85973

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design using case-control and conditional logistic regression was appropriate to evaluate rare disease with associated exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There is a small group of substantially exposed workers in the general population limiting the power to detect dose-response relationships.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Model was well described.
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 11: **Windham et al. 2006: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_Perc_OR_Q4-Neurological/Behavior
HERO ID:	103522

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Cases were identified from the California Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) which draws information on ASD by active surveillance of California Department of Developmental Services (DDS) and the Kaiser Permanente Medical Care Program. Authors estimated that these methods captured 75-80% of cases living in the area (Croen et al. 2002); authors note that extreme ends of the socioeconomic status were likely not well covered. Cases were included if they were born in 1994 and resided in one of six San Francisco Bay area counties. Controls were identified from a California 1994 linked birth-infant death certificate database using the same inclusion criteria. Controls were randomly selected and matched on birth month and sex (2 to 1).
	Metric 2: Attrition	High	× 0.4	0.4	Of the cases identified in the databases, expert review by the PI confirmed 83.3% ASD diagnoses, using the same criteria for all exclusion/inclusion by expert review. Exclusion from the control population was minimal (n=18) and was sufficiently explained.
	Metric 3: Comparison Group	High	× 0.2	0.2	There is some evidence of differences between the controls and cases; however, parental and child characteristics such as race/ethnicity, maternal education, and parity were considered as potential confounders in the statistical analysis. Demographic details provided in Table 2.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Annual average concentration estimates were drawn from EPA's National Air Toxics Assessment (U.S.EPA; 4152303). Concentration estimates were available by census tract for 1996 that matched the geocoded addresses from birth certificates. Estimates were calculated by summing concentrations across various sources (mobile, point, and area sources). This represents a well-established method of determining exposure to HAPs and was assessed consistently across groups.

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Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_Perc_OR_Q4-Neurological/Behavior
HERO ID:	103522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	For chemical specific analyses, quartiles of exposure were used. These were determined by exposure distribution quartiles in controls. This represents more than two levels of exposure. Mean exposures were 0.64-0.68 ug/m3 (DCM), 0.60-0.61 ug/m3 (Perc), and 0.17-0.19 ug/m3 (TCE).
	Metric 6:	Temporality	Low	× 0.4	1.2	Cases were diagnosed with Autism Spectrum Disorder by age 9 (sufficient window for diagnosis). Cases and controls were drawn from a population of children born in 1994; however, exposure was determined from census tract-level exposure data for birth address from 1996 exposure estimates (other option was 1994). It is unclear how stable these estimates may be from year to year. Using exposure data from 1996 may not accurately capture the exposure that occurred during gestation, but instead reflect an early childhood developmental window.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases were identified by CADDRE active surveillance of California Department of Developmental Services and Kaiser Permanente records. Identified cases were confirmed by the principal investigator by diagnosis from a qualified medical professional, qualification for special education under an autism exceptionality, or autistic behaviors appearing to meet DSM-IV criteria for ASD. This represents a well-established method of determining an autism diagnosis.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All outcomes outlined in the abstract, introduction, and methods were provided in the results. The number of cases and controls was detailed for some analyses, but not for chemical-specific analyses which would not allowed for detailed extraction of the number of cases/controls. This is not expected to have an appreciable impact on the results.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_Perc_OR_Q4-Neurological/Behavior
HERO ID:	103522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Potential confounders included maternal age, race, and education, parity, paternal race and age, low birth weight, preterm delivery, and child race. The final models include child race, maternal age, and maternal education. Cases and controls were birth month- and sex-matched. The authors stated they did not include these two variables in the final model as it made little difference.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	For controls, demographic data were stated to be abstracted from the birth certificate. Demographic information for cases was drawn from medical or DDS records. These are both reliable methods of obtaining covariate information.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Approximately 30 hazardous air pollutants (HAPs) were considered in this study. The chlorinated solvents (Perc, TCE, DCM, and vinyl chloride) tended to be correlated with each other. TCE was noted to be highly correlated to metals. Chemical-specific analyses did not control for exposure to other HAPs. Although, there was no evidence of unbalanced co-exposures by case status.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A case-control study design was used to assess relationships between exposure to HAPs during pregnancy/early childhood and the presence of ASD diagnosis at age 9.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were a sufficient number of cases and controls to detect an effect.: 284 cases, 657 controls. The study authors explicitly stated they kept birth month- and sex-matched controls whose matched cases did not meet the study's diagnostic criteria in order to maintain a larger sample size.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis was sufficient. Cut-points for quartiles of exposure and the procedure for inclusion/exclusion of potential confounders was described.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratios were calculated for the two highest quartiles of exposure using logistic regression. The models and decisions on categories of exposure were described in detail in the methods.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_Perc_OR_Q4-Neurological/Behavior
HERO ID:	103522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 12: **Siemiatycki 1991: Evaluation of Cancer Outcomes**

Study Citation:	Siemiatycki, J (1991). Risk factors for cancer in the workplace
Data Type:	Perc_exposed worker_kidney 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 and the provincial electoral list of 1981. 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	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 interviewed 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 was not estimated; study was initiated in 1979 with exposures occurring before or between 1945-1975.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histological or autopsy confirmation of primary tumor site.

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

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	ORs with 90% CIs were used.
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 results, selected for associations where power was adequate (# participants and at least 2% exposure).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	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:	Perc_exposed worker_kidney 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 13: **Asal et al. 1988: Evaluation of Cancer Outcomes**

Study Citation:	Asal, NR; Geyer, JR; Risser, DR; Lee, ET; Kadamani, S; Cherng, N (1988). Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions Cancer Detection and Prevention, 13(3-4,3-4), 263-279
Data Type:	Case-Control_RCC_Occupational_OR_males-Cancer
HERO ID:	184386

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Some key elements of the study design and information on the population (i.e., methods of participant selection) are not reported. The article cites a prior study with details on case and control selection.
	Metric 2: Attrition	Medium	× 0.4	0.8	Excluded (number not reported) were any conditions the individuals may have had during the 3 years preceding the interview.
	Metric 3: Comparison Group	High	× 0.2	0.2	Two control groups were selected. A hospital group of 313 patients were matched to the cases by age, sex, race, hospital, and date of admission. A second group of 336 sex- and age-matched population controls were selected by random digit dialing. In addition, differences in baseline characteristics of groups were considered as potential confounding variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Occupational history served as a surrogate for exposure. Full occupational histories were collected for any job held > 1 year. Subjects with the longest job held in the dry cleaning industry were considered exposed to dry cleaning solvents. Since Perc was used extensively as a primary dry cleaning solvent in the 1960s and 1970s, employment in this occupation at the time was considered an acceptable proxy for Perc exposure. Although the dates of employment are not stated in the study, publication date of 1988 and analysis of lifetime exposure is expected to result in a significant overlap with the occupation in the dry cleaning industry during a time of high Perc exposure.

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Study Citation:	Asal, NR; Geyer, JR; Risser, DR; Lee, ET; Kadamani, S; Cherng, N (1988). Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions Cancer Detection and Prevention, 13(3-4,3-4), 263-279
Data Type:	Case-Control_RCC_Occupational_OR_males-Cancer
HERO ID:	184386

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Occupation in the dry cleaning industry served as a proxy for Perc exposure. As the majority of occupational Perc exposure was limited to this industry, the use of the general population and hospitalized population (not in dry cleaning industry) as control groups resulted in to 2 exposure levels (exposed, unexposed).
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established, but it is unclear whether exposures fall within relevant exposure windows for renal cancer.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was risk of RCC. RCC diagnosis confirmed (95% by issue, 5% by X-ray).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All the study's measured outcomes are reported, effect estimates reported with confidence interval; number of cases/controls reported for most analyses.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses using statistical models for covariate adjustment.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. The paper did not describe if the interviews to gather demographic characteristics was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-pollutant exposures are likely for occupations involving perc (i.e., workers exposed to dry-cleaning solvents). However, there is no direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., case-control for assessment of rare disease in relation to dry cleaning solvent exposure), and appropriate statistical methods (i.e., multivariate logistic regression, cox linear logistic regression) were employed to analyze data.

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Study Citation:	Asal, NR; Geyer, JR; Risser, DR; Lee, ET; Kadamani, S; Cherng, N (1988). Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions Cancer Detection and Prevention, 13(3-4,3-4), 263-279
Data Type:	Case-Control_RCC_Occupational_OR_males-Cancer
HERO ID:	184386

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study included 315 RCC cases, 313 hospital controls, and 336 population controls. Limited data available for dry cleaning industry resulted in low statistical power, but ORs reported by gender (males: 3 cases, 6 controls; females: 8 cases, 1 control).
	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	Multivariate logistic regression models were used to obtain ORs and 95% confidence limits. 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	
	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 14: **Stewart et al. 1970: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_nervous-Neurological/Behavior
HERO ID:	3141

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	Sixteen healthy male subjects were recruited from laboratory personnel, ranging in age from 24 to 64 years of age. For repeated exposures, male subjects were aged 36 to 64 years. Participants were noted to be healthy for the previous 6 years. Further details on selection are not provided.
Metric 2:	Attrition	Medium	× 0.4	0.8	Only five of the sixteen recruited subjects were included in the repeated exposure group. The reason for the use of this sub-sample was not described. However, in the repeated exposure experiment, all five subjects were followed for each exposure period.
Metric 3:	Comparison Group	Medium	× 0.2	0.4	A control group was not utilized in this study design. The study authors state that they were unable to confine the same participants in a control exposure scenario, but no other information is provided. Subjects clinical chemistry, and urinalysis results were compared to reference values obtained 1 hour prior to exposure. Cognitive function test were preformed throughout exposure, and results were compared to references (source not clear).
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Purity of the test material was reported (99.6 percent) and the inhalation chamber was adequately described. The mean, standard deviation, and range of exposure over each exposure period was reported. Concentrations of perchloroethylene in the exposure chamber were determined using both infrared spectroscopy and gas chromatography with a hydrogen flame detector (GC-FID).
Metric 5:	Exposure levels	Low	× 0.2	0.6	Only one level of exposure was used for this study. There was no concurrent control and subjects could only be compared to data from prior examinations and reference values for clinical chemistry endpoints.

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_nervous-Neurological/Behavior
HERO ID:	3141

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Each subject in the repeated exposure study had been followed for six years prior to the study. It is assumed this was performed as routine occupational medical examinations and screenings. Samples were taken just prior to exposure, and effects were measured after exposure, establishing temporality between exposure and effects.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	A physical examination was performed prior to each exposure period. A pre-exposure blood sample was collected and clinical chemistry endpoints were measured. Each subject also provided urine for urinalysis. During exposure, subjective measures and measures of cognitive function (Crawford manual dexterity, Flannagan coordination, arithmetic, and inspection tests, and a modified Romberg test) were collected each hour. There was no control group, so investigators and participants would not have been blinded to exposure. This represents a mixture of methods with high validity (clinical chemistry/urinalysis) and methods with uncertain validity and a concern for lack of blinding (cognitive and subjective measures).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All outcomes outlined in the abstract, introduction, and methods were described either quantitatively or qualitatively in the results. Most figures and tables include standard error or standard deviation.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates were not included in the analysis. All subjects were adult males. The subjects are described to be of the same occupation and BMI was addressed by qualitatively comparing expired concentrations of perchloroethylene and subject BMI.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Age, sex, BMI, and occupational title were all presumably obtained by physical examination and employment records.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Inhalation chambers were monitored by IR and GC-FLD. There was no indication of co-exposures.
Domain 5: Analysis						

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_nervous-Neurological/Behavior
HERO ID:	3141

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study utilized a controlled inhalation exposure to perchloroethylene. No concurrent control group was employed and participants clinical chemistry and cognitive function results were compared to reference values.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sixteen subjects were included in the single exposure experiment while five subjects were utilized in the repeated exposure experiment. All five subjects were adult males. This represents a small sample size and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Results are presented with number of subjects, ranges and means. Analysis are well described and could be reproduced given original data.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Results were compared to reference values and described qualitatively only. So no analysis was provided. Only toxicokinetic data (elimination of perchloroethylene via exhalation) was provided in a quantitative manner.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene was measured in expired air from exposed subjects, collected in Saran bags or glass pipettes. This is a direct measurement of perchloroethylene in expired air.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	The limit of detection is not reported, however, reported data indicate that concentrations were above the limit of detection in all subjects for the duration of follow-up (16 days post exposure).
	Metric 19:	Biomarker stability	High	NA	NA	Sample storage was described. Samples collected in glass pipettes were analyzed within 16 hours and samples from Saran bags were analyzed within 2 hours of collection. There was no reported loss of samples.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	There was no documentation in regard to sample contamination.
	Metric 21:	Method requirements	Low	× 0.2	0.6	Samples from Saran bags were analyzed using infrared spectroscopy and samples from glass pipettes were analyzed using gas chromatography (assumed to be GC-FID).
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary for samples of breath.

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_nervous-Neurological/Behavior
HERO ID:	3141

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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 15: **Mandel et al. 1995: Evaluation of Cancer Outcomes**

Study Citation:	Mandel, JS; Mclaughlin, JK; Schlehofer, B; Mellemgaard, A; Helmert, U; Lindblad, P; Mccredie, M; Adami, HO (1995). International renal-cell cancer study. IV. Occupation International Journal of Cancer, 61(5,5), 601-605
Data Type:	Perc_renal cell cancer case-control study_OR_occupational_1-7years-Cancer
HERO ID:	188259

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, and 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	There was moderate attrition with response rates of 72.3% for cases and 74.7% for controls.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls were frequency matched to cases by gender and 5-year age groups and selected from populations giving rise to the cases, such as registers covering the entire population (Denmark, Uppsala), electoral rolls (Sydney), residential lists (Berlin, Heidelberg), or Health Care Financing Administration lists (Minnesota). In addition, differences in baseline characteristics of groups were considered as potential confounding variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Occupational history served as a surrogate for exposure. Participants from Australia, Denmark, Germany, Sweden, and the US were determined to be occupationally exposed to dry cleaning solvents if they reported working in the dry cleaning industry or with dry cleaning solvents for > 1 year. Since Perc was used extensively as the primary dry cleaning solvent in the 1960s and 1970s, employment in the dry cleaning industry at the time was considered an acceptable proxy for Perc exposure. Although the dates of employment are not stated in the study, the diagnosis of renal cell carcinoma in 1989-1991 and analysis of lifetime exposure is expected to result in a significant overlap with the occupation in the dry cleaning industry during a time of high Perc exposure.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Occupation in the dry cleaning industry served as a proxy for Perc exposure. As the majority of occupational Perc exposure was limited to this industry, the general population served as a reasonable control group.

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Study Citation:	Mandel, JS; Mclaughlin, JK; Schlehofer, B; Mellemgaard, A; Helmert, U; Lindblad, P; Mccredie, M; Adami, HO (1995). International renal-cell cancer study. IV. Occupation International Journal of Cancer, 61(5,5), 601-605
Data Type:	Perc_renal cell cancer case-control study_OR_occupational_1-7years-Cancer
HERO ID:	188259

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Case participants had been diagnosed with cancer between 1989 and 1991. Duration of occupational exposures (as determined by interviews) were reported, but not timing relative to cancer diagnosis. For dry-cleaning solvents, the duration of exposure was 1-7, 8-25, and 26-60 years, which is likely to encompass the etiologically relevant period of exposure. Therefore, temporality is established, and it is likely that exposures fall within relevant exposure windows for renal cancer for those participants with a higher duration of exposure (8-25, 26-60 years).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histopathologically confirmed renal cell cancer diagnosis between 1989 and 1991 served as the diagnostic criterion. 4-digit ICD-9 codes presented.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All the study's measured outcomes are reported, effect estimates (RR) reported with confidence interval; number of cases/controls reported for analyses.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses using statistical models for covariate adjustment. Specifically, the analyses were adjusted for age, study center, BMI, education, and pre-1987 smoking, which was divided into pack-year quartiles based on the separate distribution of male and female controls. Differences across centers were evaluated using heterogeneity tests.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Participants were interviewed by trained interviewers (either at home, or in a hospital) about factors including smoking habits, BMI, education, drug use, family history of cancer, and alcohol use. Four of the study centers also inquired about occupational history and exposure. The other two study centers collected occupational and exposure information elsewhere (not clearly stated how/where; this information may be included in the publication cited by this report as containing full methods description). The paper did not describe how the interviewers were trained, and if the materials/methods used to gather demographic characteristics were validated.

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Study Citation:	Mandel, JS; Mclaughlin, JK; Schlehofer, B; Mellemgaard, A; Helmert, U; Lindblad, P; Mccredie, M; Adami, HO (1995). International renal-cell cancer study. IV. Occupation International Journal of Cancer, 61(5,5), 601-605
Data Type:	Perc_renal cell cancer case-control study_OR_occupational_1-7years-Cancer
HERO ID:	188259

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The study report does not address potential co-exposures. Co-pollutant exposures are likely for occupations involving perc (i.e., workers exposed to dry-cleaning solvents). However, there is no direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., case-control for assessment of rare disease in relation to dry cleaning solvent exposure), and appropriate statistical methods (i.e., multivariate logistic regression) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Table 2 reported limited participants in dry cleaning industry (males: 8 cases, 12 controls; females: 15 cases, 16 controls). OR were reported only for males, despite the lower statistical power. However, the ORs in Tables 3 and 4 indicate >200 cases and controls.
	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	Multivariate logistic regression models were used to obtain ORs and 95% confidence limits. The variables included in the models is stated, and although the rationale for variable selection is not described they represent key potential confounders of interest (i.e., age smoking status, BMI, education). 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~~ ⟶ Medium§		~~1.6~~	
Extracted			Yes			

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Study Citation:	Mandel, JS; Mclaughlin, JK; Schlehofer, B; Mellemgaard, A; Helmert, U; Lindblad, P; Mccredie, M; Adami, HO (1995). International renal-cell cancer study. IV. Occupation International Journal of Cancer, 61(5,5), 601-605
Data Type:	Perc_renal cell cancer case-control study_OR_occupational_1-7years-Cancer
HERO ID:	188259

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: "Medium rating assigned due to use of occupation in dry cleaning industry as a surrogate of Perc exposure."

Table 16: **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_Perc_AstrocyticBrainCancer_Q1-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 reporting a hospital diagnosis of astrocytic brain tumor were 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, 30 subjects with electronics-related jobs were omitted.
	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 were used.
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_Perc_AstrocyticBrainCancer_Q1-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 the 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_Perc_AstrocyticBrainCancer_Q1-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	Covariates were characterized within the methods, study population section. Confounders not assessed by a method or instrument used in previous analyses. 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. The retrospective case-control design 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_Perc_AstrocyticBrainCancer_Q1-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 17: **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, <= 9.1 ppm*yrs PCE_B-NHL-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	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	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	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, <= 9.1 ppm*yrs PCE_B-NHL-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	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	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses using statistical models for covariate adjustment and matching by gender, region and age.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	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	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	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	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. Note: For some subgroups, effect estimate is based on a small number of cases and controls.

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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, <= 9.1 ppm*yrs PCE_B-NHL-Cancer
HERO ID:	194429

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	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 18: **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 perc-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 perc-Cancer
HERO ID:	194813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Renal cell carcinomas 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 perc-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 19: **Echeverria et al. 1995: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Echeverria, D; White, RF; Sampaio, C (1995). A behavioral evaluation of PCE exposure in patients and dry cleaners: A possible relationship between clinical and preclinical effects Journal of Occupational and Environmental Medicine, 37(6), 667-680
Data Type:	PCE_Pattern Memory_Number Correct_adjusted-Neurological/Behavior
HERO ID:	195893

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Subjects selection and inclusion/exclusion criteria are described in detail, for both exposed and unexposed subjects. High worker participation at locations where the owners agreed to participate. However, only 23 of 125 (18%) of dry cleaner shops agreed to participate. The authors noted, that, 'low participation rates among owners could not be explained by the level of exposure, quality of housekeeping, or health status of the owner'. Authors interviewed owners that did not participate. It's unlikely however that these refusals significantly biased the selection of participants. Likelihood of healthy worker selection bias is low since workers did not migrate between job titles and held multiple job titles simultaneously.
	Metric 2: Attrition	High	× 0.4	0.4	Minimal missing data. 65 of 66 subjects tested were included in the analyses. One operator was omitted because he worked with stoddard solvent.
	Metric 3: Comparison Group	High	× 0.2	0.2	Inclusion/exclusion criteria were the same for all subjects. Differences in baseline characteristics of subjects by exposure group were considered as potential confounding or stratification variables in the statistical analyses.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Lifelong chronic exposure was based on exposures associated with complete work histories, hobbies, and industrial hygiene evaluations of subjects in participating shops. PCE concentration in breath and air was assigned to each job title and one of three exposure categories. The sum of the product of an exposure for each job title multiplied by the duration of employment in months was used to compute the index. The percent time for each job within a week also was recorded since reliance on job title alone would introduce misclassification without accounting for workers who do several jobs within a week. Unclear whether methods have been previously validated, and LOD/LOQs not provided.

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Study Citation:	Echeverria, D; White, RF; Sampaio, C (1995). A behavioral evaluation of PCE exposure in patients and dry cleaners: A possible relationship between clinical and preclinical effects Journal of Occupational and Environmental Medicine, 37(6), 667-680
Data Type:	PCE_Pattern Memory_Number Correct_adjusted-Neurological/Behavior
HERO ID:	195893

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Lifetime exposure to PCE is likely to fall within the etiologically relevant window. However, it is unclear whether current exposures fall within relevant exposure windows for the outcomes of interest.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The neurobehavioral test outcomes assessed are well established. Test procedures are well described. No information is provided on whether the interviewers were trained prior to test administration. Not all patients received the exact same battery tests.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported, effect estimates and SD, and p-values reported; number of subject in each exposure category reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Analyses accounted for age, years of education, verbal skill, the frequency of alcohol consumption, hours of sleep, fatigue, mood, symptoms, medication, and secondary exposures to neurotoxins from different jobs, previous jobs, or hobbies.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Potential confounders were assessed from self-reported information and from the job matrix. It is unclear how/whether this information was validated at all.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Secondary exposures to neurotoxins from different jobs, previous jobs, or hobbies were accounted for in the analyses. The authors noted that other chemical exposure occurring in the workplace included isopropylacetate, acetone, TCE, 1.1,1-trichloroethane, and some alkaline. However, the these solvents were not detected participant breath, and the authors note 'PCE is considered the only significant solvent exposure metric'.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (cross-sectional) and appropriate statistical methods (multivariate regression) were employed to analyze data.

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Study Citation:	Echeverria, D; White, RF; Sampaio, C (1995). A behavioral evaluation of PCE exposure in patients and dry cleaners: A possible relationship between clinical and preclinical effects Journal of Occupational and Environmental Medicine, 37(6), 667-680
Data Type:	PCE_Pattern Memory_Number Correct_adjusted-Neurological/Behavior
HERO ID:	195893

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants (65) were adequate to detect an effect between the high versus low exposed groups.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of the analyses is sufficient to understand what has been done (multiple linear regression) and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Multivariate regression models were used to generate mean changes in test performance. Rationale for variable selection is 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‡			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.

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

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: **Cavalleri et al 1994: Evaluation of Ocular And Sensory Outcomes**

Study Citation:	Cavalleri, A; Gobba, F; Paltrinieri, M; Fantuzzi, G; Righi, E; Aggazzotti, G (1994). Perchloroethylene exposure can induce colour vision loss Neuroscience Letters, 179(1-2), 162-166
Data Type:	CCI_All Workers-Ocular and Sensory
HERO ID:	195942

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Some key elements of the study design were not present but available information indicates a low risk of selection bias. The study authors note how many exposed subjects and unexposed controls were identified. However, the source population for the controls, which consisted of workers without occupational or vocational exposures to solvents or other eye-toxic substances was not reported.
	Metric 2:	Attrition	High	× 0.4	0.4	No exclusion from the analysis sample and outcome data and exposure were largely complete.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Exposed subjects were matched to controls (unexposed) by sex, age, alcohol consumption, and cigarette smoking. Number of controls was reported. Controls were workers without occupational or vocational exposures to solvents or other eye-toxic substances was not discussed. The source population for the controls was not discussed.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was directly measured (personal measurements collected using passive samplers for the whole work-shift of a single day), but no description provided of the monitoring protocol (e.g., NIOSH) and validation measures applied to sampling equipment. It's unclear whether lack of exposure was confirmed in controls.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported (see Fig 1).
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established and the interval between the exposure and the outcome 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: The outcome of Color Confusion Index (CCI) was assessed using well-described methods, under standardized conditions for all subjects.

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Study Citation:	Cavalleri, A; Gobba, F; Paltrinieri, M; Fantuzzi, G; Righi, E; Aggazzotti, G (1994). Perchloroethylene exposure can induce colour vision loss Neuroscience Letters, 179(1-2), 162-166
Data Type:	CCI_All Workers-Ocular and Sensory
HERO ID:	195942

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All of the study's measured outcomes and the number exposed for each analysis are reported, Effect estimates from multivariate analyses are reported as correlation coefficient with p-values (no SDs or confidence intervals); the results of the comparison between controls and exposed workers are presented as means and SDs with p-values for significance.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Exposed subjects were matched by age, sex, alcohol consumption and cigarette smoking. Multivariate analyses also adjusted for seniority and calculated grams of pure ethanol/die (co-exposure).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on potential confounders was evaluated based on questionnaires collected by a physician during the physical examination. There is no information on whether the questionnaire was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The analyses considered calculated grams of pure ethanol/die as a potential co-exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design and appropriate statistical methods (e.g., t-tests, multivariate regression analyses) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The numbers of participants (35 exposed and 35 controls) were adequate to detect an effect in the exposed population.
	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	Comparisons between groups means assessed with appropriate techniques (t-tests and Mann-Whitney U-tests.); multivariate regression models were used to generate mean changes in color confusion index in relation to Perc (TWA levels). Rationale for variable selection is presented. Normality was assessed.
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:	Cavalleri, A; Gobba, F; Paltrinieri, M; Fantuzzi, G; Righi, E; Aggazzotti, G (1994). Perchloroethylene exposure can induce colour vision loss Neuroscience Letters, 179(1-2), 162-166
Data Type:	CCI_All Workers-Ocular and Sensory
HERO ID:	195942

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	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 21: **Altmann et al. 1990: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	L. Altmann, A. Böttger, H. Wiegand (1990). Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans International Archives of Occupational and Environmental Health, 62(7,7), 493-499
Data Type:	InhalationStudy_Germany_Perc_neurological-Neurological/Behavior
HERO ID:	195943

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	22 healthy male volunteers with a mean age of 26.5 years (range 23 to 35 years) were exposed in an inhalation chamber in Germany to 10 ppm ("control group", n=12) and 50 ppm Perc (exposed group, n=10). Participants were randomly assigned to either exposure group. Authors do not provide any details on participants recruitment.
Metric 2:	Attrition	Medium	× 0.4	0.8	Authors do not provide any details on participants recruitment, but no attrition is discussed.
Metric 3:	Comparison Group	Medium	× 0.2	0.4	The "control group" was exposed to 10 ppm which is above the odor threshold of about 5 ppm so that the participants were "naive with respect to the concentration they were exposed to." Demographic and lifestyle characteristics, besides age, were not reported for both control and exposed subjects.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Source and purity of the test article was reported and were sufficient. The inhalation chamber was adequately described. During the exposure period, Perc concentration in the chamber was measured every 5 min by gas chromatography. Perc concentrations in the blood were measured as a biomarker of exposure.
Metric 5:	Exposure levels	Medium	× 0.2	0.4	Exposure occurred in an inhalation chamber where 10 and 50 ppm Perc were dispersed using a fan. Participants were exposed for 4h. 50 ppm was the permissible workplace level in the Federal Republic of Germany. Perc levels in blood are reported as mean +/- standard deviation (SD) in each exposure group for Days 2 to 6 and three time-points in days 2 to 5.
Metric 6:	Temporality	High	× 0.4	0.4	Sensory testing was conducted on Day 1 (control, no exposure) and on Days 2-5 they started after 2-h exposure. On Day 6 some participants were tested again in the chamber with no exposure. Temporality is deemed appropriate for this endpoint.
Domain 3: Outcome Assessment					

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Study Citation:	L. Altmann, A. Böttger, H. Wiegand (1990). Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans International Archives of Occupational and Environmental Health, 62(7,7), 493-499
Data Type:	InhalationStudy_Germany_Perc_neurological-Neurological/Behavior
HERO ID:	195943

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Visuotoxicity and ototoxicity were assessed by neurophysiological and psychophysical methods to find potential sensory nervous system dysfunction at the subclinical level. Neuronal processing time and contrast perception were measured by visually evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs). Also, visual contrast sensitivity (CS) was measured in some participants by psychophysical methods (spatial two-alternative, forced-choice staircase procedure). Methods for measuring VEPs, BAEPs and CS are detailed in the manuscript. The authors report that availability of the apparatus for measuring the CS was limited and measurements were only performed on five participants, not allowing for statistical relevant statements.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	VEP peak latencies are reported as mean +/- SD in each exposure group for Days 1 to 5 (Table 3) for three out of six VEPs and in graphical form for all (Figure 1). The authors state that measurements on Day 6 were only conducted in a subset of the participants, but they do not report how many were measured, and only report measurements for one subject (Table 2). Only part of the dose-effect linear regression models are reported in the text. BAEPs results are not reported quantitatively, the authors state that differences in peak latencies between exposure groups did not reach statistical significance. Visual contrast sensitivity is reported in graphical form and in the text as sensitivity (defined as the reciprocal of the threshold contrast) and as mean differences (and SD) of the contrast sensitivity values between the control day and the last exposure day for the two groups.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	L. Altmann, A. Böttger, H. Wiegand (1990). Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans International Archives of Occupational and Environmental Health, 62(7,7), 493-499
Data Type:	InhalationStudy_Germany_Perc_neurological-Neurological/Behavior
HERO ID:	195943

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Linear regression models were used to assess the dose-effect relationship between Perc concentrations in blood and VEP changes. No covariate adjustments are mentioned. However, the authors state that participants were healthy male adults, they report age ranges and report that participants stated that they were not occupationally exposed to solvents nor using any drugs, which implies that a questionnaire was administered.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	No covariate characterization is reported, except for participants age (mean and range), healthy status and no use of drugs. All covariate collection appeared to be self-reported.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	No indication of other co-exposures of concern. According to the authors, "all subjects stated that they had had no occupational exposure to solvents and none were using any kind of drug at the time of the experiment."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	In this experimental study, healthy participants were randomly assigned to two groups exposed to Perc (10ppm and 50ppm) in an inhalation chamber. Paired analyses and a linear regression model were used to determine the relationships between Perc concentrations in blood and changes in sensory nervous system function (visual and auditory).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistical power was sufficient to determine an effect in one of the endpoints (changes in VEPs) and likely in the other endpoint with the same number of participants, although no effect was detected (changes in BAEPs). However, statistical power was insufficient for analysis of CS, as noted by the authors.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The authors do not report details on the paired analyses and linear regression model used.
	Metric 15:	Statistical models	Low	× 0.2	0.6	A linear regression model was used to determine the relationship between Perc concentrations in blood and changes in VEP. However, the authors do not provide any details on this model.
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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Study Citation:	L. Altmann, A. Böttger, H. Wiegand (1990). Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans International Archives of Occupational and Environmental Health, 62(7,7), 493-499
Data Type:	InhalationStudy_Germany_Perc_neurological-Neurological/Behavior
HERO ID:	195943

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 16:	Use of Biomarker of Exposure	High	× 0.167	0.17	Levels of Perc in blood were used as a biomarker of exposure. Perc concentration in the blood was measured immediately before exposure started (8:00am), after a 2-h inhalation period (10:00am) and at the end of exposure (12:00pm) and determined by gas chromatography.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No effect biomarker.
	Metric 18:	Method Sensitivity	Medium	× 0.167	0.33	The detection limit was 0.5 µg Perc/L blood.
	Metric 19:	Biomarker stability	Low	× 0.167	0.5	The authors do not provide details regarding sampling handling and storage history. They report blood collection times and Perc measurement method.
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	No indication that contamination occurred, but no description of ways to the authors took steps to avoid contamination.
	Metric 21:	Method requirements	Medium	× 0.167	0.33	Authors only mention that Perc concentrations in blood "were analyzed by gas chromatography (Siemens Sichromat 1) with an electron capture detector using the headspace technique."
	Metric 22:	Matrix adjustment	Low	× 0.167	0.5	Details on exposure biomarker methods and matrix adjustment are not described in this study.
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 =≥ 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 22: **Emara et al. 2010: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Emara, A. M.,Abo El-Noor, M. M.,Hassan, N. A.,Wagih, A. A. (2010). Immunotoxicity and hematotoxicity induced by tetrachloroethylene in egyptian dry cleaning workers Inhalation Toxicology, 22(2), 117-124
Data Type:	Perc_exposed workers_hematological immune-Hematological and Immune
HERO ID:	380744

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Limited information on the setting and inclusion/exclusion criteria were reported. Participants (n = 80) were disease-free, and included perc-exposed dry-cleaning workers from various workshops (not specified) and controls matched by age and lifestyle in Tanta, Egypt. Control and perc-exposed workers were further divided into 4 groups (20/group) by smoking status. The time period during which participants were recruited was not specified.
	Metric 2: Attrition	High	× 0.4	0.4	There was no reported withdrawal from the study and outcome data were complete (i.e., analyses were based on n = 20 subjects per group).
	Metric 3: Comparison Group	Medium	× 0.2	0.4	The study showed that controls and perc-exposed workers were similar with respect to age and smoking status (Table 1); it was reported that the frequency distributions of lifestyle confounding factors were not significantly different among groups. It is assumed (but not specified) that controls were recruited within a similar time frame/from a similar population as cases.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Exposure was consistently assessed in all participants using a well-established method to directly measure exposure (e.g., measurement of the perc in the blood). Perc levels were also measured at five sites within each workshop.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Two levels of exposure were reported (exposed and non-exposed).
	Metric 6: Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure and outcome Participants had been exposed to perc for approximately 7 years prior to the outcome assessment.
Domain 3: Outcome Assessment					

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Study Citation:	Emara, A. M.,Abo El-Noor, M. M.,Hassan, N. A.,Wagih, A. A. (2010). Immunotoxicity and hematotoxicity induced by tetrachloroethylene in egyptian dry cleaning workers Inhalation Toxicology, 22(2), 117-124
Data Type:	Perc_exposed workers_hematological immune-Hematological and Immune
HERO ID:	380744

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes were assessed in cases and controls using well-established methods (with respect to determination of total and differential blood counts, serum immunoglobulins, interferon-gamma and interleukin-4).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Data for measured outcomes (as reported in the methods) were provided. All data were analyzed statistically for differences between treated groups compared to controls (presented as means and SD, with numbers of cases/controls clearly specified). Pearson correlation coefficients were used to determine the relationship between perc exposure and the affected parameters.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The distribution of potential confounders did not differ significantly between cases and controls. All participants were male, and it was indicated that cases were matched to controls by age and lifestyle factors.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	The method to assess confounders was not explicitly specified, but there was little to no evidence of confounding. The study indicated only that occupational and medical history (including smoking status) "were prepared" for all participants.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	It is possible that dry cleaning workers may likewise be exposed to TCE (not mentioned or adjusted for in the analyses).
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	The study design chosen was appropriate for the research question (address the association between perc exposure and hematological/immune effects) and uses statistical analyses to address the research question (Student's t-test and ANOVA/Tukey-Kramer multiple comparison test to evaluate initial differences and Peason correlation coefficient to evaluate affected parameters).
	Metric 13:	Statistical power	Medium	× 0.25	0.5	The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	The description of the analysis is sufficient to understand what has been done and is conceptually reproducible.

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Study Citation:	Emara, A. M.,Abo El-Noor, M. M.,Hassan, N. A.,Wagih, A. A. (2010). Immunotoxicity and hematotoxicity induced by tetrachloroethylene in egyptian dry cleaning workers Inhalation Toxicology, 22(2), 117-124
Data Type:	Perc_exposed workers_hematological immune-Hematological and Immune
HERO ID:	380744

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Not Rated	NA	NA	The study did not use a statistical model.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perc levels in the blood are an adequate measure of perc exposure (with the parent chemical itself being measured). The study indicated that perc in the blood was determined to be the most reliable biological indicator or perc exposure based on data from another study (Skender et al. 1991).
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarker of effect was measured.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	The detection limit of perc in the blood was 0.5 ug/L; perc was detectable in the blood of non-exposed controls (0.11 ug/L).
	Metric 19:	Biomarker stability	High	NA	NA	The study indicated that blood samples were snap frozen and immediately stored at -20C until quantification.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	Samples are presumed to be contamination-free from the time of collection to the time of measurement.
	Metric 21:	Method requirements	Medium	× 0.2	0.4	The study used instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (GC–ECD).
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	This metric is not applicable to the biomarker.
Overall Quality Determination‡			High		1.6	
Extracted			No			

⋆ 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 23: **Toraason et al. 2003: Evaluation of Genotoxicity Outcomes**

Study Citation:	Toraason, M., Butler, M. A., Ruder, A., Forrester, C., Taylor, L., Ashley, D. L., Mathias, P., Marlow, K. L., Cheever, K. L., Krieg, E., Wey, H. (2003). Effect of perchloroethylene, smoking, and race on oxidative DNA damage in female dry cleaners Mutation Research: Genetic Toxicology and Environmental Mutagenesis, 539(1-2,1-2), 9-18
Data Type:	PERC_exposed workers_DNA damgae-Other (please specify below)
HERO ID:	628944

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Time frame in which participants were recruited, rate of participation, and exclusion criteria were not reported. The study population was dry cleaning and laundry (control) workers from shops near Cincinnati, OH.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of individuals were not reported at important stages of study. Reasons were not provided for non-participation at each stage.
	Metric 3:	Comparison Group	High	× 0.2	0.2	"Eighteen dry cleaning workers and 20 laundry workers (controls) were recruited from seven shops in and around Cincinnati, OH, USA. All participants were women, under the age of 70 who had worked in the dry cleaning or laundry industry for at least 1 year...[Referents] matched by race, smoking status, and age (±5 years when possible) to already selected dry cleaners. Ethnic differences ...were of similar distribution". "Laundry workers had not previously worked in a facility with exposure to PERC." It is assumed but not specified that exposed and referent subjects were recruited contemporaneously.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposure level for both groups measured by personal breathing zone samples collected on two days of a typical work week and by analysis for PERC in blood "collected from dry cleaners before work following three consecutive days of PERC exposure, and from launderers on a typical work day."
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Two exposure levels (exposed, unexposed).

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Study Citation:	Toraason, M., Butler, M. A., Ruder, A., Forrester, C., Taylor, L., Ashley, D. L., Mathias, P., Marlow, K. L., Cheever, K. L., Krieg, E., Wey, H. (2003). Effect of perchloroethylene, smoking, and race on oxidative DNA damage in female dry cleaners Mutation Research: Genetic Toxicology and Environmental Mutagenesis, 539(1-2,1-2), 9-18
Data Type:	PERC_exposed workers_DNA damgae-Other (please specify below)
HERO ID:	628944

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Blood was collected after 3 consecutive days PERC exposure; urine collected same day before and after shift. DNA damage was measured in urine and in same blood samples used for PERC analysis. Temporality was generally established based on duration of exposure (exposed had worked for at least a year in dry cleaning prior to evaluation of DNA damage; unexposed had no prior work with PERC exposure).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes and techniques were described and appropriate (8-OHdG in urine and hydrolyzed leukocyte DNA).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	A description of measured outcomes is reported in the methods, abstract, and/or introduction, and relevant effect estimates (levels of 8-OHdG) were reported (mean, n, and SD) for all groups.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders; referent group matched on age , race, and smoking status; additional analyses performed with stratification by smoking status and race. Covariates in multiple linear regression models were alpha- and beta–gamma-tocopherols, beta-carotene, body mass index, urinary cotinine, age, and race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	While not specified, it is assumed that smoking status was initially based on questionnaire or interview, but urinary cotinine levels were also measured. Antioxidant serum levels (considered as covariates) were also measured.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	No information regarding potential TCE exposure was reported.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Design and statistics were appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Numbers of participants (18 exposed and 20 unexposed) were small but sufficient to detect a difference in leukocyte 8-OHdG level.

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Study Citation:	Toraason, M., Butler, M. A., Ruder, A., Forrester, C., Taylor, L., Ashley, D. L., Mathias, P., Marlow, K. L., Cheever, K. L., Krieg, E., Wey, H. (2003). Effect of perchloroethylene, smoking, and race on oxidative DNA damage in female dry cleaners Mutation Research: Genetic Toxicology and Environmental Mutagenesis, 539(1-2,1-2), 9-18
Data Type:	PERC_exposed workers_DNA damgae-Other (please specify below)
HERO ID:	628944

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Multiple linear regression models were used but model building process was not fully described.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	WHO reports high correlation between PERC in blood and PERC in environment. https://www.ncbi.nlm.nih.gov/books/NBK138706/
	Metric 17:	Effect biomarker	Not Rated	NA	NA	This metric is not applicable to the study design.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	PERC in blood measured by GC/MS; the LOD was reportedly 0.023 ppm. Levels of perc TWA in laundries was below if the limit of detection.
	Metric 19:	Biomarker stability	High	NA	NA	Blood samples for measuring PERC were collected in gray-top vacutainers . Whole blood samples were kept at refrigerator temperature until analysis.
	Metric 20:	Sample contamination	High	× 0.2	0.2	Measures taken to prevent contamination before collection and during storage: "Blood samples for measuring PERC were collected in gray-top vacutainers that had been previously processed to remove volatile contaminants" and were stored until analyzed.
	Metric 21:	Method requirements	Medium	× 0.2	0.4	PERC was analyzed by GC/MS. "Detection, identification, and quantification of PERC was done by GC/MS. Quantification was achieved by isotope dilution and reference to commercially available standard compounds"
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Not adjusted for matrix.
Overall Quality Determination‡			Medium		1.8	
Extracted			No			

⋆ 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: **Anderson et al. 1999: Evaluation of Cancer Outcomes**

Study Citation:	Andersen, A; Barlow, L; Engeland, A; Kjaerheim, K; Lynge, E; Pukkala, E (1999). Work-related cancer in the Nordic countries Scandinavian Journal of Work, Environment and Health, 25(Suppl. 2,Suppl. 2), 1-116
Data Type:	Cohort_Occupational_PERC_kidney_cancer_SIR-Cancer
HERO ID:	628971

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	The Nordic population surveyed was born between 1906 and 1945 and resided in Sweden, Denmark, Finland, and Norway in 1970. Participants identified from a national census in 1970 conducted by the head of household that were economically active were included in the analysis. Cohort includes over 10 million individuals.
	Metric 2:	Attrition	High	× 0.4	0.4	This study was retrospective. All records available from the 1970 census were included in the analysis; those that were not were excluded from analysis. For the Sweden subset, only those residents who also completed at 1960 census were included, thus recent immigrants (1% of the potential participants) were excluded.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	All economically active individuals were included in the cohort. Although the qualifications for this differed slightly by country, it is not expected to impact assessment. Occupational groups were compared relative to national averages.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Occupational history served as a surrogate for exposure. All participants worked through the 1960s (Netherlands); occupation was coded based on the current occupation and industry in the 1970 census. Since Perc was used extensively as a primary dry cleaning solvent in the 1960s and 1970s, employment in the dry cleaning industry at the time was considered an acceptable proxy for Perc exposure. In this study, launderers and dry cleaners were considered together. Authors note, "launderers handle soap and other chemical cleaning agents, while persons engaged in dry-cleaning have used different types of solvents, mainly tetrachloroethylene, supplemented with trichloroethylene and fluorocarbons."
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Occupation in the dry cleaning industry served as a proxy for Perc exposure. As the majority of occupational Perc exposure was limited to this industry, the general population served as a reasonable control group.

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Study Citation:	Andersen, A; Barlow, L; Engeland, A; Kjaerheim, K; Lynge, E; Pukkala, E (1999). Work-related cancer in the Nordic countries Scandinavian Journal of Work, Environment and Health, 25(Suppl. 2,Suppl. 2), 1-116
Data Type:	Cohort_Occupational_PERC_kidney_cancer_SIR-Cancer
HERO ID:	628971

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Work histories anticipated to range from 1921-1970. Cancer diagnosis determined from 1971-1987/91. Thus a 17+ year latency applies.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	National cancer registries from Finland, Denmark, Norway, Sweden were used to assess cancer incidence. Inclusion in registries occurred based on hospital records and some were stated to be histopathologically confirmed. Outcomes were classified using the ICD-7 codes. Outcomes were measured through a different end time-point per country (Denmark followed death and emigrations through 1987, Finland 1990, Norway 1991, and Sweden only followed deaths through 1989). Those individuals which developed multiple cancers were only counted once and classified only under the initial incident cancer.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Of the economically active and inactive persons, the observed number of cancers and standardized incidence ratio was reported between 1971-1991 by country and cancer site with a 95% confidence interval by gender; number per group was reported with each data table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates considered were gender, person-years, age, period, country.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders were reported by head of household in the 1970 census.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Cancer incidence related to 54 occupational groups. No specific individual chemical exposure was assessed, but significant co-exposures would be anticipated.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Cohort study evaluated the incidence of cancer associated with occupations., including dry cleaners, which served as a proxy for Perc exposure.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Cohort included 10 millions individuals. No statistical power was reported, but the large study population provides indirect evidence of sufficient statistical power.

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Study Citation:	Andersen, A; Barlow, L; Engeland, A; Kjaerheim, K; Lynge, E; Pukkala, E (1999). Work-related cancer in the Nordic countries Scandinavian Journal of Work, Environment and Health, 25(Suppl. 2,Suppl. 2), 1-116
Data Type:	Cohort_Occupational_PERC_kidney_cancer_SIR-Cancer
HERO ID:	628971

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Calculations used for the SIRs are clear and fully presented in methods, tables, and figures. All data needed to recreate analysis is provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Risk estimates were determined with SIRs for each country and the total study population.
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 25: **Stewart et al. 1970: Evaluation of Clinical Chemistry/Biochemical Outcomes**

Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_clinicalchemistry-Clinical Chemistry/Biochemical
HERO ID:	3141

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Sixteen healthy male subjects were recruited from laboratory personnel, ranging in age from 24 to 64 years of age. For repeated exposures, male subjects were aged 36 to 64 years. Participants were noted to be healthy for the previous 6 years. Further details on selection are not provided.
	Metric 2: Attrition	Medium	× 0.4	0.8	Only five of the sixteen recruited subjects were included in the repeated exposure group. The reason for the use of this sub-sample was not described. However, in the repeated exposure experiment, all five subjects were followed for each exposure period.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	A control group was not utilized in this study design. The study authors state that they were unable to confine the same participants in a control exposure scenario, but no other information is provided. Subjects clinical chemistry, and urinalysis results were compared to reference values obtained 1 hour prior to exposure. Cognitive function test were preformed throughout exposure, and results were compared to references (source not clear).
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Purity of the test material was reported (99.6 percent) and the inhalation chamber was adequately described. The mean, standard deviation, and range of exposure over each exposure period was reported. Concentrations of perchloroethylene in the exposure chamber were determined using both infrared spectroscopy and gas chromatography with a hydrogen flame detector (GC-FID).
	Metric 5: Exposure levels	Low	× 0.2	0.6	Only one level of exposure was used for this study. There was no concurrent control and subjects could only be compared to data from prior examinations and reference values for clinical chemistry endpoints.

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_clinicalchemistry-Clinical Chemistry/Biochemical
HERO ID:	3141

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Each subject in the repeated exposure study had been followed for six years prior to the study. It is assumed this was performed as routine occupational medical examinations and screenings. Samples were taken just prior to exposure, and effects were measured after exposure, establishing temporality between exposure and effects.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	A physical examination was performed prior to each exposure period. A pre-exposure blood sample was collected and clinical chemistry endpoints were measured. Each subject also provided urine for urinalysis. During exposure, subjective measures and measures of cognitive function (Crawford manual dexterity, Flannagan coordination, arithmetic, and inspection tests, and a modified Romberg test) were collected each hour. There was no control group, so investigators and participants would not have been blinded to exposure. This represents a mixture of methods with high validity (clinical chemistry/urinalysis) and methods with uncertain validity and a concern for lack of blinding (cognitive and subjective measures).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All outcomes outlined in the abstract, introduction, and methods were described either quantitatively or qualitatively in the results. Most figures and tables include standard error or standard deviation.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates were not included in the analysis. All subjects were adult males. The subjects are described to be of the same occupation and BMI was addressed by qualitatively comparing expired concentrations of perchloroethylene and subject BMI.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Age, sex, BMI, and occupational title were all presumably obtained by physical examination and employment records.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Inhalation chambers were monitored by IR and GC-FLD. There was no indication of co-exposures.
Domain 5: Analysis						

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_clinicalchemistry-Clinical Chemistry/Biochemical
HERO ID:	3141

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study utilized a controlled inhalation exposure to perchloroethylene. No concurrent control group was employed and participants clinical chemistry and cognitive function results were compared to reference values.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sixteen subjects were included in the single exposure experiment while five subjects were utilized in the repeated exposure experiment. All five subjects were adult males. This represents a small sample size and results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Results are presented with number of subjects, ranges and means. Analysis are well described and could be reproduced given original data.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Results were compared to reference values and described qualitatively only. So no analysis was provided. Only toxicokinetic data (elimination of perchloroethylene via exhalation) was provided in a quantitative manner.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene was measured in expired air from exposed subjects, collected in Saran bags or glass pipettes. This is a direct measurement of perchloroethylene in expired air.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	The limit of detection is not reported, however, reported data indicate that concentrations were above the limit of detection in all subjects for the duration of follow-up (16 days post exposure).
	Metric 19:	Biomarker stability	High	NA	NA	Sample storage was described. Samples collected in glass pipettes were analyzed within 16 hours and samples from Saran bags were analyzed within 2 hours of collection. There was no reported loss of samples.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	There was no documentation in regard to sample contamination.
	Metric 21:	Method requirements	Low	× 0.2	0.6	Samples from Saran bags were analyzed using infrared spectroscopy and samples from glass pipettes were analyzed using gas chromatography (assumed to be GC-FID).
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary for samples of breath.

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Study Citation:	R. D. Stewart, E. D. Baretta, H. C. Dodd, T. R. Torkelson (1970). Experimental human exposure to tetrachloroethylene Archives of Environmental Health, 20(2,2), 224-229
Data Type:	perchloroethylene_controlled_inhalation_exposure_clinicalchemistry-Clinical Chemistry/Biochemical
HERO ID:	3141

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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 26: **Auperin et al. 1994: Evaluation of Cancer Outcomes**

Study Citation:	Auperin, A; Benhamou, S; Ory-Paoletti, C; Flamant, R (1994). Occupational risk factors for renal cell carcinoma: A case-control study Occupational and Environmental Medicine, 51(6,6), 426-428
Data Type:	Perc_Occupational_Renal cancer (RCC)-Cancer
HERO ID:	630334

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cases were identified from 10 hospitals in France between 1987-1991, and controls were patients for non-tobacco related diseases from the same hospitals. Patients with alcoholic cirrhosis or diabetes were excluded. One case and two controls refused participation. Cases had histologically proved renal cell carcinoma. Each case was matched for sex, age at interview (within five years), hospital, and interviewer with two controls (one control with a malignant disease and one with a non-malignant disease).
	Metric 2:	Attrition	High	× 0.4	0.4	There is no evidence that any cases or controls withdrew participation, and a minimal number of individuals refused participation (1 case, 2 controls).
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases and controls were matched by sex, age at interview (within five years), hospital, and interviewer. Individuals with tobacco-related diseases were excluded. Some characteristics, including tobacco use, were adjusted for in the analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	Occupational history (from the most recent to the first occupation) and the duration at each position (at least one year) were presented; exposure to chemical was not evaluated. Occupation was ascertained by interviews conducted between 1987-1991, the data were coded blindly with the International Standard Classification of Occupations from 1968. The occupational category of interest "textile workers and tailors" is broad and there is no other evidence in the paper that the majority of workers in these occupations were exposed primarily to perchloroethylene.
	Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	Exposure levels are not described.
	Metric 6:	Temporality	Low	× 0.4	1.2	Occupational history included all occupations ever held for at least one year. The timing of the occupation start date and the date of diagnosis are not specified explicitly, and it is unclear whether exposure windows are appropriate.
Domain 3: Outcome Assessment						

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Study Citation:	Auperin, A; Benhamou, S; Ory-Paoletti, C; Flamant, R (1994). Occupational risk factors for renal cell carcinoma: A case-control study Occupational and Environmental Medicine, 51(6,6), 426-428
Data Type:	Perc_Occupational_Renal cancer (RCC)-Cancer
HERO ID:	630334

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cases were histologically confirmed prior to occupation interviews. Methods for confirming controls were not described.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Results with confidence intervals were presented for all outcomes outlined in the abstract, introduction, and methods.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Models were adjusted for number of years at school, smoking status, and Quetelet index before diagnosis. Cases and controls were matched by age and sex.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Covariates were assessed by interview, but the validity of the interview questionnaire is unclear.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Exposure levels were not measured; occupational association with outcome was presented. There is no indication that co-exposures were accounted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design and logistic regression were appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases (7 women, 6 men) and controls (14 women, 3 men) among textile workers are adequate to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Statistical analyses were described briefly and methods were referenced. Categories for covariate classification were provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Conditional logistic regression was appropriately described.
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‡			Unacceptable⋆⋆		2.1	
Extracted			No			

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Study Citation:	Auperin, A; Benhamou, S; Ory-Paoletti, C; Flamant, R (1994). Occupational risk factors for renal cell carcinoma: A case-control study Occupational and Environmental Medicine, 51(6,6), 426-428
Data Type:	Perc_Occupational_Renal cancer (RCC)-Cancer
HERO ID:	630334

Domain	Metric	Rating†	MWF⋆	Score	Comments††

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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.

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

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: **Blair et al. 2003: Evaluation of Mortality Outcomes**

Study Citation:	Blair, A; Petralia, SA; Stewart, PA (2003). Extended mortality follow-up of a cohort of dry cleaners Annals of Epidemiology, 13(1,1), 50-56
Data Type:	Cohort_Occupational_Perc_All Cause Mortality_SMR-Mortality
HERO ID:	630365

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Participation rate, race, age, setting, selection process, inclusion and exclusion criteria, and years worked at job are reported. Analysis includes individuals who were union members for one year or more with available information necessary for epidemiologic analyses.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Analysis included only individuals who were union members for one year or more with available information necessary for epidemiologic analyses: 5,369 out of a total of 11,062 individuals, after excluding 5,272 individuals who worked less than one year and 421 who lacked the necessary demographic information. Subject characteristics are not compared between subjects included/not included in the analysis.
	Metric 3:	Comparison Group	High	× 0.2	0.2	The reference population (for calculating SMR) is the general US population, adjusted for age at death, year of death, race, and gender.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure assessment was based on occupation. Study participants worked in dry cleaning establishments. Duration of union membership was used to estimate duration of exposure. It underestimated work months when workers were delinquent in paying dues or when they worked non-union shops. It overestimated work months when members not employed in dry cleaning would pay dues in order to remain in the union health benefit plan. Study lacked detailed job histories while employed in the dry cleaning industry. Cleaners were assigned an exposure score of 40 (high exposure) for an eight-hour time-weighted average (TWA) and persons working as pressers, sewers, or at the counter were given a score of seven (medium exposure). Cohort members employed at pick-up stations where no dry cleaning occurred were assigned as unexposed (little or no exposure).
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Study reports only exposed and unexposed (general population) levels.

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Study Citation:	Blair, A; Petralia, SA; Stewart, PA (2003). Extended mortality follow-up of a cohort of dry cleaners Annals of Epidemiology, 13(1,1), 50-56
Data Type:	Cohort_Occupational_Perc_All Cause Mortality_SMR-Mortality
HERO ID:	630365

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	The temporality between exposure (employment in cleaning industry between 1948-1979) and outcome assessment (1979-1993) is adequate.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Deaths were coded according to the ICD rules in effect at the time of death and assigned rubrics according to the eighth revision (ICDA 8. 189 for kidney cancer). However, the diagnostic error rate associated with death certificates is likely to be sizable, and nondifferential misclassification of outcome in cohort mortality studies would tend to bias estimates of relative risk toward the null (especially for rare cancers with small incidence/mortality rates).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	SMRs and 95% confidence intervals reported. However, number of observed and expected cases for risk estimates were not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SMR data was adjusted for age at death, year of death, race, and sex. The study lacks information on potential confounding factors such as tobacco and alcohol use.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on age, gender, and race was likely obtained from death certificates. Information on the reliability/validity of such data sources was not provided.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential co-exposures were not specifically discussed or addressed. All workers included in the study worked in the dry-cleaning industry with little information on potential co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate study design (retrospective mortality study) was used to address the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sample size was 5,369 individuals. The study does not discuss statistical power in detail. The number of observed kidney cancer deaths were relatively low (n=8).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of the analysis is sufficiently provided in earlier report.

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Study Citation:	Blair, A; Petralia, SA; Stewart, PA (2003). Extended mortality follow-up of a cohort of dry cleaners Annals of Epidemiology, 13(1,1), 50-56
Data Type:	Cohort_Occupational_Perc_All Cause Mortality_SMR-Mortality
HERO ID:	630365

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Adjustment variables are clearly indicated. Expected numbers for the SMRs were developed from 5-year age and calendar-time mortality rates from the general United States population. Person-year accumulation began on date of entry into the union, or January 1, 1948 (whichever came later) and ended on the closing date of the study (December 31, 1993) if alive, or date of death if deceased.
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		2.0	
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 28: **Blair et al. 2003: Evaluation of Cancer Outcomes**

Study Citation:	Blair, A; Petralia, SA; Stewart, PA (2003). Extended mortality follow-up of a cohort of dry cleaners Annals of Epidemiology, 13(1,1), 50-56
Data Type:	Cohort_Occupational_Perc_Hodgkin's lymphoma_SMR-Cancer
HERO ID:	630365

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Participation rate, race, age, setting, selection process, inclusion and exclusion criteria, and years worked at job are reported. Analysis includes individuals who were union members for one year or more with available information necessary for epidemiologic analyses.
	Metric 2: Attrition	Medium	× 0.4	0.8	Analysis included only individuals who were union members for one year or more with available information necessary for epidemiologic analyses: 5,369 out of a total of 11,062 individuals, after excluding 5,272 individuals who worked less than one year and 421 who lacked the necessary demographic information. Subject characteristics are not compared between subjects included/not included in the analysis.
	Metric 3: Comparison Group	High	× 0.2	0.2	The reference population (for calculating SMR) is the general US population, adjusted for age at death, year of death, race, and gender.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure assessment was based on occupation. Study participants worked in dry cleaning establishments. Duration of union membership was used to estimate duration of exposure. It underestimated work months when workers were delinquent in paying dues or when they worked non-union shops. It overestimated work months when members not employed in dry cleaning would pay dues in order to remain in the union health benefit plan. Study lacked detailed job histories while employed in the dry cleaning industry. Cleaners were assigned an exposure score of 40 (high exposure) for an eight-hour time-weighted average (TWA) and persons working as pressers, sewers, or at the counter were given a score of seven (medium exposure). Cohort members employed at pick-up stations where no dry cleaning occurred were assigned as unexposed (little or no exposure).
	Metric 5: Exposure levels	Low	× 0.2	0.6	Study reports only exposed and unexposed (general population) levels.

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Study Citation:	Blair, A; Petralia, SA; Stewart, PA (2003). Extended mortality follow-up of a cohort of dry cleaners Annals of Epidemiology, 13(1,1), 50-56
Data Type:	Cohort_Occupational_Perc_Hodgkin's lymphoma_SMR-Cancer
HERO ID:	630365

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	The temporality between exposure (employment in cleaning industry between 1948-1979) and outcome assessment (1979-1993) is adequate.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Deaths were coded according to the ICD rules in effect at the time of death and assigned rubrics according to the eighth revision (ICDA 8. 189 for kidney cancer). However, the diagnostic error rate associated with death certificates is likely to be sizable, and nondifferential misclassification of outcome in cohort mortality studies would tend to bias estimates of relative risk toward the null (especially for rare cancers with small incidence/mortality rates).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	SMRs and 95% confidence intervals reported. However, number of observed and expected cases for risk estimates were not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SMR data was adjusted for age at death, year of death, race, and sex. The study lacks information on potential confounding factors such as tobacco and alcohol use.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on age, gender, and race was likely obtained from death certificates. Information on the reliability/validity of such data sources was not provided.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential co-exposures were not specifically discussed or addressed. All workers included in the study worked in the dry-cleaning industry with little information on potential co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate study design (retrospective mortality study) was used to address the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sample size was 5,369 individuals. The study does not discuss statistical power in detail. The number of observed kidney cancer deaths were relatively low (n=8).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of the analysis is sufficiently provided in earlier report.

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Study Citation:	Blair, A; Petralia, SA; Stewart, PA (2003). Extended mortality follow-up of a cohort of dry cleaners Annals of Epidemiology, 13(1,1), 50-56
Data Type:	Cohort_Occupational_Perc_Hodgkin's lymphoma_SMR-Cancer
HERO ID:	630365

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Adjustment variables are clearly indicated. Expected numbers for the SMRs were developed from 5-year age and calendar-time mortality rates from the general United States population. Person-year accumulation began on date of entry into the union, or January 1, 1948 (whichever came later) and ended on the closing date of the study (December 31, 1993) if alive, or date of death if deceased.
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		2.0	
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 29: **Delahunt et al. 1995: Evaluation of Cancer Outcomes**

Study Citation:	Delahunt, B; Bethwaite, PB; Nacey, JN (1995). Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry British Journal of Urology, 75(5,5), 578-582
Data Type:	Perc_Case-Control_occupational_Kidney (RCC)-Cancer
HERO ID:	630485

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Case-control study included 710 cases of non-urinary tract renal cell carcinoma reported to the New Zealand Cancer Registry (NZCR) from 1978-1986. All patients were >20 years, males and reported an ICD-9 code 189.0 (malignant neoplasms of the kidney, excluding the renal pelvis). 12,756 male control cases represented a random sample of registrations drawn from all cancer cases between 1978-1986 unrelated to renal cell carcinoma. Potential for selection bias in selecting the controls from other cancer patients if the occupational exposures are associated with increased risk of other cancers, but this would bias the results towards the null.
	Metric 2: Attrition	High	× 0.4	0.4	1,060 (718 men and 342 women) cases were originally reported during the 9-year period of the study (only individuals >20 years included). Of these participants, occupational information was available for 710 men and 204 women. Women were ultimately excluded from the study as there was a low number of participants and 83.3% reported employment in domestic, administrative or clerical roles. Reasons for any exclusion were well documented.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	12,756 male controls represented a random sample of registrations drawn from all cancer cases between 1978-1986 unrelated to renal cell carcinoma. Results for comparison of other variables between cases and controls besides occupational classification not reported, but it was assumed that cases and controls were similar.
Domain 2: Exposure Characterization					

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Study Citation:	Delahunt, B; Bethwaite, PB; Nacey, JN (1995). Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry British Journal of Urology, 75(5,5), 578-582
Data Type:	Perc_Case-Control_occupational_Kidney (RCC)-Cancer
HERO ID:	630485

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure to perchloroethylene was not measured or estimated with a job-exposure matrix. As occupation in the dry-cleaning field can serve as a surrogate for perchloroethylene exposure, this subgroup was considered exposed in this evaluation. Occupation was based on an active occupational code found in the cancer registry. Occupation is classified according to the New Zealand Standard Classification of Occupations, a modification of the International Standard Classification of Occupations. Occupation classification only reflects the current or most recent occupation at the time of registration (1978-1986), and information is not available regarding previous employment. This therefore assumes that occupation at time of diagnosis is indicative of life-time occupation. The authors note that both firefighters and painters are more likely to stay in their profession for life, and this therefore would not impact those estimates.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Employment in dry-cleaning occupations served as a surrogate for perchloroethylene exposure. As most occupational perchloroethylene exposure occurred within this field, subjects employed in other occupations were considered unexposed.
	Metric 6:	Temporality	Low	× 0.4	1.2	There is uncertainty regarding the temporality of exposure and outcome. Occupation was classified only at the time of diagnosis, and does not consider potential changes in occupation throughout time (particularly relevant for cancer where there is a long latency period).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases were selected from New Zealand Cancer Registry (NZCR) with reported ICD-9 code 189.0 (malignant neoplasms of the kidney, excluding the renal pelvis). Diagnosis was confirmed by cytology or histology in all cases. Controls were also selected from the New Zealand Cancer Registry (NZCR) as individuals having primary tumors from sites other than the urinary tract.

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Study Citation:	Delahunt, B; Bethwaite, PB; Nacey, JN (1995). Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry British Journal of Urology, 75(5,5), 578-582
Data Type:	Perc_Case-Control_occupational_Kidney (RCC)-Cancer
HERO ID:	630485

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Relative risks and 95% CI provided for each occupation group. P-values not presented. Number of cases and controls for each occupation category not reported (only counts for general occupational classifications provided but not subtypes). Stratified results by smoking history and age were not reported for all occupational groups (only firefighters, glassworkers, painters).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Relative risk measures were derived by the Mantel-Haenszel method and stratified in 10-year age groups. Risk ratios further were stratified by age and smoking history. Distributions of age and smoking status were not reported in the study. Analysis was restricted to males, ensuring sex did not confound the association. Authors mentioned other potential risk factors for renal cell carcinoma that were not considered as confounders, but could have confounded the observed associations: urbanization and SES status, dietary fat intake, body weight, coffee, and alcohol use.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Smoking status was established as self-reported in the New Zealand Cancer Registry. Smoking categories were defined as smoked (non-smokers), current smokers at time of registration (smokers), and those who ceased smoking before registration (ex-smokers). Current smokers were divided into those who smoked <10, 10-19 and >19 cigarettes per day. Age was determined through the cancer registry.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Exposure to Perc was not measured or estimated with a job-exposure matrix. Co-exposures were not measured or accounted for in the analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control study design was used to estimate relative risk for renal cell carcinoma cases for different occupations. Occupation of interest for Perc was dry cleaning. Relative risk measures were derived from Mantel-Haenszel method and stratified in 10-year age groups.

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Study Citation:	Delahunt, B; Bethwaite, PB; Nacey, JN (1995). Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand Cancer Registry British Journal of Urology, 75(5,5), 578-582
Data Type:	Perc_Case-Control_occupational_Kidney (RCC)-Cancer
HERO ID:	630485

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	1,060 total cases and 12756 controls were sufficient to detect an effect for this evaluation. Counts per occupation classification are smaller, but still likely sufficient to detect an effect. Statistical power not reported, but p values show some statistically significant correlations.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Analyses were described in sufficient detail. The relative risk measures were derived by Mantel-Haenszel method stratified by 10-year age groups and 95% CI is estimated using Miettinen's approximate method.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The relative risk measures were derived by Mantel-Haenszel method stratified by 10-year age groups and 95% CI is estimated using Miettinen's approximate method. 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		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 30: **Lynge and Thygesen 1990: Evaluation of Cancer Outcomes**

Study Citation:	Lynge, E; Thygesen, L (1990). Primary liver cancer among women in laundry and dry-cleaning work in Denmark Scandinavian Journal of Work, Environment and Health, 16(2,2), 108-112
Data Type:	Cohort_Perc_Occupational_Pancreas Cancer Incidence (women)-Cancer
HERO ID:	630736

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Cohort of laundry and dry-clean workers were identified from the Danish Occupational Cancer Register from 1970 census population, which included individuals with the industry code 860, 411, and 380 specified 'laundries, cleaning and dyeing' 'laundry worker, ironer' and 'factory hand'. The reference group is comprised of all persons economically active in 1970 in Denmark.
	Metric 2: Attrition	Medium	× 0.4	0.8	Individuals were categorized by Danish Occupational Codes. Census codes did not allow a distinction to be made between laundries on one hand and dry-cleaning shops on the other.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Reference group comprised of all persons economically active in 1970 in Denmark, which is an appropriate comparison population in this type of study.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure assessment was based on 2,886 laundries and dry-cleaning shops in Denmark in 1970. Data were not available on the possible division of labor in these small workshops. Of the 2,886 shops, 695 were known to be dry-cleaning and dyeing shops. Exposure was categorized as "exposure to solvents including tetrachloroethylene", but no quantitative measurements are available or described. For this evaluation, occupation in the dry-cleaning field served as a surrogate for perchloroethylene exposure.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Exposure assessment was based on work in 2,886 laundry and dry-cleaning shops in Denmark in 1970. Exposure levels were not included in analyses. However, results are reported comparing this population with the general population of all persons economically active in 1970, who are anticipated to have little to no perchloroethylene exposure. There is no indication of variation in duration of employment or intensity of exposure .

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Study Citation:	Lynge, E; Thygesen, L (1990). Primary liver cancer among women in laundry and dry-cleaning work in Denmark Scandinavian Journal of Work, Environment and Health, 16(2,2), 108-112
Data Type:	Cohort_Perc_Occupational_Pancreas Cancer Incidence (women)-Cancer
HERO ID:	630736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Low	× 0.4	1.2	The study includes time order. The periods of exposure were not defined. A 10-year follow up period in each 5-year age group might not be sufficient for cancer development.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Kidney cancer was classified based on the Code of international Classification of Diseases and Causes of Death (180). Subjects were identified by linkage between 1970 census data and the Danish Cancer Registry data through personal identification number. It is unclear if cancer cases were histopathologically confirmed by the Cancer Registry.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Methods were described in limited detail; number of observed and expected cancer cases are reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Sex stratified results, and age-adjusted SIR were calculated. However, no other adjustments were reported.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Age groups and gender were likely available from the Cancer registry and Census data. No other details regarding data sources, or reliability of this information were provided.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	All kidney cancer cases were engaged in laundry and dry-cleaning work, likely with potential co-exposures, especially given the different job categories within these industries. However, co-exposures are not explicitly discussed or addressed.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The numbers of cancer cases expected in the cohort were calculated by multiplying the person-years at risk during the 10-year follow-up period in each 5-year age group with the site-specific incidence rates calculated in the same way for all persons. This is an adequate approach for a cohort study.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of total participants is acceptable. There was a small number of observed cases of kidney cancer in males (6) and females (5).
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Analyses for calculating SIRs is likely reproducible given the raw data. It is unclear what kind of standardization was used (direct or indirect).

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Study Citation:	Lynge, E; Thygesen, L (1990). Primary liver cancer among women in laundry and dry-cleaning work in Denmark Scandinavian Journal of Work, Environment and Health, 16(2,2), 108-112
Data Type:	Cohort_Perc_Occupational_Pancreas Cancer Incidence (women)-Cancer
HERO ID:	630736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Standardized incidence ratio and 95% two-tailed confidence interval was calculated on the assumption that the total number of observed cases up to 30 followed a Poisson distribution, and for total numbers above 30 the distribution was normal. These are reasonable model assumptions.
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‡			Low		2.3	
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 31: **McCredie and Stewart 1993: Evaluation of Cancer Outcomes**

Study Citation:	McCredie, M; Stewart, JH (1993). Risk factors for kidney cancer in New South Wales. IV. Occupation British Journal of Industrial Medicine, 50(4,4), 349-354
Data Type:	New South Wales_Occ_Perc_case_control_Renal pelvic cancer-Cancer
HERO ID:	630760

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Participation rates among cases and controls were well documented. Cases were identified from cancer registry.
	Metric 2: Attrition	High	× 0.4	0.4	Case withdrawal was explained in detail and was primarily due to death, but this was not appreciably large and not expected to significantly impact the results. Controls similarly had low withdrawal rates and were documented in detail. There is no evidence to suggest the level of attrition in this study would appreciably bias the results. The participation rates were provided by age grouping. In men there was no significant difference in response rates, but there was a slight difference between female case and control response rates. Age was included as a confounder in the analysis.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Controls were recruited from electoral rolls using proportional random sampling based on the expected age distribution of cases. However, it is unclear that the controls were confirmed to be free of the cancer that cases had.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure was characterized by self-reported occupational exposure to general categories of chemicals, such as solvents. Elsewhere, exposure was categorized by occupational field, such as dry-cleaning industry. Subjects had at least 10 years of exposure before interview (date of interview 1989-1992). There is no mention of perchloroethylene as the primary solvent ; however dry-cleaning industry was acknowledged as source of exposure to hydrocarbons and serves as a surrogate for perchloroethylene exposure for this evaluation.
	Metric 5: Exposure levels	Low	× 0.2	0.6	There were two levels of exposure for each exposure categorization (based on industry or chemical class). These were exposed and unexposed, representing two levels of exposure.

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Study Citation:	McCredie, M; Stewart, JH (1993). Risk factors for kidney cancer in New South Wales. IV. Occupation British Journal of Industrial Medicine, 50(4,4), 349-354
Data Type:	New South Wales_Occ_Perc_case_control_Renal pelvic cancer-Cancer
HERO ID:	630760

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Questionnaires were worded in such a way that exposure could be assessed for a participants entire occupational history, but some uncertainty remains with the timing of exposure or the timing of exposure to certain chemicals. The questionnaire asks about exposure to certain chemical classes (solvents) for the duration of a year or longer.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cases were drawn from the New South Wales Central Cancer Registry, pathology labs, urologists, and radiotherapy departments and were identified by specific ICD-9 codes (189.0 & 189.1). There were some differences in confirmation diagnosis method within cases (histopathology, fine needle aspiration cytology, ultrasound).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods were presented in the results. Adjusted results were presented with numbers of exposed by case/control provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	The analysis accounted for potential confounders including age, sex, education, method of interview, BMI, cigarette smoking and analgesics containing phenacetin; duration of exposure, year span when exposure began were also considered. Marital status was similar between cases and controls.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Data on covariates were presumably self-reported via interview with a trained interviewer. It's unclear whether some data for cases were checked against medical records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is some indication that there were potential co-exposures that were not accounted for as they presented occupational exposure from a wide variety of occupations that may also be implicated in the development of kidney cancer.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This was a case-control study to determine the effect of different occupational exposures on the incidence of kidney cancer in an adult, working population. This is an effective study design to detect risk factors for an uncommon disease.

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Study Citation:	McCredie, M; Stewart, JH (1993). Risk factors for kidney cancer in New South Wales. IV. Occupation British Journal of Industrial Medicine, 50(4,4), 349-354
Data Type:	New South Wales_Occ_Perc_case_control_Renal pelvic cancer-Cancer
HERO ID:	630760

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were a sufficient number of cases and controls in this study to detect effects of particular chemical categories on the risk of developing two types of kidney cancer. For the dry-cleaning industry, the number of cases and controls exposed are quite small.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis was described in detail such that it could be reproduced given original data. Covariate analysis was described in detail.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	This study utilized multivariate logistic regression to investigate the effects of occupational exposures on kidney cancer incidence. This is an appropriate statistical model for a case-control design .
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		2.0	
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 32: **Mellemgaard et al 1994: Evaluation of Cancer Outcomes**

Study Citation:	Mellemgaard, A; Engholm, G; Mclaughlin, JK; Olsen, JH (1994). Occupational risk factors for renal-cell carcinoma in Denmark Scandinavian Journal of Work, Environment and Health, 20(3,3), 160-165
Data Type:	Denmark_occupational_perc_case control_Kidney Cancer (men)-Cancer
HERO ID:	630774

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Cases were drawn from the Danish Cancer Registry for all histologically confirmed kidney cancer (renal cell carcinoma) patients. Controls were drawn from the Central Population Register, age and sex matched. The study authors originally noticed some sampling bias due to the structure of the Central Population Registry. To correct this, they randomly resampled with respect to region (the characteristic which was originally skewed). This likely reduced any potential sampling bias, but it is unclear if this resolved the entire issue. Participation rates for both cases and controls were detailed in the study.
	Metric 2:	Attrition	High	× 0.4	0.4	Reasons for case and control withdrawal were detailed, and rates of attrition were similar between the two (approximately 75-80% follow-up for both).
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Controls were randomly drawn from the Central Population Register in Denmark, matched to cases by age (5 years intervals) and sex. Potential differences in the case and control groups including age, smoking, BMI, and SES were controlled for in the analyses. The controls were presumed free of kidney cancer because of lack of presence in the Cancer Registry and/or all pathology departments. However, no confirmatory analysis was performed in a subset of controls to make sure they are indeed free of kidney cancer.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposures were categorized by industry ('drycleaning') and occupational exposure to various broader chemical classes (e.g., 'solvents'). Subjects had at least 10 years of exposure before interview (date of interview 1989-1992). There was no detailed characterization of exposure to perchloroethylene by occupational history in a JEM and no evaluation by an industrial hygienist. Occupations were categorized by the International Standard Classification of Occupation.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There were only two levels of exposure: exposed and unexposed.

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Study Citation:	Mellemgaard, A; Engholm, G; Mclaughlin, JK; Olsen, JH (1994). Occupational risk factors for renal-cell carcinoma in Denmark Scandinavian Journal of Work, Environment and Health, 20(3,3), 160-165
Data Type:	Denmark_occupational_perc_case control_Kidney Cancer (men)-Cancer
HERO ID:	630774

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Participants were interviewed and provided work histories going back 10 years. This covers a sufficient window of exposure to establish temporality between occupational exposures and the development of kidney cancer.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases were drawn from the Danish Cancer Registry and searches in all pathology departments in Denmark. The study authors state that cases were histologically confirmed for renal cell carcinoma. ICD codes were not provided.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods was provided in the results. The numbers of cases/controls for each outcome/exposure category were listed, allowing for easy extraction and inclusion in a meta-analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Analyses accounted for age, sex (by matching), BMI, smoking, and SES. A weaker association was found with short education, but data is not shown; education is not accounted for in other models.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Participants were interviewed by trained interviewers in their homes. There was no indication of validation, but this is an acceptable method of obtaining covariate information and is not expected to appreciably bias the results. Procedures for developing pack-years smoking, BMI, and SES categories are described in detail.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Exposure to other chemicals was demonstrated through the collection of exposure to other chemicals of interest. There is limited indication that this was balanced between cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study was a case-control design, which is an appropriate study design to investigate the effects of occupational exposures on the incidence of kidney cancer.

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Study Citation:	Mellemgaard, A; Engholm, G; Mclaughlin, JK; Olsen, JH (1994). Occupational risk factors for renal-cell carcinoma in Denmark Scandinavian Journal of Work, Environment and Health, 20(3,3), 160-165
Data Type:	Denmark_occupational_perc_case control_Kidney Cancer (men)-Cancer
HERO ID:	630774

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There was a sufficient number of cases and controls to detect an effect of exposure by some occupational categories and chemical classes. However, the small number of exposed individuals (4 kidney cancer cases, 2 referents) for dry cleaning industry limits the power of the study to find an effect; However, this is common limitation in population-based studies of occupational factors.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	There was sufficient detail in the determination of covariate information and model selection (calculation of pack-years, etc.). The analysis could be reproduced given original data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Unconditional logistic regression was used to investigate the risk of renal cell carcinoma associated with various occupational exposures. This is an appropriate statistical model for the study question.
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 33: **Miligi et al. 2006: Evaluation of Cancer Outcomes**

Study Citation:	Miligi, L; Costantini, AS; Benvenuti, A; Kriebel, D; Bolejack, V; Tumino, R; Ramazzotti, V; Rodella, S; Stagnaro, E; Crosignani, P; Amadori, D; Mirabelli, D; Sommani, L; Belletti, I; Troschel, L; Romeo, L; Miceli, G; Tozzi, GA; Mendico, I; Vineis, P (2006). Occupational exposure to solvents and the risk of lymphomas Epidemiology, 17(5), 552-561
Data Type:	Very low/low PCE_exposure intensity level-Cancer
HERO ID:	630788

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, 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	Minimal subject withdrawal from the study, and outcome data and exposure were largely complete: 1428 NHL cases (of 1719 eligible in the 8 areas [83%]), 304 HD cases (of 347 [88%]), and 1530 controls (of 2086 [73%]). The reasons for non-participation were refusal of interviews (11% of NHL cases, 8% of HD cases, and 21% of the controls), subject not traced (2.4%, 2.9%, and 3.0%, respectively), and not interviewed because of illness or impairment (3.2%, 1.4%, and 3.2%, respectively).
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases and controls were similar; controls randomly were selected from the general population in each of the areas under study. 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	Occupational study population with exposure was assessed using job-specific or industry-specific questionnaires with subsequent expert ratings to assign exposure to a definitive list of agents (i.e., no employment records). Industrial hygiene experts from each geographic area examined data collected in the questionnaires, and assessed a level of probability and intensity of exposure to groups or classes of solvents as well as certain individual substances. Reviewers were blinded to disease status.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported.

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Study Citation:	Miligi, L; Costantini, AS; Benvenuti, A; Kriebel, D; Bolejack, V; Tumino, R; Ramazzotti, V; Rodella, S; Stagnaro, E; Crosignani, P; Amadori, D; Mirabelli, D; Sommani, L; Belletti, I; Troschel, L; Romeo, L; Miceli, G; Tozzi, GA; Mendico, I; Vineis, P (2006). Occupational exposure to solvents and the risk of lymphomas Epidemiology, 17(5), 552-561
Data Type:	Very low/low PCE_exposure intensity level-Cancer
HERO ID:	630788

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	The study identified newly diagnosed cases of NHL and assessed exposure via job-specific and industry specific questionnaires. It is assumed that exposure preceded the outcome but this is not clear.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	NHL cases were classified following the working formulation proposed by the U.S. National Cancer Institute. A panel of 3 pathologists reviewed all doubtful NHL diagnoses (that is, cases for whom the local pathologist had expressed uncertainties about the allocation in a specific NHL category), as well as a randomly selected 20% sample of all cases. The NHL diagnosis was confirmed for all 334 cases that were reviewed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported. Effect estimates are reported with confidence interval; number of exposed was reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. The paper 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	Co-exposures were measured and modeled separately, and the authors noted a "high degree of correlation among exposures to benzene, xylene, and toluene. For this reason, caution must be exercised when interpreting the evidence for any one of these 3 solvents." However, there does not appear to be direct evidence of an co-pollutant confounding of the relation between DCM, TCE, PCE, and NHL.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., case control study of DCM/TCE/PCE exposure in relation to a rare disease, NHL), and appropriate statistical methods (i.e., logistic regression analyses) were employed to analyze data.

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Study Citation:	Miligi, L; Costantini, AS; Benvenuti, A; Kriebel, D; Bolejack, V; Tumino, R; Ramazzotti, V; Rodella, S; Stagnaro, E; Crosignani, P; Amadori, D; Mirabelli, D; Sommani, L; Belletti, I; Troschel, L; Romeo, L; Miceli, G; Tozzi, GA; Mendico, I; Vineis, P (2006). Occupational exposure to solvents and the risk of lymphomas Epidemiology, 17(5), 552-561
Data Type:	Very low/low PCE_exposure intensity level-Cancer
HERO ID:	630788

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population.
	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	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		1.6	
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 34: **Schlehofer et al. 1995: Evaluation of Cancer Outcomes**

Study Citation:	Schlehofer, B; Heuer, C; Blettner, M; Niehoff, D; Wahrendorf, J (1995). Occupation, smoking and demographic factors, and renal cell carcinoma in Germany International Journal of Epidemiology, 24(1,1), 51-57
Data Type:	Case-Control_Occupational_Perc_RCC-Cancer
HERO ID:	630954

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	185 men and 92 women of German ethnicity were identified in 10 urology departments in the Rhein-Neckar-Odenwald area with histologically confirmed kidney cancer (renal cell cancer) from 1989 to 1991. Controls were randomly chosen from the population register of the study area and frequency matched to the cases for age (±1 years) and gender. The authors went to great efforts to ensure case completeness.
	Metric 2: Attrition	High	× 0.4	0.4	9 cases refused to participate and 42 people could not be interviewed because 23 were not reported by physicians within 6 months of diagnosis, 2 patients had secondary kidney tumor, 6 cases died before interviews, 2 cases interrupted the interview at early stage, and 9 were too ill to be interviewed. Participation rates were 84.5% among cases and 75% among controls.
	Metric 3: Comparison Group	Low	× 0.2	0.6	Controls were randomly chosen from the population register of the study area and frequency matched to the cases for age and gender. Variables that could differ between cases and controls were accounted for in the analyses. It is unclear how controls were confirmed to be disease free.
Domain 2: Exposure Characterization					

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Study Citation:	Schlehofer, B; Heuer, C; Blettner, M; Niehoff, D; Wahrendorf, J (1995). Occupation, smoking and demographic factors, and renal cell carcinoma in Germany International Journal of Epidemiology, 24(1,1), 51-57
Data Type:	Case-Control_Occupational_Perc_RCC-Cancer
HERO ID:	630954

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	No specific exposure to perchloroethylene was evaluated in this study. The study focused on occupational exposure, specific industry, or substance. Occupational exposure assessment was requested at 4 levels: 1st- all industries in which subject ever been employed; 2nd- occupations in which the subject had been trained; 3rd- precise activities the subject carried out during employment; 4th- exposure to specific substances. A subject was considered exposed to a specific industry, occupation, or substance when the duration of the exposure lasted at least 5 years. Occupation included 10 categories, and 22 substances. Broad "textile" occupational group in not an appropriate proxy for Perc exposure; no dry cleaning occupation specified; exposure to solvents included '"perchloroethylene, dyes, cadmium and mercury."
	Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	Qualitative (nominal) levels of occupational exposure assessment (industry, occupation, specific activity and substances) were included in the analysis as binary variables. Specific ranges of exposure to perchloroethylene not provided.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Interviews were performed within 6 months of tumor diagnosis of the case. Occupational history considered whether the duration of this exposure lasted at least 5 years.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Case status ascertained from urological and surgical clinics (ICD: 189.0). There cases were histologically confirmed.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	All statistical analyses are reported in sufficient detail, with numbers of cases and controls reported for each relative risk reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	All models were adjusted for age and gender. Analyses also accounted for SES, marital status, residence (urban/rural) , smoking (non-smoker, ex-smoker, and current smoker) or cigarette smoking categories.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Occupational and demographic risk factors as well as tobacco smoking were assessed via personal interviews by trained interviewers using a standardized questionnaire.

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Study Citation:	Schlehofer, B; Heuer, C; Blettner, M; Niehoff, D; Wahrendorf, J (1995). Occupation, smoking and demographic factors, and renal cell carcinoma in Germany International Journal of Epidemiology, 24(1,1), 51-57
Data Type:	Case-Control_Occupational_Perc_RCC-Cancer
HERO ID:	630954

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The analyses included various variables into exposures to account for possible co-exposure. Separated industry and occupational groups were evaluated, presumably accounting for potential co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study uses an appropriate study design for the research question. Cases and matched controls were followed in similar way. Unconditional logistic regression models were used to analyze data. Separate logistic regression models were evaluated for different groups of risk factors.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	277 incident cases and 286 controls that were frequency matched by age and gender represent an adequate sample size for the study subject population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	There is sufficient detail in the methods and analyses to ensure reproducibility if the original data were available
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The study used standard methods for case-control studies: unconditional logistic regression models. Separate logistic regression models were evaluated for different groups of risk factors such as smoking, occupational factors and demographic factors.. A simple model for occupational exposure with one risk factor was included. Multiple covariates models were investigated and compared to the results of the simple 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	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Unacceptable⋆⋆		2.1	
Extracted			No			

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Study Citation:	Schlehofer, B; Heuer, C; Blettner, M; Niehoff, D; Wahrendorf, J (1995). Occupation, smoking and demographic factors, and renal cell carcinoma in Germany International Journal of Epidemiology, 24(1,1), 51-57
Data Type:	Case-Control_Occupational_Perc_RCC-Cancer
HERO ID:	630954

Domain	Metric	Rating†	MWF⋆	Score	Comments††

** Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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.

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

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 35: **Travier et al 2002: Evaluation of Cancer Outcomes**

Study Citation:	Travier, N; Gridley, G; De Roos, AJ; Plato, N; Moradi, T; Boffetta, P (2002). Cancer incidence of dry cleaning, laundry and ironing workers in Sweden Scandinavian Journal of Work, Environment and Health, 28(5,5), 341-348
Data Type:	Sweden_occupational cohort_perc_kidney cancer_RR-Cancer
HERO ID:	631051

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	This cohort drew from the Swedish National Population and Housing Census, including participants from all over Sweden. Participants were selected using the same criteria, from the same time period that census data was collected. Subjects were followed from 1 January 1971 until the first cancer diagnosis, death, or end of follow-up (31 December 1989). They focused on persons who, at the time of either census, worked as launderers, dry cleaners, or pressers (Nordic Classification of Occupation 943 for launderers and dry cleaners and 944 for pressers) or were employed in the laundry, ironing, or dyeing industry (Swedish industrial code 880 in 1960 and 9520 in 1970). People who retired between 1960 and 1971 were included in the cohort. There is no evidence to suggest the exposure-outcome distribution in this population would be biased.
	Metric 2: Attrition	High	× 0.4	0.4	This study drew from census information which indicated that there was no attrition in the population used in the analysis.
	Metric 3: Comparison Group	High	× 0.2	0.2	Participants were drawn from national census data during the same time frame and under the same conditions. Potential confounders were assessed, and there is no evidence to suggest that groups are dissimilar.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Occupational history served as a surrogate for exposure. In this Swedish study, launderers, dry cleaners, and pressers were analyzed together, with those employed in these industries during the 1960 or 1970 census (group 1) and at both census dates (group 2) considered separately. Since Perc was used extensively as the primary dry cleaning solvent in the 1960s and 1970s, employment in the dry cleaning industry at the time was considered an acceptable proxy for Perc exposure.

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Study Citation:	Travier, N; Gridley, G; De Roos, AJ; Plato, N; Moradi, T; Boffetta, P (2002). Cancer incidence of dry cleaning, laundry and ironing workers in Sweden Scandinavian Journal of Work, Environment and Health, 28(5,5), 341-348
Data Type:	Sweden_occupational cohort_perc_kidney cancer_RR-Cancer
HERO ID:	631051

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The measure of exposure in this study was an occupational surrogate. The study authors attempted to create levels of exposure by creating categories of occupations and industry. These theoretically had 4 exposure groups: 1) subjects classified with a relevant occupational or industrial code at time of either census, 2) subjects employed as launderers, dry cleaners or pressers in the laundry, ironing or dyeing industry at time of both censuses, 3) subjects employed in relevant jobs but in other industries at time of both censuses, and 4) those in laundry, ironing or dyeing industry jobs other than launderers, dry cleaners or pressers at the time of both censuses. People who did not work as dry cleaners, launderers, or pressers and were not employed in the laundry, ironing, or dyeing industry at the time of both censuses defined the unexposed population for all the analyses of employed persons (69, 540, 184-person years). However, there is still some remaining ambiguity about the levels of exposure due to the use of occupation/industry as a measure of exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	The study design was a prospective cohort. Participants were followed from 1971 to 1989 to observe first incidence of cancer. This provides a sufficient amount of time for disease to develop and establishes exposure before disease onset.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Incident cases of kidney cancer were drawn from the Swedish national cancer register and the Cancer Environment Register III (CERIII), which records all cases of malignant tumors among people living in Sweden. This is a well-established method of obtaining cancer outcome characterization.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All PECO-related outcomes of interest outlined in the abstract, introduction, and methods were detailed in the results. RRs were provided in tables and in-text and would allow for easy extraction and inclusion in a meta-analysis. The number of person-years was reported in the methods along with the n cases in tables.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Travier, N; Gridley, G; De Roos, AJ; Plato, N; Moradi, T; Boffetta, P (2002). Cancer incidence of dry cleaning, laundry and ironing workers in Sweden Scandinavian Journal of Work, Environment and Health, 28(5,5), 341-348
Data Type:	Sweden_occupational cohort_perc_kidney cancer_RR-Cancer
HERO ID:	631051

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, sex, region of residence were all included as covariates in the final model. Smoking and other lifestyle factors were not available in the census data, thus, they were not assessed. This represents a partial list of potential confounders.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Covariates such as age (in 5-year groups), sex, and urban/rural residence were drawn from the national census data. This is self-reported information, but there is no evidence to suggest that this is not valid.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There was some potential co-exposure to other solvents used previously in the dry cleaning and laundering industry. Temporal changes in solvent use were indirectly accounted for by stratifying RRs by age group as certain age groups would be more likely to be exposed to certain chemicals in use (chemical combinations changed over time).
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This was a prospective cohort design investigating the development of cancer among those employed in the laundering or dry cleaning industry. Relative risks were calculated from multivariable Poisson regression analyses, and stratification variables included gender, 5-year age groups, 4-year calendar periods, residence regions, and urbanization levels. This is an appropriate design for assessing cancer incidence among occupational cohort.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	This study drew from the Swedish national census with an appreciably large amount of person-years available among each defined group. Effects were detected among some cancers. Note that the subpopulation case counts were particularly low for kidney cancer.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis was sufficient to understand how the study was conducted. Industrial and occupational codes were presented which would aid in the reproduction of this analysis. Detailed description included on statistical analysis and decisions for inclusion of variables - Relative risks were calculated from multivariable Poisson regression analyses, and stratification variables included gender, 5-year age groups, 4-year calendar periods, residence regions, and urbanization levels.

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Study Citation:	Travier, N; Gridley, G; De Roos, AJ; Plato, N; Moradi, T; Boffetta, P (2002). Cancer incidence of dry cleaning, laundry and ironing workers in Sweden Scandinavian Journal of Work, Environment and Health, 28(5,5), 341-348
Data Type:	Sweden_occupational cohort_perc_kidney cancer_RR-Cancer
HERO ID:	631051

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	This analysis used multivariate Poisson regression which allowed the authors to assess risk of cancer incidence over the study period. Methods for statistical models were transparent, variables for inclusion in model clearly indicated and 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‡			~~High~~ ⟶ Medium§		~~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

§ Evaluator's explanation for rating change: "Medium rating assigned due to use of occupation in dry cleaning industry as a surrogate of Perc exposure."

Table 36: **Carpenter 1937: Evaluation of Acute Toxicity/Poisoning Outcomes**

Study Citation:	C. P. Carpenter (1937). The chronic toxicity of tetrachlorethylene Journal of Industrial Hygiene and Toxicology, 19 323-336
Data Type:	Carpenter_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	58185

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	The study author selected themselves and a 4 colleagues to participate in this experiment. Four of the subjects participated in all the study at all dosage levels, and one of the subjects participated exclusively in the 2000 ppm exposure. The choice of subjects indicates a likely selection bias and no concurrent control group was reported.
	Metric 2:	Attrition	High	× 0.4	0.4	No attrition was reported. Only a select group of four individuals participated in this experiment. There was an additional individual subjected to the exposure to 2000 ppm perchloroethylene, but this was considered separately.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	No concurrent control group was reported. A blood sample and 24 hour urine sample was collected prior to exposure for comparison post exposure. For the clinical outcomes, individuals subjects could only make qualitative comparisons to their status prior to exposure. Subjects were not blinded to exposure status.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The perchloroethylene for the controlled exposure was likely to be obtained from the Eastman Kodak Company Research Laboratory, the same as in animal experiments and stated to be a commercially pure material. The inhalation chamber was described and the required amount of solvent was added to a towel on a fan. Serial measurements were taken with an interferometer to determine the actual concentration in the air. Subjects were exposed in two interspersed periods at varying levels of exposure. Exposures at varying levels were conducted in succession, potentially leading to cumulative effects.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Multiple levels of perchloroethylene exposure were utilized in this experiment, including 500 ppm, 1000 ppm, 1500 ppm, 2000 ppm, and 5000 ppm. Subjects stayed in the room as the exposure gradient was increased or left for short breaks. To evaluated the impact of cumulative exposure, subjects repeated the 2000 ppm exposure on a different day.

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Study Citation: C. P. Carpenter (1937). The chronic toxicity of tetrachlorethylene Journal of Industrial Hygiene and Toxicology, 19 323-336
Data Type: Carpenter_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID: 58185

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	The health of subjects prior to exposure was not discussed, however, no overt clinical symptoms were described. The study notes that negative effects were only experienced once inside the perchloroethylene inhalation chamber.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Participants made subjective observations about the effects of exposure such as eye irritation, salivation, nausea, and other similar symptoms. It was reported that blood pressure and pulse were measured, but no details on measurement methods were provided. A urinalysis was conducted on each participant, however, this was also not fully described. The study authors were the selected participants and blinding could not be applied.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All results outlined in the abstract, introduction, and methods were reported qualitatively.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.667	1.33	A statistical analysis was not performed, nor were covariates discussed.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	No covariates were characterized.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There was no indication of co-exposures in this controlled inhalation exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study was a controlled inhalation exposure designed to document subjective observations and changes in blood pressure and urinalysis results.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	No statistical comparison was made in this study. Additionally, each exposure level was assessed in 4-5 subjects, which raises concerns about statistical power.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	No statistical comparison was made or reported. Urine results were reported to show no variation from normal, however, the method and reference values were not described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	No statistical analysis is presented. The text notes a "significant drop" in blood pressure during exposure of 1000-1500 ppm, but not quantitative data is provided. The statistical analysis associated with the claim is not described. Urine results may have been compared to reference values or ranges, but no details are provided.

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Study Citation:	C. P. Carpenter (1937). The chronic toxicity of tetrachlorethylene Journal of Industrial Hygiene and Toxicology, 19 323-336
Data Type:	Carpenter_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	58185

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‡		Low		2.3	
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 37: **Ma et al. 2009: Evaluation of Cancer Outcomes**

Study Citation:	Ma, J; Lessner, L; Schreiber, J; Carpenter, DO (2009). Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York City Journal of Environmental and Public Health, 2009 183920
Data Type:	Dry Cleaners NYC_Kidney Cancer_Exposure level 3 vs 1-Cancer
HERO ID:	632426

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	The study population was all residents of New York City from 1993 to 2004 who were admitted as inpatients to a state-regulated hospital. Hospital discharge data were obtained from the New York Statewide Planning and Research Cooperative System (SPARCS) for the years 1993-2004.
	Metric 2: Attrition	Medium	× 0.4	0.8	Since this was a population-level study, there was no subject attrition. However, the authors studied only those zip codes where the household incomes fell in the range of $17,864 to $142,926. The was done based on evidence that rates and causes of hospitalization for individuals at both extremes of income are quite different from those in the group selected. Thus, 10 zip codes were not included because they did not meet the inclusion criteria. The author did no compare the population characteristics between participating and the nonparticipating zip codes.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	All of the studied population was recruited from New York City and had the same ICD code at the time of discharge from the hospital. However, New York State residents who obtained medical treatment in out of state hospitals were not included, and neither were patients in federal hospitals, such as VA hospitals. This may have resulted in some groups of residents (such as veterans) being excluded from the analysis.
Domain 2: Exposure Characterization					

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Study Citation:	Ma, J; Lessner, L; Schreiber, J; Carpenter, DO (2009). Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York City Journal of Environmental and Public Health, 2009 183920
Data Type:	Dry Cleaners NYC_Kidney Cancer_Exposure level 3 vs 1-Cancer
HERO ID:	632426

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The measurement of exposure was density of dry cleaning facilities using perchloroethylene in New York City. The authors used a list of dry cleaners using perc from the New York State Dept. of Environmental Conservation and determined density by taking the number of dry cleaners using perc in a zip code divided by area of the zip code. This was used as a surrogate because the authors did not have direct measurements of perc concentrations at all sites. They did not incorporate information on the volume of perc used, as this varies year by year and, in general, has declined over time due to increasing regulatory standards since 1996. Among the deficiencies in this approach are: dry cleaning facilities use differing amounts of perc, have differences in emission controls, and operate in buildings with differing structures and ventilation which would affect perc exposure. Air currents could also affect the concentration of perc in a zip code.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	5 levels of "exposures" (as defined by the density of dry cleaners per sq km) were used in the analyses.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Since the latency of exposure to kidney cancer is not exactly known, it is possible that exposures prior to 1993 (the first year of data used in the study) could have contributed to kidney cancer which would not have been included in this study. However, authors considered our study population of persons at least 45 years old, because kidney and renal cancer are rare in younger persons, and to account for the expected latency period between exposure and disease as well as the general decrease in use of perchloroethylene over time.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The outcome, kidney cancer, was assessed according the discharge diagnosis from hospital records based on ICD-9 (189.0 and 189.1). Discharge data are not able to distinguish multiple hospital discharges by a single individual from hospital discharges of distinct individuals. Therefore the outcome variable in this study is frequency of disease diagnosis at hospital discharge by zip code of patient residence, not disease incidence.

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Study Citation:	Ma, J; Lessner, L; Schreiber, J; Carpenter, DO (2009). Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York City Journal of Environmental and Public Health, 2009 183920
Data Type:	Dry Cleaners NYC_Kidney Cancer_Exposure level 3 vs 1-Cancer
HERO ID:	632426

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	All of the study's measured outcomes are outlined in the abstract, methods, and introduction. However, the number of cases/controls are not reported by exposure groups.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Analyses accounted for age, race, gender (from SPARCS), zip-code level population density, and zip-code level median household income. The zip code data were obtained from U.S. census data obtained from Claritas, Inc. which provides population totals for each zip code stratified by age, race, and gender.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Age, race, and gender were obtained from SPARCS and zip-code level population density, and zip-code level median household income. The zip code data were obtained from U.S. census data obtained from Claritas, Inc. which provides population totals for each zip code stratified by age, race, and gender.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There was no accounting for possible co-exposures in this study, which are likely given the different types of jobs in a dry cleaner shop.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This is a population-based ecological study design which is adequate to evaluate the association between density of dry cleaners and risk of and kidney cancer.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	A large population was studied, with a total of 674,519 persons diagnosed with all cancer types, and 10,916 diagnosed with kidney/renal cancer.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand what has been done in this study. Log-linear models are described in detail and the analyses would be reproducible given access to the raw data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Log-linear multivariate regression models accounted for overdispersion using a negative binomial 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	

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Study Citation:	Ma, J; Lessner, L; Schreiber, J; Carpenter, DO (2009). Association between residential proximity to PERC dry cleaning establishments and kidney cancer in New York City Journal of Environmental and Public Health, 2009 183920
Data Type:	Dry Cleaners NYC_Kidney Cancer_Exposure level 3 vs 1-Cancer
HERO ID:	632426

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‡			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 38: **Lynge et al. 2006: Evaluation of Cancer Outcomes**

Study Citation:	Lynge, E; Andersen, A; Rylander, L; Tinnerberg, H; Lindbohm, ML; Pukkala, E; Romundstad, P; Jensen, P; Clausen, LB; Johansen, K (2006). Cancer in persons working in dry cleaning in the Nordic countries Environmental Health Perspectives, 114(2,2), 213-219
Data Type:	Nordic countries_Perc_Occupational_Case-control_Kidney Cancer-Cancer
HERO ID:	632522

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	This was a nested case-cohort study. It included cohorts of all laundry and dry-cleaning workers from 1970 censuses in Denmark, Finland, Norway, and Sweden. Included 46,768 persons followed up until death, emigration, or cancer based on death and cancer registries. Cases of kidney cancer were followed from the beginning of follow-up, 9 November 1970 in Denmark and 1 January 1971 in the other countries, until the end of follow-up between 1997 and 2001.
	Metric 2: Attrition	Medium	× 0.4	0.8	Follow up began November 9, 1970 in Denmark and January 1, 1971 in the other countries. End of follow up was between 1997 and 2001. This is a 4 year difference between study subjects for end of follow up period . There were a large number of unclassifiable records for occupation in Finland and Sweden (41% and 35%, respectively,). Pension scheme data were found for 91% (151 of 166) of Danish records for employees in dry cleaning, with missing data for 5 employees. Pension scheme data were found for 75% of Finnish records.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls were randomly selected from the cohort using frequency matching by country, sex, 5-year age group, and 5-year calendar period at the time of diagnosis of the case. For kidney cancer, the numbers of controls were three times the number of cases.
Domain 2: Exposure Characterization					

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Study Citation:	Lynge, E; Andersen, A; Rylander, L; Tinnerberg, H; Lindbohm, ML; Pukkala, E; Romundstad, P; Jensen, P; Clausen, LB; Johansen, K (2006). Cancer in persons working in dry cleaning in the Nordic countries Environmental Health Perspectives, 114(2,2), 213-219
Data Type:	Nordic countries_Perc_Occupational_Case-control_Kidney Cancer-Cancer
HERO ID:	632522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposed cases and controls were laundry and dry cleaning workers; length of employment in the shop where they worked in 1970 was used as a proxy for exposure to perchloroethylene, which was identified and documented as the dominant solvent used for dry cleaning in Denmark , Finland, Sweden and Norway. The employment period of 1964 - 1979 was included. Blinded personal telephone interviews were undertaken with cases and controls in Norway and Sweden. The questionnaire asked about occupational tasks in 1970, and, if this was dry cleaning, then about length of employment in the shop, size of workforce, solvents used, and smoking/ drinking habits. No direct measurement of exposure to perc.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was categorized as exposed, dry cleaner and other exposed, other in dry cleaning, and classifiable. Exposed persons were explicitly described as dry cleaners and other workers in dry-cleaning shops with < 10 workers, other workers in dry cleaner shops, unexposed laundry workers and other persons not working in dry cleaning, and classifiable.
	Metric 6:	Temporality	Medium	× 0.4	0.8	For practical reasons, the length of employment in the shop where the subject worked in 1970 included 1964 - 1979, but the 16-year period allowed a clear distinction to be made between short-term and stable workers. Follow up began November 9, 1970 in Denmark and January 1, 1971 in the other countries. Follow up ended between 1997 and 2001.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cancer cases were identified using combined topography and morphology codes from the International Classification of Diseases for Oncology. Population, death, and cancer registries and unique personal identifiers ensured complete ascertainment of incident cancers.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outlined statistical analyses, were reported in sufficient detail. The number of cases/controls in each exposure category are reported.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Lynge, E; Andersen, A; Rylander, L; Tinnerberg, H; Lindbohm, ML; Pukkala, E; Romundstad, P; Jensen, P; Clausen, LB; Johansen, K (2006). Cancer in persons working in dry cleaning in the Nordic countries Environmental Health Perspectives, 114(2,2), 213-219
Data Type:	Nordic countries_Perc_Occupational_Case-control_Kidney Cancer-Cancer
HERO ID:	632522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Analyses accounted for smoking and alcohol use in Norway and Sweden. Analyses were also frequency matched controls by country, sex, 5-year age group, and 5-year calendar period at the time of diagnosis of the case.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on smoking and alcohol drinking were collected in Norway and Sweden from interviews. It is unclear how reliable these interviews were. Analyses also frequency matched controls by country, sex, 5-year age group, and 5-year calendar period at the time of diagnosis of the case.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Other solvents in use were white spirit and chlorofluorocarbons. However exposed study subjects were likely working is similar environments and had similar co-expsure to other solvents.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The nested case-control design was appropriate to evaluate whether there is an increased risk of kidney cancer in dry cleaners. Logistic regression models adjusted for matching criteria and, where relevant, for smoking and alcohol use.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistical power was sufficient. For example, the study identified 210 kidney cases and 2,398 controls. Because high proportion of cases and controls from Sweden and Finland were unclassifiable as to whether they had dry-cleaning or laundry work in 1970, the rate ratios were estimated for all countries together and for Denmark and Norway together.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Materials include adequate information for the analyses to be reproducible given raw data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Estimated rate ratios of cancer for dry cleaners versus unexposed controls using logistic regression adjusted for matching criteria. Risk estimates were also reported for the exposed group by length of employment.
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	

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Study Citation:	Lynge, E; Andersen, A; Rylander, L; Tinnerberg, H; Lindbohm, ML; Pukkala, E; Romundstad, P; Jensen, P; Clausen, LB; Johansen, K (2006). Cancer in persons working in dry cleaning in the Nordic countries Environmental Health Perspectives, 114(2,2), 213-219
Data Type:	Nordic countries_Perc_Occupational_Case-control_Kidney Cancer-Cancer
HERO ID:	632522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 39: **Calvert et al. 2010: Evaluation of Cancer Outcomes**

Study Citation:	Calvert, GM; Ruder, AM; Petersen, MR (2011). Mortality and end-stage renal disease incidence among dry cleaning workers Occupational and Environmental Medicine, 68(10,10), 709-716
Data Type:	TCE_exposed workers_SMR_lymphatic and haematopoietic cancer mortality-Cancer
HERO ID:	670877

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	A cohort of 1704 dry cleaner workers were identified through union records in 4 cities (San Francisco/Oakland, Chicago, Detroit, New York). They were not known to be exposed to CCl4 or trichloroethylene and had all worked 1 year prior to 1960 using PCE as the solvent. Union records may not reflect the entire population of dry cleaning workers and only a subset of those that join the union.
	Metric 2: Attrition	High	× 0.4	0.4	Of the 1704 participants in the cohort, 4 were excluded between 1996-2004 due to missing birth dates. 8-year follow up in 1996 was successful for 95% of the cohort; 5% were lost to follow up (n=79).
	Metric 3: Comparison Group	High	× 0.2	0.2	Of the 1704 participants in the cohort, 4 were excluded between 1996-2004 due to missing birth dates. 8-year follow up in 1996 was successful for 95% of the cohort; 5% lost to follow up (n=79)
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure was based on work history which was abstracted from union records. Exposure was not determined by JEM, but rather a work history of working in a shop that used PCE or a different solvent. Exposure was determined by whether a participant worked in a known PCE-shop. The study authors state that shops that used 'other solvents' "could have been PCE or another solvent." Workers with work history in these shops were considered PCE-plus and included in the overall PCE group. This could lead to some exposure misclassification.

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Study Citation:	Calvert, GM; Ruder, AM; Petersen, MR (2011). Mortality and end-stage renal disease incidence among dry cleaning workers Occupational and Environmental Medicine, 68(10,10), 709-716
Data Type:	TCE_exposed workers_SMR_lymphatic and haematopoietic cancer mortality-Cancer
HERO ID:	670877

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The cohort is divided into two groups: those who have worked primarily with PCE and those who have worked with it but employment records are uncertain to what extent. There is no attempt to quantify exposure by years worked at a PCE shop, a non-PCE shop, or a PCE-plus shop. There was no clear gradient between these two exposure groups, but exposure is expected to be similar between the groups. SMRs were presented for the entire PCE-exposed cohort compared to the general population as well, which provides two levels of exposure.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposure pre 1960 was assessed; vital status was determined in 1979 from the Social Security Administration, unions, state drivers license and motor vehicle registration authorities, IRS, and postal service. The National Death Index was assessed for vitality status from 1979 through 2004. Authors acknowledge the time frame of 8 years for follow up is rather short.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cause-specific mortality was obtained from the National Center for Health Statistics (NCHS) for the period 1940-2004. Cause-specific mortality was coded with ICD-9 codes, including the code specific for Kidney cancer (189.0-189.2).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Standard mortality ratios (SMRs) were adjusted for age, race, sex and calendar-time with and without stratification by duration of employment in PCE-using dry cleaners. Standardized incidence ratios (SIRs) calculated for ESRD for entire cohort and two subcohorts with and without stratification by duration of employment. Two-sided 95% CIs were calculated using exact Poisson distribution of the number (N) of deaths or incident ESRD cases for N<5 or Byar's approximation of Poison distribution. Duration latency calculated using exact Poisson distribution of or formulae of Breslow and Day. Significance determined if CI excluded 1.00
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SMRs and SIRs were adjusted for sex, race, age, and calendar-time. This represents a partial list of confounders, but is not expected to appreciably bias the results.

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Study Citation:	Calvert, GM; Ruder, AM; Petersen, MR (2011). Mortality and end-stage renal disease incidence among dry cleaning workers Occupational and Environmental Medicine, 68(10,10), 709-716
Data Type:	TCE_exposed workers_SMR_lymphatic and haematopoietic cancer mortality-Cancer
HERO ID:	670877

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were drawn from union records. This is not necessarily a well-established method of obtaining covariate information, but there is no evidence to suggest this is invalid.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	While PCE is main solvent, the other solvents preset were not accounted for; for the PCE-plus group it is acknowledged that there are other solvents in use but no identification of which ones or how much.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study was a retrospective cohort of dry cleaning union workers in the Bay area. This is an appropriate design to determine chronic health effects of exposure to certain chemicals.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study authors do not explicitly discuss statistical power, but there were 1704 participants in the entire cohort and effects were seen for some outcomes.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The study authors explain their criteria for each exposure classification and the calculation of SIR/SMRs. This was sufficient so that the analysis could be reproduced given original data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of SMR/SIRs for comparing rates of disease is transparent and appropriate.
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:	Calvert, GM; Ruder, AM; Petersen, MR (2011). Mortality and end-stage renal disease incidence among dry cleaning workers Occupational and Environmental Medicine, 68(10,10), 709-716
Data Type:	TCE_exposed workers_SMR_lymphatic and haematopoietic cancer mortality-Cancer
HERO ID:	670877

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 40: **Chang et al. 2003: Evaluation of Cancer Outcomes**

Study Citation:	Chang, YM; Tai, CF; Yang, SC; Chen, CJ; Shih, TS; Lin, R; Liou, SH (2003). A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan Annals of Epidemiology, 13(9,9), 652-660
Data Type:	Taiwan_perc_retrospective_cohort_cancer mortality_occupational-Cancer
HERO ID:	699203

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	The study target population was employees of a specific electronics factory in Taiwan. Participants for the this group were identified retrospectively by the Bureau of Labor Insurance computer database for years 1978-1997. The database reports employment histories, insurance status, and hospitalization data. The general Taiwanese population served as the comparison group.
	Metric 2:	Attrition	High	× 0.4	0.4	The study report suggests that the cohort was complete (i.e., included all factory workers from years 1978-1997). Also, death and cancer death information was available for all cohort members. Some assumptions were made when entering and withdrawing dates for insurance plans.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Within the study cohort, the numbers of deaths stratified by the underlying cancer cause were compared with expected numbers from death rates of the general Taiwanese population (obtained by applying Taiwanese five-year age-specific, one-calendar-year-specific, and gender-specific death rates to person-years from identical strata in the cohort). This represents covariate adjustment with appropriate choice of reference population.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	Exposure was not measured (study retrospectively examined cancer deaths among factory workers). The factory was reported to primarily have used a combination of TCE and PCE.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There were two exposure levels, exposed workers and those in the general population.
	Metric 6:	Temporality	High	× 0.4	0.4	Participants were employed at the factory between 1978 and 1997, and follow-up began in 1985 and ended in 1997. This represents sufficient time between exposure and disease.
Domain 3: Outcome Assessment						

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Study Citation:	Chang, YM; Tai, CF; Yang, SC; Chen, CJ; Shih, TS; Lin, R; Liou, SH (2003). A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan Annals of Epidemiology, 13(9,9), 652-660
Data Type:	Taiwan_perc_retrospective_cohort_cancer mortality_occupational-Cancer
HERO ID:	699203

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Deaths and cancer causes of death were obtained from the government-maintained National Mortality Database. No details were provided about how causes of death had been confirmed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Person-years were calculated for years 1985 to 1997. Expected numbers of cancer deaths for the general Taiwanese population were obtained by applying Taiwanese death rates (five-year age-specific, one-calendar-year-specific, and gender-specific) to person-years from identical strata in the cohort. Standard mortality ratios with 95% confidence intervals were reported for all types of cancers for the entire cohort.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.667	0.67	SMRs were presented with 95% confidence intervals, and were stratified by cancer cause, gender, employment duration, or time period (1985-1990 and 1991-1997). SMRs were not stratified by age; approx. 80% of participants were between ages 30 and 50.
	Metric 10:	Covariate Characterization	Medium	× 0.333	0.67	The study describes the following characteristics of the study cohort: gender, current age, time interval (cancer death between 1985-1990 or 1991-1997), age at start of work, and employment duration. These were drawn from insurance records and there is no evidence to suggest that this method is invalid.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	Exposures and co-exposures were not measured or discussed; the study retrospectively examined cancer-caused mortality among people who had worked at a specific electronics factory. The study report indicates that wells near the factory were found to have been contaminated by TCE and PCE.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This retrospective cohort study examined the association between occupational history (at a specific electronics factory in Taiwan) and cancer deaths. Mortality and labor databases were used to gather relevant information. Deaths within the exposed cohort were compared to those of the general Taiwanese population, and SMRs were calculated.

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Study Citation:	Chang, YM; Tai, CF; Yang, SC; Chen, CJ; Shih, TS; Lin, R; Liou, SH (2003). A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan Annals of Epidemiology, 13(9,9), 652-660
Data Type:	Taiwan_perc_retrospective_cohort_cancer mortality_occupational-Cancer
HERO ID:	699203

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	This study examined cancer mortality among 86,868 factory workers by calculating SMRs and 95% confidence intervals. Additionally, chi-square tests were performed to assess the statistical significance of trends related to employment duration and time period.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Deaths among the factory workers (stratified by cancer cause) were compared to those of the general Taiwanese population. SMRs and 95% confidence intervals were developed to examine relationship between cancer death and occupational history at the factory in question. Some additional analyses were applied with exclusion criteria of minimal duration of employment and latent period of 3 months, 6 months, 1 year, and 5 years, respectively, but these data were not shown in the report.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	SMRs and 95% confidence intervals were developed. The entire dataset was analyzed without exclusion. The dataset (for cancers sites with at least 3 deaths) was also analyzed according to duration of employment of (<1 year, between 1 and and 5 years, and greater than 5 years, respectively) and also by time period (cancer death occurring from 1985-1990, or 1991-1997) for dose–response relationship analyses; chi-square tests ($p<0.05$) were used to evaluate statistical significance of trends.
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‡			Unacceptable⋆⋆		1.7	
Extracted			No			

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Study Citation:	Chang, YM; Tai, CF; Yang, SC; Chen, CJ; Shih, TS; Lin, R; Liou, SH (2003). A cohort mortality study of workers exposed to chlorinated organic solvents in Taiwan Annals of Epidemiology, 13(9,9), 652-660
Data Type:	Taiwan_perc_retrospective_cohort_cancer mortality_occupational-Cancer
HERO ID:	699203

Domain	Metric	Rating†	MWF⋆	Score	Comments††

** Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 41: **Ji et al. 2005: Evaluation of Cancer Outcomes**

Study Citation:	Ji, J; Granström, C; Hemminki, K (2005). Occupational risk factors for kidney cancer: A cohort study in Sweden World Journal of Urology, 23(4,4), 271-278
Data Type:	Perc_Swedish workers-occupational_Kidney cancer (men)-Cancer
HERO ID:	699215

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	The study includes all the economically active individuals from the Swedish Family-Cancer Database (3.3 million men and 2.8 million women, recorded in any of the censuses). Cases were identified from the Swedish Cancer Registry. A four-digit diagnosis code according to the seventh revision of the International Classification of Diseases (ICD-7) has been used since 1958. Only the first primary kidney cancer was considered in the present study
	Metric 2: Attrition	High	× 0.4	0.4	No attrition, all all the economically active individuals from the Swedish Family-Cancer Database were included.
	Metric 3: Comparison Group	High	× 0.2	0.2	The comparison group was all the economically active population in Sweden.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Occupational groups were used as proxy for exposure. The occupations were obtained from the 1960, 1970, 1980, and 1990 censuses and coded according to the Nordic Occupational Classification (NYK) which is a Nordic adaptation of the International Standard Classification of Occupation from 1958. These defined 53 occupational groups including launderers and dry cleaners. No direct measurements of exposure to perc or to any other chemical in this study. But the authors state that launderers and dry cleaners often come in contact with different types of solvents and chemical cleaning agents such as the tetrachloroethylene,

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Study Citation:	Ji, J; Granström, C; Hemminki, K (2005). Occupational risk factors for kidney cancer: A cohort study in Sweden World Journal of Urology, 23(4,4), 271-278
Data Type:	Perc_Swedish workers-occupational_Kidney cancer (men)-Cancer
HERO ID:	699215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The reference group for the expected numbers of cancers were the corresponding economically active population in the Database, calculated from 5-year-age-, period- (10 years bands), socio-economic status- specific standard incidence rates for men and women who had an occupation in the either one census of the year 1960 or 1970, or had the same occupation in the two consecutive censuses of the years 1960 and 1970, or had the same occupation in the three consecutive censuses of the years 1960, 1970, and 1980. No exposure levels were measured in this study.
	Metric 6:	Temporality	Medium	× 0.4	0.8	The study used the Swedish Cancer Database to assess cancer incidence. The database included cancers diagnosed from 1961-2000 and the census information on occupations included information from occupations from 1960-1990. This study appears to have a sufficient time to detect kidney cancer after occupational exposures.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The cancer cases in this study were identified on the Swedish Cancer Registry and was estimated to be 95% complete in the 1970s and close to 100% complete in the present day. It is based based on compulsory notification of cases and a 4 digit diagnosis code is assigned according to the International Classification of Disease (ICD-7).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The tables in the studies present observed and expected cases, and standardized incidence ratios (ICR) for kidney cancer and many other types of cancers based on occupational groups.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	The results were adjusted for gender, age, period, and socioeconomic status. The authors did not consider smoking, but they did consider lung cancer risks in each occupational groups as the indication of the potential effect of smoking to the risk of kidney cancer.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on age, gender, SES, time likely from the Swedish Family- Cancer Database. No details are provided, but censuses data is also included. For cases, the Registry data is considered reliable.

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Study Citation:	Ji, J; Granström, C; Hemminki, K (2005). Occupational risk factors for kidney cancer: A cohort study in Sweden World Journal of Urology, 23(4,4), 271-278
Data Type:	Perc_Swedish workers-occupational_Kidney cancer (men)-Cancer
HERO ID:	699215

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Risks were estimated for 543 occupational groups. It is likely that within the same occupation, cases have a comparable co-exposure to other solvents (for dry-cleaners, for example)
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cohort study design was appropriate to examine the risk of occupational exposures on kidney cancer.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	This study was based on the entire working population of Sweden and included many people in each occupational group.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient information was provided in the study to reproduce the analysis that was carried out.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Standardized incidence ratios (SIRs) were calculated using all the economically active population in the database as the reference group. Confidence intervals (95% CIs) were calculated assuming a Poisson distribution.
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 42: **Sung et al. 2007: Evaluation of Cancer Outcomes**

Study Citation:	Sung, TI; Chen, PC; Lee, LJH; Lin, YP; Hsieh, GY; Wang, JD (2007). Increased standardized incidence ratio of breast cancer in female electronics workers BMC Public Health, 7 102
Data Type:	Taiwan_Occupational_Kidney cancer_perc-Cancer
HERO ID:	699225

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All key elements of study design are reported and selection in and out of the study was not likely to be biased. The total study population was 63,982. Female workers were retrospectively recruited from the database of the Bureau of Labor Insurance of Taiwan covering the period 1973–1992.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal exclusion from the analysis sample. The authors report that 64,000 female employees worked at the factory between 1973 and 1992. Three workers with cancer were excluded from analyses because their diagnoses were established prior to the time of their first employment at the factory. Fifteen more workers were excluded because each had worked less than one full day at the factory. The authors do not report any missing vital statistics data.
	Metric 3:	Comparison Group	High	× 0.2	0.2	The reference population was the general population in Taiwan during each calendar year. Expected numbers of cancer were calculated based on gender-, age-, and calendar time-specific incidence rates (five-year strata). There was no adjustment or stratification for race; however, the vast majority of people living in Taiwan are Asian.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	Employees were considered exposed if they had worked in the factory anytime during 1973-1992. The authors do not report any actual exposure data. "No data on solvent exposure had been kept by the factory, and although we attempted to produce a reconstruction of such exposure, our dataset was too limited and crude to permit any possible linkage to individual workers."
	Metric 5:	Exposure levels		NA	NA	No description is provided on the levels or range of exposure for any of the solvents the workers were exposed to. Workers were categorized as exposed and compared to the general population.

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Study Citation:	Sung, TI; Chen, PC; Lee, LJH; Lin, YP; Hsieh, GY; Wang, JD (2007). Increased standardized incidence ratio of breast cancer in female electronics workers BMC Public Health, 7 102
Data Type:	Taiwan_Occupational_Kidney cancer_perc-Cancer
HERO ID:	699225

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established and the analysis for kidney cancer incorporated a lag period of at least 10 years.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed with well-established methods. Diagnoses of cancer were determined by linking employee identification numbers for the entire cohort, from 1 Jan 1979 to 31 Dec 2001, with the data obtained from the Taiwan National Cancer Registry. The cancer registry is a population-based registry containing information on newly diagnosed cancer patients in all hospitals in Taiwan with 50 beds or more. The coding of the cancer sites was based upon the International Classification of Diseases for Oncology issued by the Department of Health.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All PECO-relevant outcomes outlined in the abstract, introduction, and methods is provided in the results. Effect estimates are reported with 95% confidence intervals in Table 5. Numbers of observed and expected cancer cases are reported for each cancer site.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	The SIRs were standardized based on gender-, age-, and calendar time-specific incidence rates (five-year strata). There was no adjustment or stratification for race; however, the clear majority of people living in Taiwan are Asian.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Age and gender of each employee were obtained from the Ministry of the Interior, within which both local and national vital statistics are centralized. The Taiwan household registration program is designed to collect and supply demographic information with every birth and death being ascertained by a formal certificate written and attested by a physician.

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Study Citation:	Sung, TI; Chen, PC; Lee, LJH; Lin, YP; Hsieh, GY; Wang, JD (2007). Increased standardized incidence ratio of breast cancer in female electronics workers BMC Public Health, 7 102
Data Type:	Taiwan_Occupational_Kidney cancer_perc-Cancer
HERO ID:	699225

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence of co-exposures in the cohort members and the co-exposures were not addressed in the analyses. According to the company's monthly magazines and labor inspection records, 15 different solvents were used in the factory. TCE was the only solvent reported for the time before 20 June 1974, while 14 other solvents were used in the factory after that date including methylene chloride and tetrachloroethylene. The authors do not report actual exposure data for any of the solvents, but state, "Based upon our in-depth review of formal inspection records, and the monthly magazines published by the company, we find that the only organic solvent under strict regulation which no longer appeared after 1974 was TCE (Table 5). We therefore suspect that TCE, and/or its mixtures, may be the most likely agent responsible for our findings. However, our results should be interpreted with caution since it is clear that co-exposure to other solvents did occur amongst our subjects."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study uses an appropriate statistical method to address the research question (the PC Life Table Analysis System Version 1.0d was used to calculate the SIRs for cancer).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants are adequate to detect an effect in the exposed population. A total of 63,982 female workers were recruited for this study providing a total follow-up period of 1,403,824 person-years (without latent periods).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand what has been done. The PC Life Table Analysis System (LTAS) Version 1.0d was used to calculate the SIRs for cancer. Expected numbers of cancer were calculated based on gender-, age-, and calendar time-specific incidence rates (five-year strata). The 95% confidence interval was calculated under the assumption that the number of incidences had a Poisson distribution. Additional analyses, including dose-response relationship (based on duration of employment), were performed only for breast, cervical, colorectal, and thyroid cancers.

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Study Citation:	Sung, TI; Chen, PC; Lee, LJH; Lin, YP; Hsieh, GY; Wang, JD (2007). Increased standardized incidence ratio of breast cancer in female electronics workers BMC Public Health, 7 102
Data Type:	Taiwan_Occupational_Kidney cancer_perc-Cancer
HERO ID:	699225

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Medium	× 0.2	0.4	The method used for calculating SIRs is transparent and appropriate for the research question. The study authors provided information on what data were available.
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‡		Unacceptable⋆⋆		0.0	
Extracted		No			

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 43: **Wilson et al. 2008: Evaluation of Cancer Outcomes**

Study Citation:	Wilson, R; Donahue, M; Gridley, G; Adami, J; El Ghormli, L; Dosemeci, M (2008). Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden American Journal of Industrial Medicine, 51(2,2), 83-99
Data Type:	Perc_Sweden_occup_Kidney cancer (renal pelvis) (men)-Cancer
HERO ID:	699229

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	This cohort consisted of all male and female Swedish residents reporting to be employed at either the 1960 or 1970 census and alive on Jan. 1971. Person-years were calculated for each member of the cohort from Jan. 1, 1971 until a diagnosis of cancer, emigration, death, or end of follow-up on Dec. 31, 1989. Cancer cases were from the Swedish Cancer-Environment Registry (CER), Version III, (transitional cell cancers of the renal pelvis (International Classification of Diseases, 7th Revision (ICD-7) code 180.1).
	Metric 2:	Attrition	High	× 0.4	0.4	No subject attrition was reported in this study.
	Metric 3:	Comparison Group	High	× 0.2	0.2	The reference population (on which the expected number of cancer cases were calculated) consisted of the total employed population defined as those individuals reporting employment at either the 1960 or 1970 census. Autopsy-only reported cases were excluded from both observed and expected rate calculations. The expected number of cases was based on the incidence rates in attained age (by 5-year-age groups), sex, site and calendar-year (by 4-year calendar periods from 1971-1989) specific cancer incidence rates.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Occupation of interest defined as work in "laundry, ironing, dyeing". Exposure to perchloroethylene was not assessed in this study. The analysis was based on classification by occupation, and risks were assessed for the following exposures: asbestos, ionizing radiation, low physical activity, and indoor work, but not for perc.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The expected cancer counts were based on cancer incidence rates in the total employed population defined as those individuals reporting employment at either the 1960 or 1970 census. Exposure levels to perc were not assessed in this study..

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Study Citation: Wilson, R; Donahue, M; Gridley, G; Adami, J; El Ghormli, L; Dosemeci, M (2008). Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden American Journal of Industrial Medicine, 51(2,2), 83-99
Data Type: Perc_Sweden_occup_Kidney cancer (renal pelvis) (men)-Cancer
HERO ID: 699229

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	The incidence of renal pelvis cancer was calculated between 1971 and 1989. Since the study used job classifications from the 1960 or 1979 censuses, the time between the reporting of the cancer and the job classification should be sufficient to detect the occurrence of the cancer.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The incidence of renal pelvis cancer was calculated based on classification from the International Classification of Diseases, 7th Revision (ICD-7) between 1971 and 1989. Cancers were limited by histology according to the Swedish Cancer Registry PAD (codes 114 and 116). Microscopic confirmation occurred for 97% of the cancers in this study.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	The results tables present all the analyses presented, i.e. the Standardized Incidence Ratios (SIRs) with the 95% confidence intervals or each occupational category. Expected number of cases are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The expected number of cases was based on the incidence rates in attained age (by 5-year-age groups), sex, site and calendar-year (by 4-year calendar periods from 1971-1989) specific cancer incidence rates.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Although it is not clearly stated, the Swedish national census and cancer registry-linked data are the sources of age, sex, calendar year.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Occupational exposure was likely subject to co-exposures, however the degree of differential co-exposure is unknown just based on the job categories.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate for the research question asked.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were a sufficient number of participants in this study (1,374) diagnosed with cancers of the renal pelvis to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	This statistical methods used were sufficiently transparent in this study.

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Study Citation:	Wilson, R; Donahue, M; Gridley, G; Adami, J; El Ghormli, L; Dosemeci, M (2008). Shared occupational risks for transitional cell cancer of the bladder and renal pelvis among men and women in Sweden American Journal of Industrial Medicine, 51(2,2), 83-99
Data Type:	Perc_Sweden_occup_Kidney cancer (renal pelvis) (men)-Cancer
HERO ID:	699229

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The calculation of the Standardized Incidence Ratio (SIR) with the 95% confidence levels was sufficient to answer the research question in this study.
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 44: **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_Perc_MultipleMyeloma_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, Perchloroethylene, 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_Perc_MultipleMyeloma_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 Perchloroethylene 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, Perchloroethylene, 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.

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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_Perc_MultipleMyeloma_Females-Cancer
HERO ID:	699234

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method and model assumptions used to calculate risk estimates for occupational exposure to TCE, Perchloroethylene, 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 45: **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_Perc_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, Perchloroethylene, 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_Perc_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 Perchloroethylene 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, Perchloroethylene, 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.

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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_Perc_NonMalignantRespiratoryDisease-Respiratory
HERO ID:	699234

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method and model assumptions used to calculate risk estimates for occupational exposure to TCE, Perchloroethylene, 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 46: **Pukkala et al. 2009: Evaluation of Cancer Outcomes**

Study Citation:	Pukkala, E; Martinsen, J; Lynge, E; Gunnarsdottir, H; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries Acta Oncologica, 48(5,5), 646-790
Data Type:	Nordic cohort_Perc_occupational_SIR_liver-Cancer
HERO ID:	699237

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Prospective cohort study included 14,902,573 individuals (2.0 million from Denmark, 3.4 million from Finland, 0.1 million from Iceland, 2.6 million from Norway and 6.8 million from Sweden) aged 30-64 years who were recruited in the 1960, 1970, 1980/81 and 1990 censuses in Denmark, Finland, Iceland, Norway and Sweden, and 2.8 million incident cancer cases diagnosed in follow up until 2005. Individual records were linked using the Nordic standard personal identity codes. Minimal potential for selection bias because selecting large sample from naturally occurring population.
	Metric 2: Attrition	High	× 0.4	0.4	All data was taken from linkage of individuals in the Denmark, Finland, Iceland, Norway and Sweden censuses with cancer and death registries from each Nordic country via personal identification numbers. Majority of cancer registries had compulsory reporting of new cases for most of the study period. Exposure and outcome data largely complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	The 15 million subject study population of different occupations were all recruited from a naturally occurring population. Expected values for SIR calculations were taken from national incidence rates. Authors justified to compare the incidence of cancer in each occupation in a given country with the general population in the same country. No evidence for differences in baseline characteristics between exposed and unexposed. Methods for study participation were detailed and no exclusion criteria included as this was a population based large cohort study from a census.
Domain 2: Exposure Characterization					

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Study Citation:	Pukkala, E; Martinsen, J; Lynge, E; Gunnarsdottir, H; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries Acta Oncologica, 48(5,5), 646-790
Data Type:	Nordic cohort_Perc_occupational_SIR_liver-Cancer
HERO ID:	699237

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure to Perchloroethylene was not measured or estimated with a job-exposure matrix. Participants were classified by occupational category according to self-reported free text questionnaires. Occupations were recorded based on the occupation in the first census the person participated in (not recording subsequent changes). Comprehensive descriptions of occupational categories are provided in the text, along with corresponding job codes used for each country. The use of occupations instead of specific exposure measurements may lead to some exposure misclassification. Dry cleaners and launderers were included as one of the occupational categories. The study authors note Perchloroethylene as one of the substances dry cleaners would be exposed to during the periods of employment included in this study.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure to Perchloroethylene was not measured or estimated, but only an occupational category was assigned. Individual participants are labeled with their primary occupation serves as an exposed/unexposed marker, indicating two levels of exposure.
	Metric 6:	Temporality	Medium	× 0.4	0.8	All subjects were disease-free at the start of the follow up minimizing potential confusion on temporality. However, minimal information about occupational history indicate it is still unclear whether exposures fall within relevant exposure windows for the outcome of interest. Overall long follow up time was likely adequate for long latency period of cancer.
Domain 3: Outcome Assessment						

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Study Citation:	Pukkala, E; Martinsen, J; Lynge, E; Gunnarsdottir, H; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries Acta Oncologica, 48(5,5), 646-790
Data Type:	Nordic cohort_Perc_occupational_SIR_liver-Cancer
HERO ID:	699237

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Nordic cancer registries and death certificates were linked with census data via personal identification number to identify incident cancer cases. Cancer cases were grouped into 49 main categories and 27 diagnostic sub groups based on national topography and morphology coding systems. Nordic cancer registries are known for high-quality cancer reporting. Authors note that any small inaccuracies in the cancer registration are not likely to affect SIR estimates because not related to occupation; likelihood of getting proper diagnosis of cancer does not vary between occupations. There is also high accuracy in the linkage of census data, the mortality and emigration data and the cancer incidence data since was based on the unique personal identity codes.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Comprehensive description of all measured outcomes is reported. The observed numbers of cancer cases and the SIRs for each Nordic country, and the respective information for the five countries combined together with the 95% confidence interval for the SIR are presented in tables for each diagnostic group and gender. Data for additional cancer sub-sites is presented in online supplemental material. All information is readily extractable.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SIRs were separated by gender and occupational category, and then stratified into 8 5-year attained age categories and 5-year calendar periods. Although age, gender and time were considered as potential covariates, additional information about participants, including smoking status, alcohol habits or physical activity, was not included in the analysis but could have potentially contributed to residual confounding (non-exchangeability due to common causes of exposure and outcome).
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Information on age, gender and time covariates were assessed using the Nordic censuses, which have been shown to be valid and reliable. No evidence method has poor validity.

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Study Citation:	Pukkala, E; Martinsen, J; Lynge, E; Gunnarsdottir, H; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries Acta Oncologica, 48(5,5), 646-790
Data Type:	Nordic cohort_Perc_occupational_SIR_liver-Cancer
HERO ID:	699237

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is potential for co-exposure confounding in this study, as exposure categories were roughly defined as occupational categories with no corresponding measured or estimated exposure levels. No adjustments were made in the computations for co-exposure confounding, and more granularity in the exposure definition is needed to prevent impact on effect estimates. The study authors state "Some carcinogenic substances found in working places may be associated with the development of non-Hodgkin lymphoma. These include 2,3,7,8-Tetrachlorodibenzopara-dioxin (TCDD), nonarsenical insecticides, Tetrachloroethylene, and Trichloroethylene."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Large prospective cohort study using census data linked to cancer registries in 5 Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) provided an appropriate study design to detect incident cancer cases across different occupation groups. Study size (close to 15 million) was sufficiently large to detect incident cancer cases for kidney cancer (outcome of interest). Calculation of SIRs separated by gender and occupational category and stratified into age group and 5-year calendar periods was appropriate statistical test to detect cancer rates different than expected in different occupational groups.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Very large sample sizes in this study (15 million) were sufficient to detect an effect in the exposure population and subgroups. 43,496 total launderers were included in the study (the occupation category of interest for Perchloroethylene) which is sufficient. Important to note that due to the huge size of the study, many of the observations that are statistically significant correspond to such a small deviation from unity that it has no practical implication.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Method for calculating SIRs was transparent, variables included were clearly stated and defined, and model assumptions were met. SIRs were separated by gender and occupational category, and then stratified into 8 5-year attained age categories and 5-year calendar periods. 95% confidence intervals were provided assuming a Poisson distribution of the observed number of cases.

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Study Citation:	Pukkala, E; Martinsen, J; Lynge, E; Gunnarsdottir, H; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kjaerheim, K (2009). Occupation and cancer - follow-up of 15 million people in five Nordic countries Acta Oncologica, 48(5,5), 646-790
Data Type:	Nordic cohort_Perc_occupational_SIR_liver-Cancer
HERO ID:	699237

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Method for calculating SIRs was transparent, variables included were clearly stated and defined, and model assumptions were met. SIRs were separated by gender and occupational category, and then stratified into 8 5-year attained age categories and 5-year calendar periods. 95% confidence intervals were provided assuming a Poisson distribution of the observed number of cases.
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 47: **Carpenter 1937: Evaluation of Clinical Chemistry/Biochemical Outcomes**

Study Citation:	C. P. Carpenter (1937). The chronic toxicity of tetrachlorethylene Journal of Industrial Hygiene and Toxicology, 19 323-336
Data Type:	Carpenter_controlled_inhalation_exposure_clinicalchem-Clinical Chemistry/Biochemical
HERO ID:	58185

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	The study author selected themselves and a 4 colleagues to participate in this experiment. Four of the subjects participated in all the study at all dosage levels, and one of the subjects participated exclusively in the 2000 ppm exposure. The choice of subjects indicates a likely selection bias and no concurrent control group was reported.
	Metric 2:	Attrition	High	× 0.4	0.4	No attrition was reported. Only a select group of four individuals participated in this experiment. There was an additional individual subjected to the exposure to 2000 ppm perchloroethylene, but this was considered separately.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	No concurrent control group was reported. A blood sample and 24 hour urine sample was collected prior to exposure for comparison post exposure. For the clinical outcomes, individuals subjects could only make qualitative comparisons to their status prior to exposure. Subjects were not blinded to exposure status.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The perchloroethylene for the controlled exposure was likely to be obtained from the Eastman Kodak Company Research Laboratory, the same as in animal experiments and stated to be a commercially pure material. The inhalation chamber was described and the required amount of solvent was added to a towel on a fan. Serial measurements were taken with an interferometer to determine the actual concentration in the air. Subjects were exposed in two interspersed periods at varying levels of exposure. Exposures at varying levels were conducted in succession, potentially leading to cumulative effects.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Multiple levels of perchloroethylene exposure were utilized in this experiment, including 500 ppm, 1000 ppm, 1500 ppm, 2000 ppm, and 5000 ppm. Subjects stayed in the room as the exposure gradient was increased or left for short breaks. To evaluated the impact of cumulative exposure, subjects repeated the 2000 ppm exposure on a different day.

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Study Citation: C. P. Carpenter (1937). The chronic toxicity of tetrachlorethylene Journal of Industrial Hygiene and Toxicology, 19 323-336
Data Type: Carpenter_controlled_inhalation_exposure_clinicalchem-Clinical Chemistry/Biochemical
HERO ID: 58185

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	The health of subjects prior to exposure was not discussed, however, no overt clinical symptoms were described. The study notes that negative effects were only experienced once inside the perchloroethylene inhalation chamber.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Participants made subjective observations about the effects of exposure such as eye irritation, salivation, nausea, and other similar symptoms. It was reported that blood pressure and pulse were measured, but no details on measurement methods were provided. A urinalysis was conducted on each participant, however, this was also not fully described. The study authors were the selected participants and blinding could not be applied.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All results outlined in the abstract, introduction, and methods were reported qualitatively.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.667	1.33	A statistical analysis was not performed, nor were covariates discussed.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	No covariates were characterized.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There was no indication of co-exposures in this controlled inhalation exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study was a controlled inhalation exposure designed to document subjective observations and changes in blood pressure and urinalysis results.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	No statistical comparison was made in this study. Additionally, each exposure level was assessed in 4-5 subjects, which raises concerns about statistical power.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	No statistical comparison was made or reported. Urine results were reported to show no variation from normal, however, the method and reference values were not described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	No statistical analysis is presented. The text notes a "significant drop" in blood pressure during exposure of 1000-1500 ppm, but not quantitative data is provided. The statistical analysis associated with the claim is not described. Urine results may have been compared to reference values or ranges, but no details are provided.

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Study Citation:	C. P. Carpenter (1937). The chronic toxicity of tetrachlorethylene Journal of Industrial Hygiene and Toxicology, 19 323-336
Data Type:	Carpenter_controlled_inhalation_exposure_clinicalchem-Clinical Chemistry/Biochemical
HERO ID:	58185

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‡		Low		2.3	
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 48: **Seldén and Ahlborg 2011: Evaluation of Cancer Outcomes**

Study Citation:	Seldén, AI; Ahlborg, G (2011). Cancer morbidity in Swedish dry-cleaners and laundry workers: Historically prospective cohort study International Archives of Occupational and Environmental Health, 84(4,4), 435-443
Data Type:	Perc_Prospective Cohort_occupational_Kidney cancer-Cancer
HERO ID:	699243

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	A prospective cohort study was conducted on a national cohort of 10,389 dry-cleaning and laundry workers. Workers were recruited in 1984 in Sweden and followed for new cancer cases from 1985-2006. New cancer cases were identified by matching with the Swedish Cancer Register, and expected frequencies were computed from national reference data. Workers were recruited after contacting 1,254 companies across Sweden identified from another nationwide study on dry-cleaning workers (Olsen et al. 1990), and information was obtained from 461 for this study. Subjects excluded if: exposure ceased before 1973, exposure commenced after 1983, duration of employment <1 month, deceased 1973-1984, emigrated 1973-1984, or identity unclear.
	Metric 2: Attrition	High	× 0.4	0.4	Of the 10,389 original subjects reported by the companies, 949 subjects were excluded and 9,440 included in final sample. These workers were followed from 1985-2006, and follow-up was complete for 90.9% of the cohort (2,810 men and 6,630 women) which represents minimal loss to follow up. Outcome and exposure information largely complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	Expected frequencies were computed from national reference data in Sweden accounting for sex, 5-year age group, calendar year and cancer cause. This is an adequate comparison group for an ecological analysis.
Domain 2: Exposure Characterization					

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Study Citation:	Seldén, AI; Ahlborg, G (2011). Cancer morbidity in Swedish dry-cleaners and laundry workers: Historically prospective cohort study International Archives of Occupational and Environmental Health, 84(4,4), 435-443
Data Type:	Perc_Prospective Cohort_occupational_Kidney cancer-Cancer
HERO ID:	699243

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Although no information on Perchloroethylene exposure at the company or individual level was available, estimates of the proportion of Perchloroethylene and other detergents employed (as reported by the companies over the period of interest) were used as proxy. Each subject was assigned undefined exposure categories with no associated quantitative levels (known use of Perchloroethylene in facility, no use of Perchloroethylene, use of combined products). In Sweden, Perchloroethylene has been used almost exclusively for dry-cleaning since the 1950. The study concluded from outside historical data that Perchloroethylene levels in the 1970s were on the order of 100-200 mg/m3 (15-30 ppm). Duration of employment was also used as a proxy for duration of exposure.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	SIRs were calculated using the national rates as reference for each cancer of interest.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality of exposure and outcome is established in this prospective cohort as only incident cases of cancer were included. Follow up period from 1985-2006 considered sufficient for the long latency period of cancer. Occupational history of the cohort members was only available for 11 year period, suggesting potential confounding from occupational exposures prior to this period.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Incident cases of malignant tumors in the cohort, coded to the 7th revision of the International Classification of Diseases (ICD-7), were obtained by matching to the Swedish National Cancer Register for the period 1985–2006. The Swedish National Cancer Register is a well-established data source, and there is no evidence of poor validity.

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Study Citation:	Seldén, AI; Ahlborg, G (2011). Cancer morbidity in Swedish dry-cleaners and laundry workers: Historically prospective cohort study International Archives of Occupational and Environmental Health, 84(4,4), 435-443
Data Type:	Perc_Prospective Cohort_occupational_Kidney cancer-Cancer
HERO ID:	699243

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Standardized incidence ratios (SIRs) were calculated and reported for each cancer site of interest by comparing the outcome with the expected numbers of cancer derived from a computation of the person-years under observation with sex, 5-year age group, calendar year and cause-specific national rates. 95% confidence intervals were reported for each cancer sub-type, calculated assuming a Poisson distribution of observed events. SIRs reported separately by sex, but breakdown by exposure category/laundry sites and duration of employment not reported for all cancer sub-types (missing for kidney cancer).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SIRs were computed with consideration for sex, 5-year age group, person-years under observation, calendar years and cause-specific national rates. This method of adjustment (using a population-based comparison group) is adequate in ecological studies.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Details were no provided, but covariates considered (age and sex) were likely assessed from linking personal identification numbers of each cohort member with the national population register/national cause-of-death register. No additional covariates measured.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Primary exposure was working in a dry-cleaning facility. It is unknown if workers had differential co-exposures (possible even in the same job category if the shop uses different combinations of solvents)
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A prospective cohort study of dry-cleaning and laundry workers used a large sample (n = 9,440) followed over a long period of 1985–2006 suitable to account for the long latency period of cancer. SIRs computed to compare incidence rates to expected deaths in the population.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Overall cohort size was large (n = 9,440). and adequate length of follow-up. Overall number of person-years 188,094 (men 55,798, women 132,296). There were small numbers of observed kidney cancer cases (n=10 males, n=19 females) reflecting the nature of a rare cancer site. Resulting SIRs had large confidence intervals due to the small sample size (male: 0.51-1.94, and female: 0.62-1.60).

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Study Citation:	Seldén, AI; Ahlborg, G (2011). Cancer morbidity in Swedish dry-cleaners and laundry workers: Historically prospective cohort study International Archives of Occupational and Environmental Health, 84(4,4), 435-443
Data Type:	Perc_Prospective Cohort_occupational_Kidney cancer-Cancer
HERO ID:	699243

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Detailed description of analysis is provided which is sufficient for reproducibility of analyses. The calculation of the SIR is clearly described and all component variables noted.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Standardized incidence ratios (SIRs) were calculated and reported for each cancer site of interest by comparing the outcome with the expected numbers of cancer derived from a computation of the person-years under observation with sex, 5-year age group, calendar year and cause-specific national rates. 95% confidence intervals were reported for each cancer sub-type, calculated assuming a Poisson distribution of observed events. Model assumptions were met and the variables used were clearly stated and appropriate.
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 49: **Brüning et al. 2003: Evaluation of Cancer Outcomes**

Study Citation:	Brüning, T; Pesch, B; Wiesenhütter, B; Rabstein, S; Lammert, M; Baumüller, A; Bolt, H (2003). Renal cell cancer risk and occupational exposure to trichloroethylene: Results of a consecutive case-control study in Arnsberg, Germany American Journal of Industrial Medicine, 43(3), 274-285
Data Type:	Case control study-excess risk of renal cell carcinoma-self assessed exposure to Perc-Cancer
HERO ID:	701363

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	162 incident eligible cases were identified of which 134 participated in the study. Cases with diagnosis before June 1, 1992 were not eligible.
	Metric 2:	Attrition	High	× 0.4	0.4	For cases that had already deceased, next of kin interviews took place to include the cases (n=21).
	Metric 3:	Comparison Group	High	× 0.2	0.2	3:1 frequency matched to cases by sex and age within area and time frame.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Data collected by questionnaire from similar study for comparison. No employee records were evaluated. Frequency and duration of TCE and Perchloroethylene exposure were self-assessed.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Only 2 levels of exposure intensity (low/high) or duration of exposure measured in 3-2 levels.
	Metric 6:	Temporality	High	× 0.4	0.4	Data provided for time between the last or first exposure (<5 year to 20+ years).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histologically confirmed diagnosis of renal cell carcinoma.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	ORs were reported with CIs and are appropriate.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for gender, age and smoking status.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Data gathered by questionnaire is considered adequate to compare results using same questionnaire in another study.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Other chemical agent worker exposures were not appropriating adjusted for which could result in biased exposure-outcome association.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design using case-control and conditional logistic regression was appropriate to evaluate rare disease with associated exposures.

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Study Citation:	Brüning, T; Pesch, B; Wiesenhütter, B; Rabstein, S; Lammert, M; Baumüller, A; Bolt, H (2003). Renal cell cancer risk and occupational exposure to trichloroethylene: Results of a consecutive case-control study in Arnsberg, Germany American Journal of Industrial Medicine, 43(3), 274-285
Data Type:	Case control study-excess risk of renal cell carcinoma-self assessed exposure to Perc-Cancer
HERO ID:	701363

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Small number of cases; number of controls was increased to increase power.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Model was well described.
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§		~~1.5~~	
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

§ Evaluator's explanation for rating change: "Study relies on self-assessed exposure information which has low reliability and is subject to recall bias."

Table 50: **Kalkbrenner et al. 2010: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Kalkbrenner, A.E., Daniels, J.L., Chen, J.C., Poole, C., Emch, M., Morrissey, J (2010). Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8 Epidemiology, 21(5), 631-641
Data Type:	Perc_autism spectrum disorder (ASD)_children-Neurological/Behavior
HERO ID:	737424

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Cases identified through ADDM network in 8 NC counties (2002-2004) or all of WV (2000-2002) and based on DSM-IV-TR. Participants limited to children who resided in study location at time of birth, confirmed by matching birth certificates. In NC, 220 of 311 children identified with ASD had a matching birth certificate, and 206 of those were born in the surveillance counties and eligible for inclusion. In WV, 189 of 257 children identified with ASD had a matching birth certificate, and a census tract was determined for 177 of those and they were eligible for inclusion.
	Metric 2: Attrition	Medium	× 0.4	0.8	There was a moderate amount of exclusions, but reasons were documented (i.e., those without in-state birth certificates, a 1/3 random sampling of WV controls, and those lacking Census tract data) and handled adequately. Approximately 33% of NC cases, 30% of WV cases, 33% of NC controls, and 75% of WV controls (or 23% of those randomly sampled) were excluded from the analysis.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls identified during the same time as cases through school system based on speech and language impairment w/o documentation of other developmental problems. Table 1 indicates cases can controls were similar, except for covariates that were included in statistical models (i.e., maternal age, smoking in pregnancy, maternal marital status and education, race, census tract median household income, urbanicity).
Domain 2: Exposure Characterization					

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Study Citation:	Kalkbrenner, A.E., Daniels, J.L., Chen, J.C., Poole, C., Emch, M., Morrissey, J (2010). Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8 Epidemiology, 21(5), 631-641
Data Type:	Perc_autism spectrum disorder (ASD)_children-Neurological/Behavior
HERO ID:	737424

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure based on modeled data because ambient measurements not made during period of interest, and residence at birth was used to assign Census-tract-specific concentrations. Data for each census tract based on National Air Toxics Assessment-1996 estimates, with primary inputs from the National Emissions Inventory and additional inputs from meteorological and secondary-pollutant formation data. Estimated PAH exposures are intended to reflect individual perinatal exposures. Authors note potential for exposure misclassification.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Provides clean air background levels of pollutants and levels in NC and WV (urban, not urban, and whole state). But analysis based only on comparison of 20th and 80th percentiles of log-transformed concentrations among controls.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Authors note exposure assigned during the perinatal period, but subjects born between 1994-1996 (NC) and 1992-1994 (WV) and exposure based on 1996 data, so unclear if exposure is within relevant window. Outcome measurements made between 2002-2004 (NC) and 2000-2002 (WV).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcome based on DSM-IV-TR definition of ASD regardless of previous diagnosis. Controls were children in the surveillance system with speech and language impairments, but no indication of other serious developmental problems (e.g., ASD, ID). identified from group with equivalent access to developmental evaluations. All participants were 8 years old, the age at which most ASD-affected children have been identified.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	OR and 95% CI reported, and number of cases and total number of participants reported for each analysis. All outlined statistical analyses, including sensitivity analyses, were reported with sufficient detail.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Models adjusted for sampling variables, demographic information from birth certificate and census (maternal age, smoking in pregnancy, maternal marital status and education, race, census tract median household income, urbanicity), and co-varying air pollutants.

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Study Citation:	Kalkbrenner, A.E., Daniels, J.L., Chen, J.C., Poole, C., Emch, M., Morrissey, J (2010). Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8 Epidemiology, 21(5), 631-641
Data Type:	Perc_autism spectrum disorder (ASD)_children-Neurological/Behavior
HERO ID:	737424

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Demographic covariates determined from birth certificate and census data. Additional data source for covariates is not explicitly reported, but demographic information is also assumed to have been collected from the ADDM records. There is no evidence of poor validity.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	All pollutants included in a semi-Bayes hierarchical model that adjusted the beta coefficient for each pollutant toward the mean of its exchangeability group.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate statistical methods were used (Semi-Bayes logistic regression accounting for multiple comparisons in this case-control study).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Case and control sample sizes are sufficient to detect an effect. In combined WV+NC analyses, 374 cases and 2803 controls were included.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The statistical methods for the semi-Bayes hierarchical model were well described.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The assumptions for the statistical model were described and met. Authors discussed reasoning for including a priori covariates.
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			

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Study Citation:	Kalkbrenner, A.E., Daniels, J.L., Chen, J.C., Poole, C., Emch, M., Morrissey, J (2010). Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8 Epidemiology, 21(5), 631-641
Data Type:	Perc_autism spectrum disorder (ASD)_children-Neurological/Behavior
HERO ID:	737424

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 51: **Forand et al. 2012: Evaluation of Cardiovascular Outcomes**

Study Citation:	Forand, S. P., Lewis-Michl, E. L., Gomez, M. I. (2012). Adverse birth outcomes and maternal exposure to trichloroethylene and tetrachloroethylene through soil vapor intrusion in New York State Environmental Health Perspectives, 120(4), 616-621
Data Type:	Ecological study of adverse birth outcomes among residents exposed to Perc through soil vapor intrusion-major cardiac defects-Cardiovascular
HERO ID:	827030

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Geocoding identified 1090 live births in the TCE study area (1978-2002) and 3.6 million births in the comparison group for the same time (NY State). The number of missing or implausible records was low, 3.2% and 5.9% and numbers were similar between the exposed and comparison groups.
	Metric 2:	Attrition	High	× 0.4	0.4	The number of missing or implausible records was low, 3.2% and 5.9% and numbers were similar between the exposed and comparison groups.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Race, SES and smoking were dissimilar between the exposed areas and NY State, but these covariates were adjusted for in analyses or evaluated as confounders in subgroup analyses.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Areas with anticipated soil vapor intrusion were identified using soil vapor and indoor air sampling (25% of homes) in contaminated areas. Two contaminated areas were identified, one predominantly TCE and one predominantly PCE. Exposure gradient and/or individual household exposures could not be assigned. These "exposed" groups were compared to NY State birth statistics.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Two groups of exposed vs. unexposed are described.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Birth records from 1978-2002. Exposures through soil vapor intrusion may date back the 1970s. TCE was identified in groundwater in 1980. Mitigation systems installed in 2002.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Birth weight and gestational age from birth certificates; birth defects from birth defect registry using ICD-9 codes.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Effect estimates and variability (CI) were reported for each studied outcome
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Forand, S. P., Lewis-Michl, E. L., Gomez, M. I. (2012). Adverse birth outcomes and maternal exposure to trichloroethylene and tetrachloroethylene through soil vapor intrusion in New York State Environmental Health Perspectives, 120(4), 616-621
Data Type:	Ecological study of adverse birth outcomes among residents exposed to Perc through soil vapor intrusion-major cardiac defects-Cardiovascular
HERO ID:	827030

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Factors known to be associated with LBW and SGA, and birth defects were adjusted for in statistical models; smoking behavior during pregnancy differed between the exposed areas and NYS and a subgroup analysis was conducted for LBW and SGA for the years 1998 - 2002, when these data were more complete. Not expected to be a confounder for birth defects. Some residual confounding from SES is possible.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Data is from birth records. These data are generally valid in birth certificates.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Areas with vapor intrusion primarily from TCE or PCE were identified using sampling and modeling by the NY State Department of Health.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Ecological study evaluated association between birth outcomes and exposure to PERC or TCE though indoor air linked to soil contamination using Poisson regression.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Case number were adequate to detect a change, due to use of a very large control population. For some birth defects, exposed cases were low.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Statistical methods (Poisson regression) clearly described and a list of covariates used to adjust the model provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Adjusted risk ratios calculated using Poisson regression. Model assumptions 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			

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Study Citation:	Forand, S. P., Lewis-Michl, E. L., Gomez, M. I. (2012). Adverse birth outcomes and maternal exposure to trichloroethylene and tetrachloroethylene through soil vapor intrusion in New York State Environmental Health Perspectives, 120(4), 616-621
Data Type:	Ecological study of adverse birth outcomes among residents exposed to Perc through soil vapor intrusion-major cardiac defects-Cardiovascular
HERO ID:	827030

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 52: **Lipworth et al. 2011: Evaluation of Cancer Outcomes**

Study Citation:	Lipworth, L., Sonderman, J.S., Mumma, M.T., Tarone, R.E., Marano, D.E., Boice, J.D., McLaughlin, J.K. (2011). Cancer mortality among aircraft manufacturing workers: An extended follow-up Journal of Occupational and Environmental Medicine, 53(9), 992-1007
Data Type:	Lockheed Martin cohort (perc-1-4 years extraction)-Cancer
HERO ID:	1235276

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Cohort included workers employed on or after January 1, 1960 for at least one year. Workers were identified using 3 overlapping sources.
	Metric 2: Attrition	High	× 0.4	0.4	Vital status was unknown for 1336 (1.7%) of subjects. This did not differ between the factory and non-factory workers. 83 also died outside the US. All were considered lost to follow-up and assumed to be alive until their last known employment date or date of last known residential address in the United States. All non-factory workers were considered to have no chemical exposure and were not included in internal analyses. This is considered an acceptable reason for exclusion.
	Metric 3: Comparison Group	High	× 0.2	0.2	Expected deaths were based on race, age, calendar year, and sex-specific rates in the general population of California for white workers. For non-white workers, the US general population rates were used because the racial composition was more like the US population than California. For internal cohort analyses, RR were based on years of exposure (routine or intermittent). The reference group for the categorical analyses was 9520 factory workers with no exposure to solvents or chromates.
Domain 2: Exposure Characterization					

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Study Citation:	Lipworth, L., Sonderman, J.S., Mumma, M.T., Tarone, R.E., Marano, D.E., Boice, J.D., McLaughlin, J.K. (2011). Cancer mortality among aircraft manufacturing workers: An extended follow-up Journal of Occupational and Environmental Medicine, 53(9), 992-1007
Data Type:	Lockheed Martin cohort (perc-1-4 years extraction)-Cancer
HERO ID:	1235276

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Complete job histories were compiled based on employee work history cards, personnel files, and retirement records. Work histories were reviewed along with historical records of job descriptions, including chemical use patterns, and industrial hygiene surveys (noted that a detailed description was previously published by Marano et al., 2000, HERO ID699188). Subjects were classified as having routine, intermittent, or no likely exposure to chromates, TCE, Perc, and mixed solvents and the duration was determined. Due to lack of historical air sampling prior to 1970s, exposure was classified based on exposure potential and duration in specific jobs. Exposure was classified as intermittent for 55% of the 5830 PCE exposed workers (Marano et al., 2000, HERO ID699188) . Therefore, the frequency and intensity of exposure was varied within each category of exposure duration resulting in bias toward the null of unknown magnitude due to non-differential misclassification.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Although evaluation was based on exposed versus unexposed, they also evaluated exposure by years of exposure, which had 4 groupings.
	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. No lagged analyses were conducted.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Vital status was assessed by linkage with the California Death Statistical Master File, National Death Index, Social Security Administration's Death Master File, and Comserv, Inc, a computer service firm specializing in locating death records, as well as Lockheed Martin pension and other records. All questionable matches were individually reviewed. Underlying cause of death was sought from the California Death Statistical Master File for those dying in California and from the NDI for non-California residents dying from 1979-2008. A trained nosologist coded causes of death from death certificates according to ICD codes used at the time of death.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Sufficient information is provided.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Lipworth, L., Sonderman, J.S., Mumma, M.T., Tarone, R.E., Marano, D.E., Boice, J.D., McLaughlin, J.K. (2011). Cancer mortality among aircraft manufacturing workers: An extended follow-up Journal of Occupational and Environmental Medicine, 53(9), 992-1007
Data Type:	Lockheed Martin cohort (perc-1-4 years extraction)-Cancer
HERO ID:	1235276

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments were made for age, race, and sex, as well as calendar year. For RR assessment, date of birth was accounted for in the analysis as well as date of hire, date of termination, sex, and race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Information was obtained from mortality statistics and work records.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Among the PCE exposed workers, 76%, 39%, 56% and 5% were also exposed to chromate, TCE, routine use of mixed solvents and asbestos, respectively (Marano et al.2000). However, the associations were all null. Therefore, confounding from co-pollutants is of less concern.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design is appropriate. Lagged analyses were not conducted resulting the inclusion of potentially irrelevant exposure time prior to cancer development.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistical power may be adequate depending on the prevalence of exposure and desired magnitude of association the study was designed for.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient details are provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Models 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‡			High		1.6	
Extracted			Yes			

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Study Citation:	Lipworth, L., Sonderman, J.S., Mumma, M.T., Tarone, R.E., Marano, D.E., Boice, J.D., McLaughlin, J.K. (2011). Cancer mortality among aircraft manufacturing workers: An extended follow-up Journal of Occupational and Environmental Medicine, 53(9), 992-1007
Data Type:	Lockheed Martin cohort (perc-1-4 years extraction)-Cancer
HERO ID:	1235276

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 53: **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_Perc_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 quintiles 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_Perc_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_Perc_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 $=\geq 1$ 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 54: **Aschengrau et al 2011: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Aschengrau, A., Weinger, J.M., Janulewicz., P.A., Romano, M.E., Gallagher, L.G., Winter, M.R., Martin, B.R., Vieira, V.M., Webster, T.F., White, R.F., Ozonoff, D.M. (2011). Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 10 102
Data Type:	PCE_Multiple Adult Behaviors-Neurological/Behavior
HERO ID:	2127838

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. Although loss to follow up bias is of concern due to the large attrition among both exposed and unexposed subjects, the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2: Attrition	Low	× 0.4	1.2	There was large subject attrition (~70%) during the study among exposed and unexposed subjects. Table 1 includes a description of the selection, enrollment, and initial and final exposure status of the study subjects. Although 30.6% of exposed subjects and 29.1% unexposed subjects based on their initial exposure status were available for the analysis, the majority was based on lack of response or refusal to participate, which was similar across the groups. See comments section below for author commentary on the low participation rate of this study. There were few that were excluded during exposure assessment.
	Metric 3: Comparison Group	High	× 0.2	0.2	Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization					

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Study Citation:	Aschengrau, A., Weinger, J.M., Janulewicz., P.A., Romano, M.E., Gallagher, L.G., Winter, M.R., Martin, B.R., Vieira, V.M., Webster, T.F., White, R.F., Ozonoff, D.M. (2011). Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 10 102
Data Type:	PCE_Multiple Adult Behaviors-Neurological/Behavior
HERO ID:	2127838

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A non-direct exposure was used (i.e., modeling of historical exposure based on residence) that incorporated a leaching and transport model into the publicly available software (EPANET); methodology and analysis of the water modeling activities and validation data were published in peer reviewed reports demonstrating "a reasonable correlation between our exposure estimates and PCE concentrations in historical water samples"; however the authors noted non-differential bias was likely in dichotomous comparisons (any exposure vs. none) and for exposure at the highest PCE tertile, and there was a potential over- or under-estimation at the middle and lower PCE tertiles.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	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	Temporality is established and the interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	A self-administered questionnaire was used and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of outcome misclassification (e.g., differential reporting of outcome by exposure status).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All the study's measured outcomes are reported, effect estimate with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Aschengrau, A., Weinger, J.M., Janulewicz., P.A., Romano, M.E., Gallagher, L.G., Winter, M.R., Martin, B.R., Vieira, V.M., Webster, T.F., White, R.F., Ozonoff, D.M. (2011). Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 10 102
Data Type:	PCE_Multiple Adult Behaviors-Neurological/Behavior
HERO ID:	2127838

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses using statistical models for covariate adjustment.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. The paper did not describe if the self-administered questionnaire used to gather demographic characteristics was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Any co-exposures to pollutants that are not PCE that would likely bias the results were not likely to be present. Additionally, there is no direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of risk behavior disease in relation to PCE exposure, and appropriate statistical methods (i.e., generalized estimating equations) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Although the authors noted that the low response rate reduced the statistical power of the study, it is unlikely that the number of participants included in the analysis was inadequate to detect an effect in the exposed population and/or subgroups of the total population.
	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	Generalized estimating equations were used to generate Risk 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	

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Study Citation:	Aschengrau, A., Weinger, J.M., Janulewicz., P.A., Romano, M.E., Gallagher, L.G., Winter, M.R., Martin, B.R., Vieira, V.M., Webster, T.F., White, R.F., Ozonoff, D.M. (2011). Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 10 102
Data Type:	PCE_Multiple Adult Behaviors-Neurological/Behavior
HERO ID:	2127838

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‡			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 55: **Christensen et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Christensen, K.Y., Vizcaya, D., Richardson, H., Lavoué, J., Aronson, K., Siemiatycki, J. (2013). Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal Journal of Occupational and Environmental Medicine, 55(2), 198-208
Data Type:	Case-control study, occupational exposure to chlorinated solvents and various cancer types; Perc prostate-Cancer
HERO ID:	2127914

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Some key elements of the study design were not present but assumed to be present in related publications. Of the cited studies, one was publicly available (Siemiatycki et al 1987). Available information indicates a low risk of selection bias.
	Metric 2:	Attrition	Medium	× 0.4	0.8	No information was provided on subjects who declined to be interviewed, but participation was reasonable (82% for cases and 72% for controls). Outcome data and exposure information were complete for participants.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The study used both population control and cancer control groups.; both were drawn from the region where the cases were identified. Timing of the population control selection was not reported. Characteristics of cases and controls were described.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was assessed based on self-reported job history translated into exposure by chemists and industrial hygienists. Authors reported that there was no indication that completeness or validity of job histories differed between cases and controls.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Perc exposure was characterized as "any" or "substantial exposure" (the latter assessed based on confidence, frequency, and relative concentration of predicted exposure). The referent group had + 2 levels of exposure.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Based on a related publication, (Siemiatycki et al 1987), during recruitment lung cancer cases were excluded in the second , third, and sixth years, rectal cancer cases were excluded in the first and second year and prostate cancer case was excluded for some of the fourth year and all of the fifth year.
Domain 3: Outcome Assessment						

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Study Citation:	Christensen, K.Y., Vizcaya, D., Richardson, H., Lavoué, J., Aronson, K., Siemiatycki, J. (2013). Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal Journal of Occupational and Environmental Medicine, 55(2), 198-208
Data Type:	Case-control study, occupational exposure to chlorinated solvents and various cancer types; Perc prostate-Cancer
HERO ID:	2127914

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cases were limited to incident, histologically confirmed cancers. Controls were interviewed to establish medical history for selected conditions but medical records were not reviewed for confirmation.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Data for all outcomes were reported in tables with measures of precision.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Distribution of primary covariates was reported and did not differ substantially between groups for most cancer types. Statistical methods for covariate adjustment were used.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates and confounders assessed by subject interview; there is no indication that this method had poor validity. No method validation reported.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposures to other chlorinated solvents were likely, given the overlapping job-exposure combinations; the study did not control for co-exposures or even report the distributions of co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case control study was used and appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The 3730 cancer cases and 533 population controls were sufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of analysis sufficient to be conceptually reproducible.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The method for calculating risk estimates is transparent, but the method for selecting covariates to consider was not reported.
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		2.0	

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Study Citation:	Christensen, K.Y., Vizcaya, D., Richardson, H., Lavoué, J., Aronson, K., Siemiatycki, J. (2013). Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal Journal of Occupational and Environmental Medicine, 55(2), 198-208
Data Type:	Case-control study, occupational exposure to chlorinated solvents and various cancer types; Perc prostate-Cancer
HERO ID:	2127914

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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 56: **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 Perc 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 the 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 Perc 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 like 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 Perc 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 agreed 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 Perc 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 57: **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:	PCE_female_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	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	Participation rates were 92% and 94% for glioma and meningioma cases, respectively. Participation rate among controls was 86%.
	Metric 3:	Comparison Group	High	× 0.2	0.2	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	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	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	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	ICD-Oncology codes were 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:	PCE_female_subjects_possibleexp_Glioma-Cancer
HERO ID:	2128240

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported. Effect estimates were reported with confidence interval and number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	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	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	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	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	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.
	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.

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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:	PCE_female_subjects_possibleexp_Glioma-Cancer
HERO ID:	2128240

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	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 58: **Rowe et al. 1952: Evaluation of Acute Toxicity/Poisoning Outcomes**

Study Citation:	V. K. Rowe, D. D. McCollister, H. C. Spencer, E. M. Adams, D. D. Irish (1952). Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects Archives of Environmental and Occupational Health, 5 566-579
Data Type:	Rowe_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	58210

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Participant selection was not discussed and it cannot be determined whether selection bias had occurred. Study subjects were not described.
	Metric 2:	Attrition	Low	× 0.4	1.2	The number of subjects in each exposure group varied from 2-6 subjects/group. Participants left the chambers at will upon observing mild-severe effects. Due to lack of reporting, it could not be determined if attrition, exclusion, or withdrawal from the study occurred.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	A control group was not utilized in this study design. Subjects were only be compared to baseline or reference measurements.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The source of the test material was not reported, but the purity was reported to be 99.9 percent. The inhalation chamber was described and concentrations of gas were monitored using the Davis Micro Gas Analyzer, but the method of determination is still unclear. Duration of exposure varied significantly within and across exposure groups without detailed reporting, thus air concentrations are not sufficient to determine exposure.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Multiple levels of exposure (100, 200, 280, 600, and 1000 ppm) were utilized in this study and a dose-response relationship between exposure level and clinical observations was noted. Subjects voluntarily exited chambers upon acute symptoms, resulting in variations in duration across and within exposure groups (e.g. 1065 ppm for 1-2 minutes; 216 ppm for 0.75-2 hours), but specifics are not provided. Thus, the air concentrations may not be reflective of the true exposure gradient.
	Metric 6:	Temporality	Medium	× 0.4	0.8	There is little information on subject status prior to exposure. Subjects began reporting symptoms once the controlled exposure commenced which establishes temporality.
Domain 3: Outcome Assessment						

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Study Citation:	V. K. Rowe, D. D. McCollister, H. C. Spencer, E. M. Adams, D. D. Irish (1952). Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects Archives of Environmental and Occupational Health, 5 566-579
Data Type:	Rowe_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	58210

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Only clinical observations were reported. There was no control group, so investigators and participants would not have been blinded to exposure. These would be subjective measures and may introduce observer's bias.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Outcomes were not outlined in the abstract, introduction, or methods. Clinical observations were reported qualitatively.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	A quantitative analysis was not performed. Study subjects were not described and it cannot be determined if the subjects differ in demographic or lifestyle characteristics.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	There is no information on covariate collection and covariates were not reported for the study.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	Inhalation chambers were monitored by a Davis Micro Gas Analyzer. There was no indication of co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This experiment was designed to investigate the acute effects of a single controlled exposure to perchloroethylene at several concentrations (100, 200, 280, 600, and 1000 ppm) using an inhalation chamber.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sample sizes were not explicitly stated, but the text indicates a relatively small number of subjects (2-6 subjects/concentration). Results should be interpreted with caution.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Some pieces of information were not present that would inhibit the ability to reproduce the experiment including the sample size and duration of exposure.
	Metric 15:	Statistical models	Low	× 0.2	0.6	No statistical analysis was performed for controlled human exposures.
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	

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Study Citation:	V. K. Rowe, D. D. McCollister, H. C. Spencer, E. M. Adams, D. D. Irish (1952). Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects Archives of Environmental and Occupational Health, 5 566-579
Data Type:	Rowe_controlled_inhalation_exposure_acutetox-Acute Toxicity/Poisoning
HERO ID:	58210

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 20: Sample contamination		NA	NA	
	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 59: **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_Perc_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% of 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	The 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 analyses were 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_Perc_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 window 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	The analysis adjusted for age group, sex, age, and education.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained via a questionnaire and 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	

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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_Perc_cumulative_include proxy_glioma-Cancer
HERO ID:	2128307

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.

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

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 60: **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 (Perc any exposure pooled 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 was 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 (Perc any exposure pooled 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 with 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 Perc 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 (Perc any exposure pooled 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 61: **Vlaanderen et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Vlaanderen, J; Straif, K; Pukkala, E; Kauppinen, T; Kyyronen, P; Martinsen, J; Kjaerheim, K; Tryggvadottir, L; Hansen, J; Sparen, P; Weiderpass, E (2013). Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries Occupational and Environmental Medicine, 70(6), 393-401
Data Type:	Perc_intensity x prevalence_Kidney Cancer-Cancer
HERO ID:	2128436

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. The study population was all individuals, 30-64 years old, who were included in the 1960, 1970, 1980-81 and/or 1990 censuses in the four countries, and still alive and residing in the countries on January 1st in the year following the census. Cases were identified by linking to national cancer and population registries for December 31, 2003, 2004 or 2005 depending on the country. Five controls per case were "randomly selected from all cohort members alive and free of cancer at the time of diagnosis of the case", matching for age within 1 year, country and sex. Controls were selected from the same source population as cases.
	Metric 2: Attrition	High	× 0.4	0.4	All incident cases extracted from cohort.
	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, with matching for age (±1 year), country and sex.
Domain 2: Exposure Characterization					

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Study Citation:	Vlaanderen, J; Straif, K; Pukkala, E; Kauppinen, T; Kyyronen, P; Martinsen, J; Kjaerheim, K; Tryggvadottir, L; Hansen, J; Sparen, P; Weiderpass, E (2013). Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries Occupational and Environmental Medicine, 70(6), 393-401
Data Type:	Perc_intensity x prevalence_Kidney Cancer-Cancer
HERO ID:	2128436

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The occupational population relied upon employment records to construct a job-matrix for four calendar periods covering 1945–1994. Cases and controls were assigned an occupational code for each calendar year of his or her working career based on the occupational codes recorded in the censuses. Exposure during each period was assigned based on generic JEM constructed using expertise and data specific to the Nordic countries; the JEM included chemical concentration data (Kauppinen et al. 2009). Although there was no specific evidence in the paper, exposure misclassification may be "considerable" because the prevalence of TCE or perc exposure in most job categories was low ("as low as 5%") resulting in a wide variation in exposure frequency and intensity in the exposed resulting in a bias toward the null. The census occupational information does not include job task data or information about changes between each census increasing the potential for exposure misclassification.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	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	Temporality is established and the interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows (i.e., impact of lag times on results were assessed by comparing the fit of the models including cumulative exposure variables with 0, 1, 5, 10 and 20 years of lag-time).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed in cases (i.e., case definition) and controls using well-established methods (cancer registry, identified with ICD-7 codes). Subjects had been followed for the same length of time in all study groups,
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported and effect estimates are reported with a confidence interval. The number of exposed cases is reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Vlaanderen, J; Straif, K; Pukkala, E; Kauppinen, T; Kyyronen, P; Martinsen, J; Kjaerheim, K; Tryggvadottir, L; Hansen, J; Sparen, P; Weiderpass, E (2013). Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries Occupational and Environmental Medicine, 70(6), 393-401
Data Type:	Perc_intensity x prevalence_Kidney Cancer-Cancer
HERO ID:	2128436

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Cases matched to controls for age (±1 year), country and sex. There was no adjustment for potential confounding factors (excluding co-exposures) in statistical models; no adjustment for tobacco smoking, alcohol consumption, and hepatitis B and C viruses in this study. However, the authors consider these factors to not appreciably bias the results.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Some primary confounders (i.e. country, age, gender) were assessed with matching. Errors in these data are not a concern.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Moderate correlations were reported between perc and TCE; co-exposures to pollutants were appropriately measured and directly adjusted for in the models.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., nested case-control for assessment of rare diseases in relation to perc or TCE exposure) and appropriate statistical methods (i.e., conditional logistic regression) were employed to analyze matched data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population.
	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	Conditional logistic regression models were used to generate hazard ratios. 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	
	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:	Vlaanderen, J; Straif, K; Pukkala, E; Kauppinen, T; Kyyronen, P; Martinsen, J; Kjaerheim, K; Tryggvadottir, L; Hansen, J; Sparen, P; Weiderpass, E (2013). Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries Occupational and Environmental Medicine, 70(6), 393-401
Data Type:	Perc_intensity x prevalence_Kidney Cancer-Cancer
HERO ID:	2128436

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Overall Quality Determination‡		~~High~~ ⟶ Medium§		~~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

§ Evaluator's explanation for rating change: "Although this was a large, well-conducted study based on complete ascertainment of cancer cases using national cancer registries and a country-specific JEM, the sensitivity of the study to detect any associations that may exist was limited, but improved by restricting the analysis to the high exposure group where prevalence was likely greater compared to the entire study population, due to exposure misclassification inherent in the generic JEM and resulting bias toward the null."

Table 62: **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_Perc_MycosisFungoides_OR_aboveMedian_Males-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, were used. Patients were from 6 European countries: Denmark, Sweden, France, Germany, Italy, and Spain. Controls were 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	There was moderate attrition due to patients removed from the 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 were used (2846).
	Metric 3: Comparison Group	High	× 0.2	0.2	Key elements of the study design are reported and 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 were 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 were used. Next of kin completed interviews for 4 cases and 95 controls. Exposure was determined with JEM developed by the French Institute of Health Surveillance using jobs/industries assigned based on interviews by trained coders using international standards.

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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_Perc_MycosisFungoides_OR_aboveMedian_Males-Cancer
HERO ID:	2129849

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	There were multiple levels of exposure. Participants were classified by probability of exposure, exposure frequency, and exposure intensity. Results were reported according to unexposed, above median and below median. Details of exposure intensity by chemical was not reported. This is sufficient exposure to detect an effect.
	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 were reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Confounders considered in the adjusted analysis included the following: 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 there is no direct evidence that co-exposures differ across cases and controls.
Domain 5: Analysis						

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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_Perc_MycosisFungoides_OR_aboveMedian_Males-Cancer
HERO ID:	2129849

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The 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. The number of exposed cases was relatively low (27 trichloroethylene, 6 perchloroethylene, 9 methylene chloride), but sufficient to detect an effect.
	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 63: **Ruckart et al. 2013: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case--control study Environmental Health: A Global Access Science Source, 12 104
Data Type:	PCE_neural tube defects-Growth (early life) and Development
HERO ID:	2214077

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. Cases and controls were identified through a survey of parents residing on base during pregnancy and confirmed by medical records. Birth certificate data to identify 12,493 children born between 1968 and 1985 to mothers who lived at Camp Lejeune at the time of delivery.
	Metric 2:	Attrition	Medium	× 0.4	0.8	The participation rate was 76% (referral process, birth certificate availability). Outcome and exposure data were largely complete, confirm 15 NTDs, confirmed 24 oral clefts, and 13 cancers. Unable to obtain medical confirmation for 6 reported cases, 7 were ineligible, 8 refused to provide medical records, and 33 were confirmed not to have the reported condition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases and controls recruited from the same source population at the same time with the number of controls and eligibility criteria described.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A less-established method of non-direct exposure was used (i.e., modeling of historical exposure based on residence). Methodology and analysis of the water modeling activities were published in peer reviewed reports - potential validation data presented there, and there was little to no evidence that the method had poor validity and exposure misclassification is likely to be non-differential (e.g., errors in basing exposure on residence; estimates of water consumed).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	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	Temporality is established and the interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows.

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case--control study Environmental Health: A Global Access Science Source, 12 104
Data Type:	PCE_neural tube defects-Growth (early life) and Development
HERO ID:	2214077

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Hematopoietic cancers confirmed; extensive efforts were made to confirm self-reported cases. by obtaining vital records information and medical records from providers or the National Personnel Records Center. In addition, for reported cases of spina bifida and oral clefts, we offered to pay for medical visits to obtain confirmation by the current medical provider.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of cases/controls reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders including mother's residential history one year before and after birth of the child; maternal water usage; mother's medical history during pregnancy; family history of birth defects; maternal smoking, alcohol use, and occupation; and father's lifestyle habits and occupational history.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed from telephone survey (Table 2 risk factors). However, it is unclear whether the telephone survey was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and modeled separately, but the authors noted the number of cases were insufficient to run co-pollutant models. Consequently, the authors noted "it is difficult to distinguish effects of one chemical independent of the other."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., case-control) for assessment of a rare disease in relation to perc exposure, and appropriate statistical methods (i.e., logistic regression) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases was limited (13 to 24 confirmed cases), but adequate to detect an effect in the exposed population. The outcomes are rare diseases.

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case--control study Environmental Health: A Global Access Science Source, 12 104
Data Type:	PCE_neural tube defects-Growth (early life) and Development
HERO ID:	2214077

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	Unconditional logistic regression modeling was used to generate ORs. Rationale for variable selection is stated. Unconditional logistic 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‡			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 64: **Ruckart et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case--control study Environmental Health: A Global Access Science Source, 12 104
Data Type:	Low (> 0 < 44 ppb)_PCE_childhood cancers-Cancer
HERO ID:	2214077

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. Cases and controls were identified through a survey of parents residing on base during pregnancy and confirmed by medical records.. Birth certificate data to identify 12,493 children born between 1968 and 1985 to mothers who lived at Camp Lejeune at the time of delivery.
	Metric 2:	Attrition	Medium	× 0.4	0.8	The participation rate was 76% (referral process, birth certificate availability). Outcome and exposure data were largely complete, confirm 15 NTDs, Confirmed 24 oral clefts, and 13 cancers. Unable to obtain medical confirmation for 6 reported cases, 7 were ineligible, 8 refused to provide medical records, and 33 were confirmed not to have the reported condition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases and controls recruited from the same source population at the same time with the number of controls and eligibility criteria described.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A less-established method of non-direct exposure was used (i.e., modeling of historical exposure based on residence); methodology and analysis of the water modeling activities were published in peer reviewed reports - potential validation data presented there, and there was little to no evidence that the method had poor validity and exposure misclassification is likely to be non-differential (e.g., errors in basing exposure on residence; estimates of water consumed).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	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	Temporality is established and the interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows.
Domain 3: Outcome Assessment						

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case--control study Environmental Health: A Global Access Science Source, 12 104
Data Type:	Low ($> 0 < 44$ ppb)_PCE_childhood cancers-Cancer
HERO ID:	2214077

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Hematopoietic cancers confirmed; Extensive efforts were made to confirm self-reported cases. by obtaining vital records information and medical records from providers or the National Personnel Records Center. In addition, for reported cases of spina bifida and oral clefts, we offered to pay for medical visits to obtain confirmation by the current medical provider.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of cases/controls reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders including mother's residential history one year before and after birth of the child; maternal water usage; mother's medical history during pregnancy; family history of birth defects; maternal smoking, alcohol use, and occupation; and father's lifestyle habits and occupational history.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed from telephone survey (Table 2 risk factors). However, it is unclear whether the telephone survey was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and modeled separately, but the authors noted the number of cases were insufficient to run co-pollutant models. Consequently, the authors noted "it is difficult to distinguish effects of one chemical independent of the other."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., case-control) for assessment of a rare disease in relation to perc exposure, and appropriate statistical methods (i.e., logistic regression) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases was limited (13 to 24 confirmed cases), but adequate to detect an effect in the exposed population. The outcomes are rare diseases.
	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.

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: A case--control study Environmental Health: A Global Access Science Source, 12 104
Data Type:	Low (> 0 < 44 ppb)_PCE_childhood cancers-Cancer
HERO ID:	2214077

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Unconditional logistic regression modeling was used to generate ORs. Rationale for variable selection is stated. Unconditional logistic 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‡			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 =≥ 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 65: **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_Perc_Neuroblastoma_OR_IQR_5km_v2-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 were randomly selected from California birth records (no cancer diagnosis before age 6) and frequency matched by year of birth; children who had died of other causes prior to age 6 were excluded. A large number of participants were excluded due to missing information on length of gestation. In general, demographic characteristics of cases and controls were similar, but there were some differences 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 was based on exact home address, but for those born in 1990-1997, geocoding was based on zip code (potential for exposure misclassification). The assumption that birth certificate address was consistent throughout the pregnancy provides an additional potential bias.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	An exposure-response estimate was 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_Perc_Neuroblastoma_OR_IQR_5km_v2-Cancer
HERO ID:	2225094

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure was 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 was 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 was 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_Perc_Neuroblastoma_OR_IQR_5km_v2-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 were explicitly stated for each model. Number of cases/controls used in each analysis are presented for 5km and 2.5 km radii.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression was 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 were 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_Perc_Neuroblastoma_OR_IQR_5km_v2-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 66: **von Ehrenstein et al. 2014: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	von Ehrenstein, OS; Aralis, H; Cockburn, M; Ritz, B (2014). In utero exposure to toxic air pollutants and risk of childhood autism Epidemiology, 25(6), 851-858
Data Type:	Case-Control_Perc_Childhood_Autism___OR_5km-Neurological/Behavior
HERO ID:	2453135

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Key elements of the study design are reported. Children were born in 1995-2006 to mothers residing within 5 km of air-toxics monitoring stations in Los Angeles County. Birth records were linked to records of diagnosis of primary autistic disorder at the California Department of Developmental Services (1998-2009). 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 loss or exclusion of subjects. Study linked 80% of case records. Total cohort of 148,722 births were included in the analysis. Birth records with implausible gestational lengths or birth weights excluded (n=1436), as were children who died before age 6 (n=492).
	Metric 3: Comparison Group	High	× 0.2	0.2	Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis. Comparison group was selected from the same regions and birth registries. Cases were predominantly male (81%), while controls were evenly distributed between genders. Cases had older mothers with more education and a higher percentage of private insurance. There is a potential that these factors may have increased diagnosis, which was adjusted for in the analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Exposure assessment is based on direct measurement data of PCE, TCE, and DCM in air during the actual months of pregnancy in close proximity of the mother's residence. Exposure for each trimester and entire pregnancy was estimated from air-toxics monitoring stations within 3-5 km of maternal address. Study considered 24 pollutants with available data.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	Average exposure per trimester and pregnancy provide continuous metrics sufficient to detect an exposure-response estimate.

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Study Citation:	von Ehrenstein, OS; Aralis, H; Cockburn, M; Ritz, B (2014). In utero exposure to toxic air pollutants and risk of childhood autism Epidemiology, 25(6), 851-858
Data Type:	Case-Control_Perc_Childhood_Autism___OR_5km-Neurological/Behavior
HERO ID:	2453135

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Study tracks maternal exposure during pregnancy and captures children until ~ 6 years old, which establishes temporality and covers the critical exposure window and expected diagnostic time.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Autism cases from the California Department of Developmental Services were diagnosed with severe autism at 36-71 months (1998-2009) using the Diagnostic and Statistical Manual of Mental Disorders. Validation studies are cited. Expressive-language phenotype was used a measure of severity. There is a possibility that some controls are cases, if they did not utilize the state services (moved out of state, alternative treatments, not aware of services offered). However, this is unlikely to result in differential reporting of autism by exposure status.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The results discussed in the introduction/methods were fully provided and extractable. Effect estimates were reported with confidence interval; number of cases was reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment. Specifically, risk estimates were adjusted for maternal age, race/ethnicity, nativity, education, insurance type (SES surrogate), maternal birth place, parity, child sex, and birth year.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Source of covariate data was not stated (presumed to be the birth and diagnosis records), and it is unknown whether method validation was conducted. However, there is little to no evidence that the source was expected to introduce systematic bias.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The study considered the correlated nature of the pollutant mixture. Specifically, perchloroethylene was highly correlated (>90%) with benzene, 1,3-butadiene, toluene and ortho-xylene. However, methylene chloride and trichloroethylene were not strongly correlated with other pollutants. Moreover, there does not appear to be direct evidence of an unbalanced provision of additional co-exposures across the primary study groups.

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Study Citation:	von Ehrenstein, OS; Aralis, H; Cockburn, M; Ritz, B (2014). In utero exposure to toxic air pollutants and risk of childhood autism Epidemiology, 25(6), 851-858
Data Type:	Case-Control_Perc_Childhood_Autism___OR_5km-Neurological/Behavior
HERO ID:	2453135

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 5: Analysis					
	Metric 12: Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to PCE/TCE/DCM exposure), and appropriate statistical methods (i.e., unconditional logistic regression models) were employed to analyze data.
	Metric 13: Statistical power	Medium	× 0.2	0.4	Sufficient study size to detect an effect. In the analysis of risk of autism associated with exposures within a 5 km buffer, there were 619 cases exposed to PCE, 641 cases exposed to DCM, and 624 cases exposed to TCE (Table 2).
	Metric 14: Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient detail to understand analysis and reproduce, if provided with all data.
	Metric 15: Statistical models	Medium	× 0.2	0.4	Logistic regression modeling was used to generate ORs. 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	
	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 67: **Everatt et al. 2013: Evaluation of Genotoxicity Outcomes**

Study Citation:	R. Everatt, G. Slapšyte, J. Mierauskiene, V. Dedonyte, L. Bakiene (2013). Biomonitoring study of dry cleaning workers using cytogenetic tests and the comet assay Journal of Occupational and Environmental Hygiene, 10(11,11), 609-621
Data Type:	Perc_exposed workers_CA_MN_DNA_damage-Other (please specify below)
HERO ID:	2546715

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Low	× 0.4	1.2	Setting (dry cleaning shops in Vilnius, Lithuania) and inclusion/exclusion criteria (female, <65 yoa) were reported, but participation rate was not reported.
	Metric 2: Attrition	Low	× 0.4	1.2	Numbers of individuals were not reported at important stages of study and reasons were not provided for non-participation at each stage.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Comparison group "consisted of 29 supermarket workers, not exposed to PCE and comparable according to age and socioeconomic status". It is inferred but not specified that the comparison group was drawn from the same location in Lithuania. Key characteristics of both groups (age, smoking status, alcohol consumption, diagnostic radiation, BMI) were reported and statistical analysis did not show differences between the groups.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Perc concentrations in personal breathing zone of workers were measured on 2 consecutive workdays during the work shift and analyzed by GC/FID; however, monitoring for Perc at the workplace of controls was not performed.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Perc levels across exposed subjects ranged from ND to 77.5 mg/m3 (mean 31.4 mg/m3). Analyses were performed comparing the exposed and control groups (2 only; no exposure data for controls).
	Metric 6: Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure and outcome. Workers were exposed for an average of 8.9 yrs prior to blood sampling for cytogenetic analysis.
Domain 3: Outcome Assessment					

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Study Citation:	R. Everatt, G. Slapšyte, J. Mierauskiene, V. Dedonyte, L. Bakiene (2013). Biomonitoring study of dry cleaning workers using cytogenetic tests and the comet assay Journal of Occupational and Environmental Hygiene, 10(11,11), 609-621
Data Type:	Perc_exposed workers_CA_MN_DNA_damage-Other (please specify below)
HERO ID:	2546715

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Blood samples for cytogenetic analysis were obtained during the work day on different days scheduled so that all subjects at a given facility were available on the same day, resulting in some variability across facilities (with respect to the time of day). Exposed subjects were sampled after at least one full day of exposure; variability in the days of exposure prior to sampling is therefore likely. Cytogenetic evaluations were described. Scoring criteria were cited to other publications. Scoring was conducted blind.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Measured outcomes were reported, and results reported for individual subjects (both exposed and controls) as well as in summary form (mean, SD, and n).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	The major potential confounders were considered via stratified analyses and as independent variables in the regression analysis.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Potential confounders (including co-exposures) were evaluated by questionnaire; the study did not report whether the questionnaire was validated.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	It is inferred, but not specified, that perc was the major chemical used at the dry cleaning shops. Other potential exposures at dry cleaning shops were not characterized.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate, and statistical methods were appropriate to the outcome of interest.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants per group (29-30) was sufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Multiple regression analyses were performed; these considered potential covariates and alternative metrics of exposure (e.g. duration and frequency of exposure)
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	R. Everatt, G. Slapšyte, J. Mierauskiene, V. Dedonyte, L. Bakiene (2013). Biomonitoring study of dry cleaning workers using cytogenetic tests and the comet assay Journal of Occupational and Environmental Hygiene, 10(11,11), 609-621
Data Type:	Perc_exposed workers_CA_MN_DNA_damage-Other (please specify below)
HERO ID:	2546715

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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		2.0	
Extracted			No			

⋆ 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 68: **Tucker et al. 2011: Evaluation of Genotoxicity Outcomes**

Study Citation:	J. D. Tucker, K. J. Sorensen, A. M. Ruder, L. T. Mckernan, C. L. Forrester, M. A. Butler (2011). Cytogenetic analysis of an exposed-referent study: perchloroethylene-exposed dry cleaners compared to unexposed laundry workers Environmental Health: A Global Access Science Source, 10 16
Data Type:	Perc_Chromosome damage in peripheral blood-Other (please specify below)
HERO ID:	2576781

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Participant selection methods were reported briefly. Some key elements (e.g., participation rate, characteristics of non participants) were not reported; however, the study cites some of the methods to other publications.
	Metric 2: Attrition	High	× 0.4	0.4	There was minimal loss to follow-up. The study indicated that 20 laundry workers were initially recruited, but that only 18 provided blood samples for analysis. Otherwise, data were reported n = 18 exposed and n = 18 unexposed workers (all blood samples collected were analyzed).
	Metric 3: Comparison Group	High	× 0.2	0.2	Cases and referents were all female and recruited from the same area (southwest OH) and from similar industries (dry cleaning and laundry). Referents were matched on age, race, and smoking status.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Perc was measured in air samples in both exposed and referent workplaces according to NIOSH methods, and perc levels in blood were analyzed as well. The measurement of blood perc levels was cited to another publication (Ashley et al. 1992).
	Metric 5: Exposure levels	Low	× 0.2	0.6	The study evaluates effects in exposed and unexposed populations.
	Metric 6: Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure and outcome. Workers had worked in their respective industries (dry cleaning or laundry) for at least one year prior to the analyses of chromosomal damage. Blood collection for outcome evaluation was conducted after 3 consecutive days of Perc exposure.
Domain 3: Outcome Assessment					

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Study Citation:	J. D. Tucker, K. J. Sorensen, A. M. Ruder, L. T. Mckernan, C. L. Forrester, M. A. Butler (2011). Cytogenetic analysis of an exposed-referent study: perchloroethylene-exposed dry cleaners compared to unexposed laundry workers Environmental Health: A Global Access Science Source, 10 16
Data Type:	Perc_Chromosome damage in peripheral blood-Other (please specify below)
HERO ID:	2576781

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The outcome (chromosomal damage) was assessed in cases and referents using whole chromosome painting. Aberrations were counted by type (rather than differentiating between specific aberrations of the same type); however, there was no evidence that these methods had poor validity.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	The measured outcomes described in the abstract/methods were reported, with some omissions. In general, regression analyses for perc exposure and chromosomal aberration types were not shown (reported qualitatively as negative). Correlation analyses for PCE blood level and percent of cells with different types of chromosomal aberrations (including confidence intervals) were shown (Table 2).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	The study indicated that multiple linear regression models included cigarette use (pack years), log cumulative alcohol intake, and age as covariates.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	The study indicated that covariates (e.g., smoking and drinking histories) were based on interviews (with no evidence that the methods were invalid).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Study did not provide details of the chemicals used at the dry cleaning facilities from which exposed subjects were drawn, nor did the exposure analyses include other analytes. It is not clear that Perc was the only/primary chemical used at the facilities.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question (e.g. assess the association between perc exposure levels and chromosomal damage).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants were adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The analyses were described in limited detail and were likely not sufficient to be reproducible.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Multiple linear regression models were used, but it is not clear how variables for inclusion/exclusion were selected.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	J. D. Tucker, K. J. Sorensen, A. M. Ruder, L. T. Mckernan, C. L. Forrester, M. A. Butler (2011). Cytogenetic analysis of an exposed-referent study: perchloroethylene-exposed dry cleaners compared to unexposed laundry workers Environmental Health: A Global Access Science Source, 10 16
Data Type:	Perc_Chromosome damage in peripheral blood-Other (please specify below)
HERO ID:	2576781

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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			No			

⋆ 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 69: **Stewart et al. 1961: Evaluation of Acute Toxicity/Poisoning Outcomes**

Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report-Acute Toxicity/Poisoning
HERO ID:	58214

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	This case-study followed an accidental exposure to perchloroethylene. An adult male presented to the Dow Chemical medical center was examined after collapsing in work area with high perchloroethylene air concentrations without wearing personal protective equipment.
Metric 2:	Attrition	High	× 0.4	0.4	Only one subject was assessed in this study. He was followed for six weeks following treatment at the medical center and was not lost to follow-up during this period.
Metric 3:	Comparison Group	Medium	× 0.2	0.4	The study was a case report of a single individual. No other individuals were included in the study. Some demographic details on the patient were provided. Previous medical history was predicted to be a factor in the outcomes assessed.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	The exposure was reported to be about 50 percent perchloroethylene and 50 percent Stoddard solvent. One study author recreated a simulated exposure using known information about the exposure episode. Information on the circumstances surrounding the exposure was reported in detail. Samples from the simulated exposure were collected in Saran bags and analyzed by infrared spectrometer (Perkin-Elmer Model 12C). Additionally, expired air samples from the patient were collected in saran bags and measured using the same method. The simulated exposure was not a validated method of exposure assessment, however, the patient's exposure was also directly assessed by perchloroethylene in expired air.
Metric 5:	Exposure levels	Low	× 0.2	0.6	Simulated exposure levels varied by location in the recreated work environment. This was a case of a single exposure event of an individual and repeated exposure measurements in expired air were determined over a six-week interval. Average exposure during the 3.5 hour window of exposure was estimated to be 393 ppm.

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Study Citation: R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type: Perchloroethylene_accidental_exposure_case_report-Acute Toxicity/Poisoning
HERO ID: 58214

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established. The exposure preceded the symptoms presented by the patient. The patient's medical history was reviewed along with the symptoms and the study authors report there was no contributory pre-existing illness present.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Upon admittance to the hospital, a physical exam was conducted to evaluate acute effects (alterations in heart rate, blood pressure, respiration rate). During the six weeks of follow-up, clinical chemistry data (complete blood count and urinalysis) were collected. No further information was specified about outcome measurement, but it was presumably done in the medical clinic using the same methods each time.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	The abstract and introduction suggest statistical comparisons were intended to be made between clinical chemistry endpoints and perchloroethylene concentrations in expired air, however, this was not described. Clinical chemistry values from each follow-up visit are provided, along with the normal range.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates were not reported to be adjusted for in this analysis, however, adjustment in this case may not be appropriate.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Some covariates were discussed (previous physical health, occupational details), but these were not adjusted in the analysis. The sources were not provided, but assumed to be collected from medical and job records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The accidental solvent exposure was described as being 50 percent perchloroethylene and 50 percent Stoddard solvent (hydrocarbon mixture). This exposure was not accounted for in the statistical comparison, however, the study authors state Stoddard solvent was not detectable in the patient's expired air.
Domain 5: Analysis						

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report-Acute Toxicity/Poisoning
HERO ID:	58214

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This case study reported the symptoms and effects from a single accidental exposure to a relatively high concentration of perchloroethylene. Only one individual was exposed from this event and was followed for six weeks post-exposure event. No statistical analysis was conducted, but clinical chemistry endpoints were compared with the normal ranges.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	In this case series study, only one person was exposed and followed for six weeks.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The exposure event was described in detail, however, some details on the simulated exposure were missing. Statistical comparisons were not adequately described and it is unclear what comparisons were to be made.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The abstract and introduction suggest statistical comparisons were intended to be made between clinical chemistry endpoints and perchloroethylene concentrations in expired air, however, this was not described. It is unclear if statistical methods were appropriate.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene in expired air is a direct measure of exposure to perchloroethylene.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarkers of effect.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	Perchloroethylene was detected in expired air for a majority of the follow-up period (21 days post exposure). The LOD was reported.
	Metric 19:	Biomarker stability	Low	× 0.2	0.6	Storage history of the expired air was not reported. Stability of perchloroethylene in the expired air is unclear.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	No information was available on sample contamination, but there was no indication contamination occurred.
	Metric 21:	Method requirements	Low	× 0.2	0.6	This study utilized infrared spectroscopy to determine perchloroethylene concentrations.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary.
Overall Quality Determination‡			Medium		2.1	
Extracted			Yes			

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report-Acute Toxicity/Poisoning
HERO ID:	58214

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 70: **Bove et al. 2014: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13(1), 10
Data Type:	Cumulative PCE and ALS retrospective cohort study-Neurological/Behavior
HERO ID:	2799547

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, and the reported information indicates selection in or out of the study and participation is not likely to be biased. Description was provided for the two cohorts. Participation is not a concern as subjects were evaluated through data linkages.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete. Subjects were considered lost to follow-up if their vital status was unknown, but were included in the person-years through the last known date alive. It was noted that 1.3% of the exposed population and 1.5% of the reference population was lost to follow-up.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A less-established method of non-direct exposure was used (i.e., modeling of historical exposure based on residence). Methodology and analysis of the water modeling activities were published in peer reviewed reports; validation data was potentially presented there, and there was little to no evidence that the method had poor validity and exposure misclassification is likely to be non-differential (e.g., errors in basing exposure on residence; estimates of water consumed).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure was sufficient to develop an exposure-response estimate; exposure ranged from 0-783.3 ug/L, which was used to calculate cumulative exposure in ug/L-months that was broken into 4 different exposure levels.

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13(1), 10
Data Type:	Cumulative PCE and ALS retrospective cohort study-Neurological/Behavior
HERO ID:	2799547

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. Monthly estimates were conducted from 1975 to 1985 with mortality follow-up from 1979 to 2008.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed using well-established methods. Personal identifier information from the Defense Manpower Data Center was matched to the Social Security Administration Death Master File and Office of Research, Evaluation and Statistics Presumed Living Search to determine vital status. The National Death Index was also searched.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported; effect estimates are reported with confidence interval. The number of exposed participants are reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Appropriate adjustments or explicit considerations were made for potential confounders (except smoking) in the final analyses through the use of statistical models for covariate adjustment. Individual level smoking data were not available.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. Data on smoking was not available; the authors evaluated smoking-related diseases not known to be associated with solvent exposure to evaluate possible confounding by smoking, but it is unclear if this approach has been previously validated in a population with information on smoking.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and modeled separately because contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease. However, there does not appear to be direct evidence of an unbalanced provision of additional co-exposures across the primary study groups.
Domain 5: Analysis						

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13(1), 10
Data Type:	Cumulative PCE and ALS retrospective cohort study-Neurological/Behavior
HERO ID:	2799547

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to perc exposure) and appropriate statistical methods (i.e., Cox regression model) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants were adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data. Specific details were provided of the Life Table Analysis System used to compute cause-specific, standardized mortality ratios and 95% confidence intervals, as well as the Cox extended regression models used to calculate hazard ratios.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Cox regression modeling was used to generate HRs. 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	
	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 =≥ 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 71: **Bove et al. 2014: Evaluation of Cancer Outcomes**

Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13(1), 10
Data Type:	Cumulative PCE and kidney cancer retrospective cohort study-Cancer
HERO ID:	2799547

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, and the reported information indicates selection in or out of the study and participation is not likely to be biased. Description was provided for the two cohorts. Participation is not a concern as subjects were evaluated through data linkages.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete. Subjects were considered lost to follow-up if their vital status was unknown, but were included in the person-years through the last known date alive. It was noted that 1.3% of the exposed population and 1.5% of the reference population was lost to follow-up.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A less-established method of non-direct exposure was used (i.e., modeling of historical exposure based on residence). Methodology and analysis of the water modeling activities were published in peer reviewed reports; validation data was potentially presented there, and there was little to no evidence that the method had poor validity and exposure misclassification is likely to be non-differential (e.g., errors in basing exposure on residence; estimates of water consumed).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure was sufficient to develop an exposure-response estimate; exposure ranged from 0-783.3 ug/L, which was used to calculate cumulative exposure in ug/L-months that was broken into 4 different exposure levels.

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13(1), 10
Data Type:	Cumulative PCE and kidney cancer retrospective cohort study-Cancer
HERO ID:	2799547

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. Monthly estimates were conducted from 1975 to 1985 with mortality follow-up from 1979 to 2008.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed using well-established methods. Personal identifier information from the Defense Manpower Data Center was matched to the Social Security Administration Death Master File and Office of Research, Evaluation and Statistics Presumed Living Search to determine vital status. The National Death Index was also searched.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported; effect estimates are reported with confidence interval. The number of exposed participants are reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Appropriate adjustments or explicit considerations were made for potential confounders (except smoking) in the final analyses through the use of statistical models for covariate adjustment. Individual level smoking data were not available.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. Data on smoking was not available; the authors evaluated smoking-related diseases not known to be associated with solvent exposure to evaluate possible confounding by smoking, but it is unclear if this approach has been previously validated in a population with information on smoking.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and modeled separately because contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease. However, there does not appear to be direct evidence of an unbalanced provision of additional co-exposures across the primary study groups.
Domain 5: Analysis						

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13(1), 10
Data Type:	Cumulative PCE and kidney cancer retrospective cohort study-Cancer
HERO ID:	2799547

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to perc exposure) and appropriate statistical methods (i.e., Cox regression model) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants were adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data. Specific details were provided of the Life Table Analysis System used to compute cause-specific, standardized mortality ratios and 95% confidence intervals, as well as the Cox extended regression models used to calculate hazard ratios.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Cox regression modeling was used to generate HRs. 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	
	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 72: **McLean et al. 2014: Evaluation of Cancer Outcomes**

Study Citation:	McLean, D; Fleming, S; Turner, MC; Kincl, L; Richardson, L; Benke, G; Schlehofer, B; Schlaefer, K; Parent, ME; Hours, M; Krewski, D; van Tongeren, M; Sadetzki, S; Siemiatycki, J; Cardis, E (2014). Occupational solvent exposure and risk of meningioma: Results from the INTEROCC multicentre case-control study Occupational and Environmental Medicine, 71(4), 253-258
Data Type:	Case-Control_Occupational_Perc_TCE_DCM_Menigioma-Cancer
HERO ID:	2799576

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	INTEROCC study from 10 study centers in Australia, Canada, France, Germany, Israel, New Zealand, and the UK conducted from 2004-2007. Total study considered 1906 cases and 5565 controls. The sampling time frame depended on the local situation in each country. The age range of cases varied in some centers. Although there are differences in time frame and selection methods, there is nothing to indicate that selection was not representative of the exposure-outcome distribution.
	Metric 2:	Attrition	Low	× 0.4	1.2	Participation rate of 81% of cases, and 50% of controls. Reasons for exclusion from participation were not stated..
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls randomly selected from source population were matched on birth year (5 years), sex, and study region. Cases had a higher percentage of females (73% vs. 55%), a lower education, and lower SES. No difference were observed in smoking habits.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Job histories were collected from interviews (computer assisted, trained face-to-face, ~5% by proxy). For any job > 6 months, the job title, specific tasks, company name, description of activities at company, and start/end years were collected. Trained occupational hygienists coded jobs based on international standards. Participants were linked to probability and intensity of exposure to 29 chemical agents via a job-exposure matrix subject to peer review. "Exposed" group had an exposure probability of > 25% and occupational exposure of at least a year.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was assessed as ever or never exposed. However, exposures would be unacceptable for perc and DCM because there were no subjects exposed.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Study used a 5-year lag, and considered 1 and 10 year lags (data not provided). It is unclear if this covers the relevant window.

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Study Citation:	McLean, D; Fleming, S; Turner, MC; Kincl, L; Richardson, L; Benke, G; Schlehofer, B; Schlaefer, K; Parent, ME; Hours, M; Krewski, D; van Tongeren, M; Sadetzki, S; Siemiatycki, J; Cardis, E (2014). Occupational solvent exposure and risk of meningioma: Results from the INTEROCC multicentre case-control study Occupational and Environmental Medicine, 71(4), 253-258
Data Type:	Case-Control_Occupational_Perc_TCE_DCM_Menigioma-Cancer
HERO ID:	2799576

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Meningioma diagnosis (75% histological, 25% unequivocal diagnostic imaging) was sole outcome of interest. Details were provided in cited study (Cardis et al. 2007).
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	Due to limited exposure, the ORs proposed in the text were not calculated for relevant chemicals. However, they were included in the tables with numbers of cases and controls so it could be assessed.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.667	0.67	Analysis was adjusted for sex, age, country-region, and education. Sensitivity analysis evaluated proxy respondents, subjects > 69 yrs old, subjects with neurofibromatosis and tuberous sclerosis, and uncertain exposure.
	Metric 10:	Covariate Characterization	Medium	× 0.333	0.67	Demographic, SES and lifestyle factors were collected by in person interviews.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	No exposure to relevant chemicals, so co-exposure were not relevant.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Unacceptable	× 0.667	0.44	The study design was not appropriate for the relevant research questions, as no exposure occurred in cases.
	Metric 13:	Statistical power	Unacceptable	× 0.333	0.11	No cases were exposed to perc, TCE or DCM with a probability > 25%. Only 11 controls were exposed to TCE. Therefore, no OR were calculated for these chemicals.
	Metric 14:	Reproducibility of analyses	Not Rated	NA	NA	Not relevant, as there was no analysis for relevant chemicals.
	Metric 15:	Statistical models	Not Rated	NA	NA	Not relevant, as there was no analysis for relevant chemicals.
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:	McLean, D; Fleming, S; Turner, MC; Kincl, L; Richardson, L; Benke, G; Schlehofer, B; Schlaefer, K; Parent, ME; Hours, M; Krewski, D; van Tongeren, M; Sadetzki, S; Siemiatycki, J; Cardis, E (2014). Occupational solvent exposure and risk of meningioma: Results from the INTEROCC multicentre case-control study Occupational and Environmental Medicine, 71(4), 253-258
Data Type:	Case-Control_Occupational_Perc_TCE_DCM_Menigioma-Cancer
HERO ID:	2799576

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Unacceptable⋆⋆		2.4	
Extracted		No			

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 73: **Talibov et al. 2014: Evaluation of Cancer Outcomes**

Study Citation:	Talibov, M; Lehtinen-Jacks, S; Martinsen, JI; Kjærheim, K; Lynge, E; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kauppinen, T; Kyyrönen, P; Pukkala, E (2014). Occupational exposure to solvents and acute myeloid leukemia: A population-based, case-control study in four Nordic countries Scandinavian Journal of Work, Environment and Health, 40(5), 511-517
Data Type:	Perc_nested case-control_exposed workers_AML_cancer_low-Cancer
HERO ID:	2799600

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	The nested case-control study included cases and controls identified from the Nordic Occupational Cancer Study (NOCCA) cohort. 15,332 incident cases of acute myeloid leukemia (AML) were diagnosed in Finland, Norway, Sweden and Iceland from 1961-2005 and 76,660 controls were matched by year of birth, sex, and country included. Five controls per case were randomly selected among persons who were alive and free from AML on the date of diagnosis of the case (hereafter the "index date" of the case–control set). Cases and controls could have a history of any cancer other than AML and were matched for the year of birth, sex, and country. Persons with minimum age of 20 years at index date, and having occupational information from at least one census record, were included in the present study.
	Metric 2:	Attrition	High	× 0.4	0.4	Cases and controls were selected from very large cohort. No subjects from Denmark were included because individual records were not available. Initial subjects were 1,5332 cases of AML in Finland, Norway, Sweden, and Iceland diagnosed from 1961-2005 and 76,600 controls matched by year of birth, sex, and country (5 matched controls per case). Of these, 350 cases (2.3%) and 2155 controls (2.8%) were excluded because they were either <20 years old or had no occupational record.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases diagnosed from 1961-2005 and controls were matched by year of birth, sex, and country (5 matched controls per case). For exposure analysis (cases and controls combined), the comparison group was unexposed based on JEM. There is no evidence that groups were not similar.
Domain 2: Exposure Characterization						

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Study Citation:	Talibov, M; Lehtinen-Jacks, S; Martinsen, JI; Kjærheim, K; Lynge, E; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kauppinen, T; Kyyrönen, P; Pukkala, E (2014). Occupational exposure to solvents and acute myeloid leukemia: A population-based, case-control study in four Nordic countries Scandinavian Journal of Work, Environment and Health, 40(5), 511-517
Data Type:	Perc_nested case-control_exposed workers_AML_cancer_low-Cancer
HERO ID:	2799600

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure to solvents and other occupational factors was estimated based on conversion of occupational codes to quantitative amounts of exposure with the NOCCA job exposure matrix. Census records were used to determine occupational information for all subjects, which was then interpreted using the job exposure matrix that covers 300 occupations and 29 exposure agents for periods: 1945-59, 1960-74, 1975-84, and 1985-94. Estimates take into account proportion of exposed and mean level of exposure in exposed in specific time period and occupation. Cumulative exposure was estimated based on entire working career. The main analysis only included exposures that occurred prior to 10 years before index date (importance of earlier exposures for AML). Some potential for exposure misclassification due to 1) heterogeneity in exposure levels within jobs and 2)individual work histories that were based on census records that are a snapshot of a job held by individual at the time of the census. The data did not provide information on the changes of the job or tasks during the entire working career of an individual. In this study, it was assumed that an individual held his/her occupation until the mid-year between two censuses.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The study selected values corresponding to the 50th and 90th percentiles of cumulative exposure distribution among all exposed case/control subjects as cut-off points for categorization. The study defined exposure values of 0–50th percentile inclusive as "low" (TCE: <= 16.2 ppm/year; DCM: <=9.9 ppm/year; Perc: <-12.1 ppm/year), 50–90th percentile inclusive as "moderate" (TCE: 16.2-121 ppm/year; DCM: 9.9-64.6 ppm/year; Perc: 12.1-106 ppm/year), and >90th percentile of exposure distribution as "high" (TCE: >121 ppm/year; DCM: >64.6 ppm/year; Perc: >106 ppm/year). Individuals with 0 exposure were used as the reference group.

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Study Citation:	Talibov, M; Lehtinen-Jacks, S; Martinsen, JI; Kjærheim, K; Lynge, E; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kauppinen, T; Kyyrönen, P; Pukkala, E (2014). Occupational exposure to solvents and acute myeloid leukemia: A population-based, case-control study in four Nordic countries Scandinavian Journal of Work, Environment and Health, 40(5), 511-517
Data Type:	Perc_nested case-control_exposed workers_AML_cancer_low-Cancer
HERO ID:	2799600

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Cumulative exposure was estimated based on entire working career, capturing all relevant exposure information. The main analysis only included exposures that occurred prior to 10 years before index date (importance of earlier exposures for AML). Study sufficiently accounted for the long latency period of AML.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Census records were linked to data from cancer registries and national population registries for information on cancer, death and emigration. Acute Myeloid Leukemia (AML) cases were identified from Nordic cancer registries, which are valid sources for outcome measurement. Study does not provide substantial detail on the use of these registries.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	The number of cases and controls in the "no exposure" group used as a referent group was not explicitly stated, but can be calculated based on reported total number of cases and control and reported subject numbers in low-, moderate, and high-exposure groups. Data not shown for all of the analyses (e.g. different lag-times). Sufficient description of measured outcomes is reported. Hazard Ratios with 95% confidence intervals were reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Controls were matched for sex, age, and country. Analyses were stratified by sex and age. All analyses were also done with different lag time assumptions. Study did not control for smoking and genetic factors that have been previously linked to AML. Authors note that smoking and genetic factors would likely only have a minor confounding effect on the estimates.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Sex, age, and country were all determined based on valid Nordic national censuses (Finland, Iceland, Norway, Sweden) in 1960, 1970, 1980/1981, and/or 1990.

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Study Citation:	Talibov, M; Lehtinen-Jacks, S; Martinsen, JI; Kjærheim, K; Lynge, E; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kauppinen, T; Kyyrönen, P; Pukkala, E (2014). Occupational exposure to solvents and acute myeloid leukemia: A population-based, case-control study in four Nordic countries Scandinavian Journal of Work, Environment and Health, 40(5), 511-517
Data Type:	Perc_nested case-control_exposed workers_AML_cancer_low-Cancer
HERO ID:	2799600

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Study attempted to control for the impact of additional measured co-exposures. Model 1 included benzene and toluene but not ARHC; Model 2 included ARCH but neither benzene nor toluene. All other solvents were included in both models, which were also adjusted for ionizing radiation and formaldehyde as co-factors. The results from both models were similar. Therefore, only the results of Model 1 were presented, except for the ARHC results, which can only come from Model 2.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Nested case-control study within the larger Nordic Occupational Cancer Study (NOCCA) cohort was an appropriate study design to investigate the impact of exposures on acute myeloid leukemia. Exposure determined from job exposure matrices. Hazard ratios with 95% confidence intervals estimated by conditional logistic regression, which is appropriate for the nested case-control design.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Study has a large number of participants adequate to detect an effect in the exposured population and subgroups (15,332 cases and 76,660 controls). Study authors state: "These numbers are so high that our study is unlikely to lack power and miss an effect should one exist in our data."
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Detailed description of analysis is provided, including process for selection variables and rationale for stratification (see metric 15).
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Model for calculating hazard ratio is transparent and all model assumptions were met. Conditional logistic regression was used to estimate hazard ratios and 95% confidence intervals. Test for trend was performed for a dose-response relationship between exposure factors and AML. Variable selection for the final main-effects model was based on the "purposeful covariate selection" procedure. Two alternative main-effects models included (see above). Analyses stratified by age and sex was conducted to explore potential age- and sex-specific interactions with exposure. All analyses were done with different lag time assumptions (0, 3, 5, 7, 10, and 20 years).
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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Study Citation:	Talibov, M; Lehtinen-Jacks, S; Martinsen, JI; Kjærheim, K; Lynge, E; Sparén, P; Tryggvadottir, L; Weiderpass, E; Kauppinen, T; Kyyrönen, P; Pukkala, E (2014). Occupational exposure to solvents and acute myeloid leukemia: A population-based, case-control study in four Nordic countries Scandinavian Journal of Work, Environment and Health, 40(5), 511-517
Data Type:	Perc_nested case-control_exposed workers_AML_cancer_low-Cancer
HERO ID:	2799600

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 74: **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 (perc men CEI 2)-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 without 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 (perc men CEI 2)-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 (perc men CEI 2)-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 75: **Ruckart et al. 2014: Evaluation of Reproductive Outcomes**

Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2014). Evaluation of contaminated drinkiweight at Marine Corps Base Camp Lejeune, North Carolina: A cross-sectional studyng water and preterm birth, small for gestational age, and birth Environmental Health: A Global Access Science Source, 13 99
Data Type:	Camp Lejeune Perc birthweight mean diff Q4 v unexposed OR-Reproductive
HERO ID:	2799701

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Birth certificates from mothers living at Camp Lejeune were searched for singleton births weighing >= 500 g and a term length of 28-47 weeks. 11896 total records were retrieved. Approximately 113 births were excluded due to missing information. From the eligible population, there was no indication of bias for selection in or out of the study or analysis sample.
	Metric 2: Attrition	High	× 0.4	0.4	There was minimal subject exclusion or loss to follow-up. Approximately 130 births of over 10,000 were excluded due to incomplete data on gestational age. This was adequately explained by the study authors.
	Metric 3: Comparison Group	High	× 0.2	0.2	Methods of participant selection were adequately defined. Military rank was used as a surrogate measure of SES. Potential risk factors, including participant demographics and characteristics, were considered in the model and included in an adjusted model if the change from the unadjusted model results was >10%. The final model was determined by backward stepwise elimination, eliminating covariates with associations closest to the null without changing the results by greater than 10%.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Exposure was assessed by maternal residential address and a modeled historical reconstruction of drinking water contamination. Details on the water modeling can be found in ASTDR 2007 (HERO ID 730410). Model estimates were based on water sampling performed throughout the base. This represents a less-established method of exposure assessment. The nature of the setting and study population leads to some potential for differential exposure misclassification. Working and living on base may lead to misclassification of exposure as consuming or using water at a different part of the base may result in different exposure than the residence. This would likely bias the results towards the null.

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2014). Evaluation of contaminated drinkiweight at Marine Corps Base Camp Lejeune, North Carolina: A cross-sectional studyng water and preterm birth, small for gestational age, and birth Environmental Health: A Global Access Science Source, 13 99
Data Type:	Camp Lejeune Perc birthweight mean diff Q4 v unexposed OR-Reproductive
HERO ID:	2799701

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	There were five levels of exposure used in the analysis of each chemical (PCE and TCE). Exposure levels were represented as the mean monthly exposure level during a pregnancy which included non-overlapping categories of unexposed, < median exposure value, greater than or equal to the median exposure value, greater than or equal to the 75th percentile exposure value, and greater than or equal to the 90th percentile exposure value. This represents multiple levels of exposure and is adequate to detect a trend or exposure-response relationship. Due to the large number of participants in this cohort (over 10,000) there were still sufficient numbers (approximately 800 births) in the 90th percentile to detect an effect.
	Metric 6:	Temporality	High	× 0.4	0.4	This study modeled exposure to PCE and TCE through drinking water during pregnancy and reported associations between these exposures and pregnancy outcomes. This demonstrates temporality as the exposure was measured during pregnancy, prior to the birth outcome.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes including preterm birth (<37 weeks gestation), term low birth weight (>=37 weeks and <2500g birthweight), and for small for gestational age. Three categorizations were evaluated for small for gestational age: births weighing less than 5th or 10th percentile based on sex- and race-specific gestational norms from New Jersey, and sex-specific growth curves from California. The method of calculating small for gestational age (SGA) can be found in a prior publication (Bove et al. 1995; HERO ID 194932).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Outcomes listed in the abstract, introduction, and methods were all presented in the results. Results for each outcome were presented clearly in easily extractable tables with clear numbers of participants in each category for transparent tabulation.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2014). Evaluation of contaminated drinkiweight at Marine Corps Base Camp Lejeune, North Carolina: A cross-sectional studyng water and preterm birth, small for gestational age, and birth Environmental Health: A Global Access Science Source, 13 99
Data Type:	Camp Lejeune Perc birthweight mean diff Q4 v unexposed OR-Reproductive
HERO ID:	2799701

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Military rank was used as a surrogate measure of SES. Potential risk factors, including participant demographics and characteristics, and prenatal care, were considered in the model and included in an adjusted model if the change from the unadjusted model results was >10%. The final model was determined by backward stepwise elimination, eliminating covariates with associations closest to the null without changing the results by greater than 10%.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Covariates such as demographic information were collected from personnel records of the military base. This serves the function of a registry or database and serves as a well-established method of assessing covariates.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Among this population, there was co-exposure to TCE, PCE, and benzene. Study authors state that when two chemicals were independently associated with one outcome, a model with terms for exposure to both chemicals was analyzed to see if this drove down the association. In combined models, TCE remained associated with each outcome that was analyzed in this way. This represents consideration and adjustment for co-exposures. However, the study also mentions that they were unable to account for certain maternal characteristics such as alcohol consumption, weight gain during pregnancy, and smoking status, which could affect the results of the study.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study investigated the odds of several birth outcomes with exposure to PCE and TCE. The study design was a retrospective cohort and assessed the association between pregnancy outcomes and exposure during pregnancy. This is an appropriate choice of study design with no apparent issues.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were a total of 11,896 live births to be included in these analyses. This represents a sufficient number of participants to detect an effect in the exposed population. There are no apparent issues with sample size. The size of the study population is a strength of this study.

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Study Citation:	Ruckart, PZ; Bove, FJ; Maslia, M (2014). Evaluation of contaminated drinkiweight at Marine Corps Base Camp Lejeune, North Carolina: A cross-sectional studyng water and preterm birth, small for gestational age, and birth Environmental Health: A Global Access Science Source, 13 99
Data Type:	Camp Lejeune Perc birthweight mean diff Q4 v unexposed OR-Reproductive
HERO ID:	2799701

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analyses were described in detail, sufficient to reproduce the analysis conceptually. Characterization of covariates and categorization of exposure and outcome were explained in detail, so there are no apparent issues.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for calculating risk estimates (odds ratio) is transparent and the methods clearly state the procedure for including and removing covariates from final adjusted models. The final model (generalized estimating equations (GEE) modeling using an exchangeable correlation structure) was determined by backward stepwise elimination, eliminating covariates with associations closest to the null without changing the results by greater than 10%.
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 76: **Silver et al. 2014: Evaluation of Renal Outcomes**

Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_RenalDisease_HazardRatio-Renal
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Retrospective NIOSH cohort was composed of 34,494 workers employed in microelectronics and business machine facility for at least 91 days 1969-2001. Foreign nationals and those without a valid social security number (1486) were excluded, as mortality was tracked using this identifier. All key elements of the study design are reported.
	Metric 2:	Attrition	High	× 0.4	0.4	Small exclusion was based on social security number (~4%), which was used to identify outcomes.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were drawn from the full risk set, with the conditions that controls started work at age less than the case's death and survived longer than the case. Mean data for the full cohort is available, but not broken down by case/control for each outcome. While there may have been differences between cases and controls, statistical models controlled for sex and pay code. Cases could serve as controls for other outcomes.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Department/year-exposure matrix was presented in previous publication (Fleming 2013 - HERO 2128566). Chemical use and exposure determined from interviews and company records: industrial hygiene monitoring (1980-2002), industrial hygiene department documents (1974-2002), and environmental impact assessments (1974-1980; 1985-2002). Estimates of quantities of volatile organics were from ATSDR study of community air quality (1969-1980). Work histories were from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and were linked to individual work history.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The range and distribution of the cumulative exposure scores were presented (see Fleming 2013 - HERO 2128566), and the prevalence of Perc was low (e.g., 15.1% with likely Perc exposure among hourly workers). This could bias effect estimates toward the null.

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_RenalDisease_HazardRatio-Renal
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Average of 24-29 years of follow-up with a 10 year lag was used, which is reasonable for cancer outcomes. However, the population is noted to be relatively young, so mortality rates may be bias towards the null.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Vital status determined in 2009 by searches of social security administration death master file, national death index, and internal revenue service. Death certificates from state vital statistics offices were used when COD not provided by NDI. ICD codes for cause of death confirmed by a certified nosologist.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of relevant outcomes from the abstract/methods are fully provided and extractable. Data presented included number of observations, standardized mortality ratios with 95% confidence intervals, and hazard ratio with 95% confidence intervals.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates accounted for in the regression models, including paycode (salaried or hourly) as a surrogate for SES, birth year (20 year cohorts), duration of employment prior to 1969, and manufacturing eras (based on process and chemical use). Authors did not adjust for race, due to missing data (16%) and low variation (87% white). Variables with >20% change was considered a confounder and included in the regression models. Birth cohort adjustment was an approach to consider smoking. Models for hazard ratios were ultimately adjusted for paycode and sex.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were determined from employment records at the factory (2 databases with some conflicts).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential co-exposures were not fully quantified or considered in the models, despite 3 chemicals and 3 chemical classes being considered explicitly within the cohort.
Domain 5: Analysis						

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_RenalDisease_HazardRatio-Renal
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Use of regression models for hazard ratio are appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort contains sufficient participants to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The process of creating the regression models was described in detail.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Calculations for standardized mortality ratios and regression models for hazard ratios were 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	
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 77: **Silver et al. 2014: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_NervousSystemDisease_HazardRatio-Neurological/Behavior
HERO ID:	2799800

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Retrospective NIOSH cohort was composed of 34,494 workers employed in microelectronics and business machine facility for at least 91 days 1969-2001. Foreign nationals and those without a valid social security number (1486) were excluded, as mortality was tracked using this identifier. All key elements of the study design are reported.
	Metric 2: Attrition	High	× 0.4	0.4	Small exclusion was based on social security number (~4%), which was used to identify outcomes.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls were drawn from the full risk set, with the conditions that controls started work at age less than the case's death and survived longer than the case. Mean data for the full cohort is available, but not broken down by case/control for each outcome. While there may have been differences between cases and controls, statistical models controlled for sex and pay code. Cases could serve as controls for other outcomes.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Department/year-exposure matrix was presented in previous publication (Fleming 2013 - HERO 2128566). Chemical use and exposure determined from interviews and company records: industrial hygiene monitoring (1980-2002), industrial hygiene department documents (1974-2002), and environmental impact assessments (1974-1980; 1985-2002). Estimates of quantities of volatile organics were from ATSDR study of community air quality (1969-1980). Work histories were from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and were linked to individual work history.
	Metric 5: Exposure levels	Low	× 0.2	0.6	The range and distribution of the cumulative exposure scores were presented (see Fleming 2013 - HERO 2128566), and the prevalence of Perc was low (e.g., 15.1% with likely Perc exposure among hourly workers). This could bias effect estimates toward the null.

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_NervousSystemDisease_HazardRatio-Neurological/Behavior
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Average of 24-29 years of follow-up with a 10 year lag was used, which is reasonable for cancer outcomes. However, the population is noted to be relatively young, so mortality rates may be bias towards the null.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Vital status determined in 2009 by searches of social security administration death master file, national death index, and internal revenue service. Death certificates from state vital statistics offices were used when COD not provided by NDI. ICD codes for cause of death confirmed by a certified nosologist.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of relevant outcomes from the abstract/methods are fully provided and extractable. Data presented included number of observations, standardized mortality ratios with 95% confidence intervals, and hazard ratio with 95% confidence intervals.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates accounted for in the regression models, including paycode (salaried or hourly) as a surrogate for SES, birth year (20 year cohorts), duration of employment prior to 1969, and manufacturing eras (based on process and chemical use). Authors did not adjust for race, due to missing data (16%) and low variation (87% white). Variables with >20% change was considered a confounder and included in the regression models. Birth cohort adjustment was an approach to consider smoking. Models for hazard ratios were ultimately adjusted for paycode and sex.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were determined from employment records at the factory (2 databases with some conflicts).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential co-exposures were not fully quantified or considered in the models, despite 3 chemicals and 3 chemical classes being considered explicitly within the cohort.
Domain 5: Analysis						

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_NervousSystemDisease_HazardRatio-Neurological/Behavior
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Use of regression models for hazard ratio are appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort contains sufficient participants to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The process of creating the regression models was described in detail.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Calculations for standardized mortality ratios and regression models for hazard ratios were 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	
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 78: **Silver et al. 2014: Evaluation of Cancer for testicular cancer outcome Outcomes**

Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_TesticularCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Retrospective NIOSH cohort was composed of 34,494 workers employed in microelectronics and business machine facility for at least 91 days 1969-2001. Foreign nationals and those without a valid social security number (1486) were excluded, as mortality was tracked using this identifier. All key elements of the study design are reported.
	Metric 2:	Attrition	High	× 0.4	0.4	Small exclusion was based on social security number (~4%), which was used to identify outcomes.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were drawn from the full risk set, with the conditions that controls started work at age less than the case's death and survived longer than the case. Mean data for the full cohort is available, but not broken down by case/control for each outcome. While there may have been differences between cases and controls, statistical models controlled for sex and pay code. Cases could serve as controls for other outcomes.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Department/year-exposure matrix was presented in previous publication (Fleming 2013 - HERO 2128566). Chemical use and exposure determined from interviews and company records: industrial hygiene monitoring (1980-2002), industrial hygiene department documents (1974-2002), and environmental impact assessments (1974-1980; 1985-2002). Estimates of quantities of volatile organics were from ATSDR study of community air quality (1969-1980). Work histories were from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and were linked to individual work history.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The range and distribution of the cumulative exposure scores were presented (see Fleming 2013 - HERO 2128566), and the prevalence of Perc was low (e.g., 15.1% with likely Perc exposure among hourly workers). This could bias effect estimates toward the null.

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_TesticularCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Average of 24-29 years of follow-up with a 10 year lag was used, which is reasonable for cancer outcomes. However, the population is noted to be relatively young, so mortality rates may be bias towards the null.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Testicular cancer incidence determined from cancer registries of New York (1976-2009) and Pennsylvania (1985-2009), separated by all workers and long term workers (3+ years).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of relevant outcomes from the abstract/methods are fully provided and extractable. Data presented included number of observations, standardized mortality ratios with 95% confidence intervals, and hazard ratio with 95% confidence intervals.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates accounted for in the regression models, including paycode (salaried or hourly) as a surrogate for SES, birth year (20 year cohorts), duration of employment prior to 1969, and manufacturing eras (based on process and chemical use). Authors did not adjust for race, due to missing data (16%) and low variation (87% white). Variables with >20% change was considered a confounder and included in the regression models. Birth cohort adjustment was an approach to consider smoking. Models for hazard ratios were ultimately adjusted for paycode and sex.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were determined from employment records at the factory (2 databases with some conflicts).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential co-exposures were not fully quantified or considered in the models, despite 3 chemicals and 3 chemical classes being considered explicitly within the cohort.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Use of regression models for hazard ratio are appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort contains sufficient participants to detect an effect.

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_TesticularCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The process of creating the regression models was described in detail.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Calculations for standardized mortality ratios and regression models for hazard ratios were 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	
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 79: **Silver et al. 2014: Evaluation of Cancer for all cancers outcomes other than testicular cancer Outcomes**

Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_BladderUrinaryCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Retrospective NIOSH cohort was composed of 34,494 workers employed in microelectronics and business machine facility for at least 91 days 1969-2001. Foreign nationals and those without a valid social security number (1486) were excluded, as mortality was tracked using this identifier. All key elements of the study design are reported.
	Metric 2:	Attrition	High	× 0.4	0.4	Small exclusion was based on social security number (~4%), which was used to identify outcomes.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were drawn from the full risk set, with the conditions that controls started work at age less than the case's death and survived longer than the case. Mean data for the full cohort is available, but not broken down by case/control for each outcome. While there may have been differences between cases and controls, statistical models controlled for sex and pay code. Cases could serve as controls for other outcomes.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Department/year-exposure matrix was presented in previous publication (Fleming 2013 - HERO 2128566). Chemical use and exposure determined from interviews and company records: industrial hygiene monitoring (1980-2002), industrial hygiene department documents (1974-2002), and environmental impact assessments (1974-1980; 1985-2002). Estimates of quantities of volatile organics were from ATSDR study of community air quality (1969-1980). Work histories were from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and were linked to individual work history.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The range and distribution of the cumulative exposure scores were presented (see Fleming 2013 - HERO 2128566), and the prevalence of Perc was low (e.g., 15.1% with likely Perc exposure among hourly workers). This could bias effect estimates toward the null.

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_BladderUrinaryCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Average of 24-29 years of follow-up with a 10 year lag was used, which is reasonable for cancer outcomes. However, the population is noted to be relatively young, so mortality rates may be bias towards the null.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Vital status determined in 2009 by searches of social security administration death master file, national death index, and internal revenue service. Death certificates from state vital statistics offices were used when COD not provided by NDI. ICD codes for cause of death confirmed by a certified nosologist.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of relevant outcomes from the abstract/methods are fully provided and extractable. Data presented included number of observations, standardized mortality ratios with 95% confidence intervals, and hazard ratio with 95% confidence intervals.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates accounted for in the regression models, including paycode (salaried or hourly) as a surrogate for SES, birth year (20 year cohorts), duration of employment prior to 1969, and manufacturing eras (based on process and chemical use). Authors did not adjust for race, due to missing data (16%) and low variation (87% white). Variables with >20% change was considered a confounder and included in the regression models. Birth cohort adjustment was an approach to consider smoking. Models for hazard ratios were ultimately adjusted for paycode and sex.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were determined from employment records at the factory (2 databases with some conflicts).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Potential co-exposures were not fully quantified or considered in the models, despite 3 chemicals and 3 chemical classes being considered explicitly within the cohort.
Domain 5: Analysis						

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Study Citation:	Silver, SR; Pinkerton, LE; Fleming, DA; Jones, JH; Allee, S; Luo, L; Bertke, SJ (2014). Retrospective cohort study of a microelectronics and business machine facility American Journal of Industrial Medicine, 57(4), 412-424
Data Type:	NIOSHOccupationalCohort_Perc_BladderUrinaryCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Use of regression models for hazard ratio are appropriate.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort contains sufficient participants to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The process of creating the regression models was described in detail.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Calculations for standardized mortality ratios and regression models for hazard ratios were 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	
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 80: **Stewart et al. 1961: Evaluation of Cardiovascular Outcomes**

Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_bloodpressure-Cardiovascular
HERO ID:	58214

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	This case-study followed an accidental exposure to perchloroethylene. An adult male presented to the Dow Chemical medical center was examined after collapsing in work area with high perchloroethylene air concentrations without wearing personal protective equipment.
Metric 2:	Attrition	High	× 0.4	0.4	Only one subject was assessed in this study. He was followed for six weeks following treatment at the medical center and was not lost to follow-up during this period.
Metric 3:	Comparison Group	Medium	× 0.2	0.4	The study was a case report of a single individual. No other individuals were included in the study. Some demographic details on the patient were provided. Previous medical history was predicted to be a factor in the outcomes assessed.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	The exposure was reported to be about 50 percent perchloroethylene and 50 percent Stoddard solvent. One study author recreated a simulated exposure using known information about the exposure episode. Information on the circumstances surrounding the exposure was reported in detail. Samples from the simulated exposure were collected in Saran bags and analyzed by infrared spectrometer (Perkin-Elmer Model 12C). Additionally, expired air samples from the patient were collected in saran bags and measured using the same method. The simulated exposure was not a validated method of exposure assessment, however, the patient's exposure was also directly assessed by perchloroethylene in expired air.
Metric 5:	Exposure levels	Low	× 0.2	0.6	Simulated exposure levels varied by location in the recreated work environment. This was a case of a single exposure event of an individual and repeated exposure measurements in expired air were determined over a six-week interval. Average exposure during the 3.5 hour window of exposure was estimated to be 393 ppm.

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_bloodpressure-Cardiovascular
HERO ID:	58214

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established. The exposure preceded the symptoms presented by the patient. The patient's medical history was reviewed along with the symptoms and the study authors report there was no contributory pre-existing illness present.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Upon admittance to the hospital, a physical exam was conducted to evaluate acute effects (alterations in heart rate, blood pressure, respiration rate). During the six weeks of follow-up, clinical chemistry data (complete blood count and urinalysis) were collected. No further information was specified about outcome measurement, but it was presumably done in the medical clinic using the same methods each time.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	The abstract and introduction suggest statistical comparisons were intended to be made between clinical chemistry endpoints and perchloroethylene concentrations in expired air, however, this was not described. Clinical chemistry values from each follow-up visit are provided, along with the normal range.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates were not reported to be adjusted for in this analysis, however, adjustment in this case may not be appropriate.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Some covariates were discussed (previous physical health, occupational details), but these were not adjusted in the analysis. The sources were not provided, but assumed to be collected from medical and job records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The accidental solvent exposure was described as being 50 percent perchloroethylene and 50 percent Stoddard solvent (hydrocarbon mixture). This exposure was not accounted for in the statistical comparison, however, the study authors state Stoddard solvent was not detectable in the patient's expired air.
Domain 5: Analysis						

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_bloodpressure-Cardiovascular
HERO ID:	58214

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This case study reported the symptoms and effects from a single accidental exposure to a relatively high concentration of perchloroethylene. Only one individual was exposed from this event and was followed for six weeks post-exposure event. No statistical analysis was conducted, but clinical chemistry endpoints were compared with the normal ranges.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	In this case series study, only one person was exposed and followed for six weeks.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The exposure event was described in detail, however, some details on the simulated exposure were missing. Statistical comparisons were not adequately described and it is unclear what comparisons were to be made.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The abstract and introduction suggest statistical comparisons were intended to be made between clinical chemistry endpoints and perchloroethylene concentrations in expired air, however, this was not described. It is unclear if statistical methods were appropriate.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.2	0.2	Perchloroethylene in expired air is a direct measure of exposure to perchloroethylene.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarkers of effect.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	Perchloroethylene was detected in expired air for a majority of the follow-up period (21 days post exposure). The LOD was reported.
	Metric 19:	Biomarker stability	Low	× 0.2	0.6	Storage history of the expired air was not reported. Stability of perchloroethylene in the expired air is unclear.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	No information was available on sample contamination, but there was no indication contamination occurred.
	Metric 21:	Method requirements	Low	× 0.2	0.6	This study utilized infrared spectroscopy to determine perchloroethylene concentrations.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary.
Overall Quality Determination‡			Medium		2.1	
Extracted			Yes			

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_bloodpressure-Cardiovascular
HERO ID:	58214

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 81: **Bove et al. 2014: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13 68
Data Type:	PCE_Parkinson's Disease_BG QC-Neurological/Behavior
HERO ID:	2800329

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, 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	There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A less-established method of non-direct exposure was used (i.e., modeling of historical exposure based on residence); methodology and analysis of the water modeling activities were published in peer reviewed reports - potential validation data presented there, and there was little to no evidence that the method had poor validity and exposure misclassification is likely to be non-differential (e.g., errors in basing exposure on residence; estimates of water consumed).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Range and distribution of exposure was sufficient to develop an exposure-response estimate; the analysis used exposure as a continuous variable.
	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.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed using well-established methods.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	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						

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13 68
Data Type:	PCE_Parkinson's Disease_BG QC-Neurological/Behavior
HERO ID:	2800329

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment; although no data for smoking was available, other smoking related diseases were analyzed and inverse associations with transformed PCE were reported for COPD and CVD as well as leukemias suggesting a potential for confounding of unknown magnitude.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. Primary confounders (excluding co-exposures) were assessed). Selection of covariates for inclusion in the model was based on 10% change rule and smoking was evaluated by analyzing associations with smoking-related diseases. Alcohol consumption is not considered a risk factor for leukemia.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and modeled separately, but the authors noted that '. . . cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease. . . ' An inverse association also was reported for the other contaminants, therefore confounding was possible.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to perchloroethylene exposure, and appropriate statistical methods (i.e., Cox regression model) were employed to analyze data. However, results using both log 10 transformed and untransformed exposures were reported with no analyses provided to support selection of one over the other.
	Metric 13:	Statistical power	Unacceptable	× 0.2	0.04	The number of participants and cases were not adequate to evaluate dose-response in the exposed population. For example, there were only 5 cases of Parkinson's Disease. The study authors state this may be in part due to the relatively young nature of the cohort. The majority of participants were under 65 and only 14% had died.
	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.

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13 68
Data Type:	PCE_Parkinson's Disease_BG QC-Neurological/Behavior
HERO ID:	2800329

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Medium	× 0.2	0.4	Cox regression modeling was used to generate HRs. 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	
	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‡		Unacceptable⋆⋆		1.7	
Extracted		No			

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 82: **Bove et al. 2014: Evaluation of Cancer Outcomes**

Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13 68
Data Type:	PCE_log10_Kidney Cancer_BG QC-Cancer
HERO ID:	2800329

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, 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	There was minimal subject loss to follow up during the study (or exclusion from the analysis sample) and outcome and exposure data were largely complete.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The investigators developed a database of the spatial and temporal distribution of contaminants in drinking water computing monthly average estimates of concentrations in the Hadnot Point distribution system for 1973 - 1985; methodology and analysis of the water modeling activities were published in peer reviewed reports - potential validation data presented there, and there was little to no evidence that the method had poor validity; exposure misclassification is likely to be non-differential (e.g., exposure data available only during work hours, no information about water consumption or other activities that would result in dermal exposure such as showering or washing hands).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Range and distribution of exposure was sufficient to develop an exposure-response estimate; the analysis used exposure as a continuous variable.
	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.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed using well-established methods.

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13 68
Data Type:	PCE_log10_Kidney Cancer_BG QC-Cancer
HERO ID:	2800329

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	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	Medium	× 0.5	1	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment; although no data for smoking was available, other smoking related diseases were analyzed and inverse associations with transformed PCE were reported for COPD and CVD as well as leukemias suggesting a potential for confounding of unknown magnitude.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. Primary confounders (excluding co-exposures) were assessed). Selection of covariates for inclusion in the model was based on 10% change rule and smoking was evaluated by analyzing associations with smoking-related diseases. Alcohol consumption is not considered a risk factor for leukemia.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and modeled separately, but the authors noted that '. . . cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease. . . ' An inverse association also was reported for the other contaminants, therefore confounding was possible.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort) for assessment of a rare disease in relation to perchloroethylene exposure, and appropriate statistical methods (i.e., Cox regression model) were employed to analyze data. However, results using both log 10 transformed and untransformed exposures were reported with no analyses provided to support selection of one over the other.
	Metric 13:	Statistical power	Unacceptable	× 0.2	0.04	The number of participants and cases were not adequate to evaluate dose-response in the exposed population. For example, kidney cancer had 7 cases. The study authors state this may be in part due to the relatively young nature of the cohort. The majority of participants were under 65 and only 14% had died.

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Study Citation:	Bove, FJ; Ruckart, PZ; Maslia, M; Larson, TC (2014). Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study Environmental Health: A Global Access Science Source, 13 68
Data Type:	PCE_log10_Kidney Cancer_BG QC-Cancer
HERO ID:	2800329

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	Cox regression modeling was used to generate HRs. 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	
	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‡			Unacceptable**		1.7	
Extracted			No			

** Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 83: **Chaigne et al 2015: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Chaigne, B; Lasfargues, G; Marie, I; Hüttenberger, B; Lavigne, C; Marchand-Adam, S; Maillot, F; Diot, E (2015). Primary Sjögren's syndrome and occupational risk factors: A case-control study Journal of Autoimmunity, 60 80-85
Data Type:	occupational (France) ever Perc exposure_primary Sjogren's syndrome-Hematological and Immune
HERO ID:	2902069

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Some key elements of the study design were not present but available information indicates a low risk of selection bias. Eligibility and participation rates were not reported, however exclusion criteria was noted. It appears that all patients with primary Sjogren's syndrome from different hospitals in France from 2010-2013 were included. Recruitment for controls was not provided, but there is no indication of selection bias.
	Metric 2:	Attrition	High	× 0.4	0.4	There is no apparent attrition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were age and gender matched and selected from the same departments during the same time period. Provided information does not indicate any differences in terms of smoking habits, SES, or socio-professional categories.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Occupational exposure was assessed by industrial hygienists and occupational practitioners. Exposure was semiquantified based on the experts' knowledge of the industrial process and its evolution over time. Exposure was also evaluated using the French job-exposure matrix (link provided, but not working). All employment periods in which subjects worked more than 6 months was included. An exposure score was calculated (methods reported).
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Only evaluated as ever/never or low and high final cumulative exposure score.
	Metric 6:	Temporality	Low	× 0.4	1.2	Although occupational exposure was retrospectively assessed, the study authors acknowledge that they cannot distinguish between exposures that pre-dated or post-dated the onset of the disease.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Primary Sjogren's syndrome was diagnosed in the hospital and was defined according to the American-European Consensus Group criteria.

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Study Citation:	Chaigne, B; Lasfargues, G; Marie, I; Hüttenberger, B; Lavigne, C; Marchand-Adam, S; Maillot, F; Diot, E (2015). Primary Sjögren's syndrome and occupational risk factors: A case-control study Journal of Autoimmunity, 60 80-85
Data Type:	occupational (France) ever Perc exposure_primary Sjogren's syndrome-Hematological and Immune
HERO ID:	2902069

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	For chemicals of interest all outcomes outlined in the abstract, introduction, and methods were reported. Effect estimates (odds ratios) are reported with a 95% confidence interval along with the number of cases and controls.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The study does not appear to adjust for any covariates. However, controls were sex and age matched and there does not appear to be any differences between the groups in terms of smoking or SES.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained during a 30-minute interview; a less established method to assess confounders with no method validation.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Subjects had several periods of exposure to different categories of exposure that were not mutually exclusive and these were not adjusted for in the analysis. Nor was there enough information provided on the different types of work to know if there would be a differential co-exposure that could affect the results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design is appropriate. The study is a case-control study, which is appropriate for studying a rare disease like primary Sjogren's syndrome especially when evaluating many different possible exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sample size is sufficient overall (175 cases and 350 controls) but the number of exposed cases and controls small (e.g. 15 cases and 12 controls for ever/never exposure).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	It was only noted that a conditional maximum likelihood estimate was calculated, but this appears to be sufficient information.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Method is transparent (a conditioned maximum likelihood estimate of the odds ratio and 95% confidence intervals using GraphPad Prism version 6.00 software) 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	

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Study Citation:	Chaigne, B; Lasfargues, G; Marie, I; Hüttenberger, B; Lavigne, C; Marchand-Adam, S; Maillot, F; Diot, E (2015). Primary Sjögren's syndrome and occupational risk factors: A case-control study Journal of Autoimmunity, 60 80-85
Data Type:	occupational (France) ever Perc exposure_primary Sjogren's syndrome-Hematological and Immune
HERO ID:	2902069

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‡			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 84: **Aschengrau et al. 2015: Evaluation of Cancer Outcomes**

Study Citation:	Aschengrau, A; Winter, MR; Vieira, VM; Webster, TF; Janulewicz, PA; Gallagher, LG; Weinberg, J; Ozonoff, DM (2015). Long-term health effects of early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 14 36
Data Type:	early life exposure to PCE and risk of chronic conditions-Cancer
HERO ID:	2966280

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 (e.g., setting, participation rate described at all steps of the study, inclusion and exclusion criteria, and methods of participant selection). Although loss to follow up bias is of concern due to the large attrition among both exposed and unexposed subjects, the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2:	Attrition	Unacceptable	× 0.4	0.16	There was large subject attrition (~70%) during the study. Table 1 includes a description of the selection, enrollment, and initial and final exposure status of the study subjects. Approximately 30.6% of exposed subjects selected for the study based on their initial exposure status were available for the analysis. Approximately 29.1% of unexposed subjects selected for the study based on their initial exposure status were included in the analysis sample.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Subjects were similar (e.g., recruited from the same eligible population with the same method of ascertainment and within the same time frame using the same inclusion and exclusion criteria, and were of similar age (NTP, 2015a). Differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis. Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis.
Domain 2: Exposure Characterization						

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Study Citation:	Aschengrau, A; Winter, MR; Vieira, VM; Webster, TF; Janulewicz, PA; Gallagher, LG; Weinberg, J; Ozonoff, DM (2015). Long-term health effects of early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 14 36
Data Type:	early life exposure to PCE and risk of chronic conditions-Cancer
HERO ID:	2966280

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A non-direct exposure was used (i.e., modeling of historical exposure based on residence) that incorporated a leaching and transport model into the publicly available software (EPANET). Methodology and analysis of the water modeling activities were published in peer reviewed reports - potential validation data presented there. There was little to no evidence that the method had poor validity and exposure misclassification is likely to be non-differential (e.g., errors in basing exposure on residence; estimates of water consumed).
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	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	Temporality is established and the interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	A self-administered questionnaire was used and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of outcome misclassification (e.g., differential reporting of outcome by exposure status).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the study's measured outcomes are reported and effect estimates are reported with confidence intervals. In addition, the number of exposed is reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. The paper did not describe if the survey used to gather demographic characteristics was validated.

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Study Citation:	Aschengrau, A; Winter, MR; Vieira, VM; Webster, TF; Janulewicz, PA; Gallagher, LG; Weinberg, J; Ozonoff, DM (2015). Long-term health effects of early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 14 36
Data Type:	early life exposure to PCE and risk of chronic conditions-Cancer
HERO ID:	2966280

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Any co-exposures to pollutants that are not PCE that would likely bias the results were not likely to be present. Additionally, there is no direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of chronic disease in relation to PCE exposure), and appropriate statistical methods (i.e., generalized estimating equations) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Although the authors noted that the low response rate reduced the statistical power of the study, it is unlikely that the number of participants included in the analysis was inadequate to detect an effect in the exposed population and/or subgroups of the total population.
	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	Generalized estimating equations were used to generate Risk 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‡			Unacceptable⋆⋆		1.9	
Extracted			No			

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Study Citation:	Aschengrau, A; Winter, MR; Vieira, VM; Webster, TF; Janulewicz, PA; Gallagher, LG; Weinberg, J; Ozonoff, DM (2015). Long-term health effects of early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: A retrospective cohort study Environmental Health: A Global Access Science Source, 14 36
Data Type:	early life exposure to PCE and risk of chronic conditions-Cancer
HERO ID:	2966280

Domain	Metric	Rating†	MWF⋆	Score	Comments††

** Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 85: **Talbott et al 2015: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Talbott, EO; Marshall, LP; Rager, JR; Arena, VC; Sharma, RK; Stacy, SL (2015). Air toxics and the risk of autism spectrum disorder: The results of a population based case-control study in southwestern Pennsylvania Environmental Health: A Global Access Science Source, 14 80
Data Type:	CaseControl_Childhood_PERC_AutismSpectrumDisorder_OR_Q4-Neurological/Behavior
HERO ID:	3007486

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	217 autism spectrum disorder (ASD) cases born 2005-2009 were obtained from 6 counties in SW Pennsylvania using an outreach campaign targeted at ASD specialty diagnostic/treatment centers, private pediatric/psychiatry practices, school-based special needs programs, and autism support groups. Approximately 43% of cases living in the area were estimated to be obtained.
	Metric 2: Attrition	Medium	× 0.4	0.8	Of the 299 cases that wanted to participate, 56 were excluded (see below), 26 were not interested or able to complete the full interview. Of the 3254 mailed requests for interview controls, 250 returned contact sheets. Of these 24 were ineligible or unable to be contacted. All eligible birth certificate controls were included. Participants were excluded if adopted, parents were non-English speaking, parent wasn't available for interview, child lived outside the US, or 2000 census tract could not be matched birth certificate address.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Interview controls (224) were recruited from a random selection of birth registries at same time/counties as the cases; frequency matched to year of birth, sex and race. Birth certificate controls (4971) were drawn from birth registries in the same time/counties weighted with sex ratio and year of birth. An ASD diagnosis was not evaluated in the birth certificate controls, although 16 cases captured in this set were excluded. Cases had more preterm birth and multiple births than controls. Interview controls included more white and higher educated mothers than cases. Birth certificate controls had fewer white and higher educated mothers. All of these differences were considered as potential confounders and/or analyzed via sensitivity analysis.
Domain 2: Exposure Characterization					

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Study Citation:	Talbott, EO; Marshall, LP; Rager, JR; Arena, VC; Sharma, RK; Stacy, SL (2015). Air toxics and the risk of autism spectrum disorder: The results of a population based case-control study in southwestern Pennsylvania Environmental Health: A Global Access Science Source, 14 80
Data Type:	CaseControl_Childhood_PERC_AutismSpectrumDisorder_OR_Q4-Neurological/Behavior
HERO ID:	3007486

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Ambient hazardous air pollution concentrations for 30 air toxics were estimated using modeled data from the US EPA 2005 NATA assessment (average by census tract), including DCM, PERC, and TCE. For cases and interview controls, residential history from 3 months prior to pregnancy through 2 years old were geocoded, verified, and assigned a census tract (based on 2000 codes). Exposures were determined for pregnancy, 1st and 2nd years of life. For analysis using birth certificate controls, only the residence at time of birth was used to estimate exposure.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Quartiles of exposure were determined for cases, interview controls and birth certificate controls for methylene chloride (239-273 ng/m3), perchloroethylene (94-267 ng/m3), and trichloroethylene (71-85 ng/m3). For cases evaluated against birth certificate controls, quartiles were split as follows: DCM 244.06 ng/m3, 266.47 ng/m3, 272.48 ng/m3; Perc 100.08 ng/m3, 214.81 ng/m3, 267.36 ng/m3; TCE 70.55 ng/m3, 74.33 ng/m3, and 82.46 ng/m3.
	Metric 6:	Temporality	Medium	× 0.4	0.8	For cases and interview controls, exposure was modeled using data from 3 months prior to pregnancy through 2 years of age, which is anticipated to cover the critical window of exposure. Age of children at outcome assessment not stated. Participating children were born 2005-2009, and the study was published in 2015 with exposure data accessed in 2014.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The ASD outcome required a score of 15+ on the Social Communication Questionnaire (autistic features screen), as well as written documentation of a diagnosis by a child psychologist or psychiatrist. Outcome was assessed in cases and interview controls. The ASD outcome was not assessed in the birth certificate controls.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Odds ratios reported with 95% confidence intervals for adjusted models. Singleton sensitivity analysis data included in supplemental material and Table 5 for methylene chloride (statistically significant). Number of cases/controls for each analysis provided. Co-exposure correlations and factor analysis not fully presented.

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Study Citation:	Talbott, EO; Marshall, LP; Rager, JR; Arena, VC; Sharma, RK; Stacy, SL (2015). Air toxics and the risk of autism spectrum disorder: The results of a population based case-control study in southwestern Pennsylvania Environmental Health: A Global Access Science Source, 14 80
Data Type:	CaseControl_Childhood_PERC_AutismSpectrumDisorder_OR_Q4-Neurological/Behavior
HERO ID:	3007486

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 4: Potential Counfounding/Variable Control					
Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for mother's age, education, race, smoking status, as well as child's year of birth and sex. Sensitivity analysis was conducted to evaluate the high rate of multiple births in cases, relative to controls (8.4% cases; ~4% controls).
Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Trained interviewers interviewed mothers with structured questionnaire for demographics, SES, residential history, occupational history (maternal and paternal), family history of ASD, smoking history, maternal reproductive history, and child's medical history. Birth weight and preterm births were determined from birth certificates.
Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Several of the air toxics studied were reported to be highly corelated, and PCA found 75% of the pollutant variance could be attributed to 7 factors. Details not provided. Abstract states "unclear if these chemicals are risk factors themselves or if they reflect the effect of a mixture of pollutants." However, no indication that these co-exposures differed across cases and controls.
Domain 5: Analysis					
Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A case-control study was utilized to construct OR for ASD. Exposure quartiles determined with NATA model using location data from pregancy-2 years. Logistic regression utilized to determine OR across quantiles.
Metric 13:	Statistical power	Medium	× 0.2	0.4	The 217 cases, 224 interview controls, and 4971 birth certificate cases were sufficient to detect an effect for methylene chloride and air pollutants not relevant to this evaluation. Statistical power not reported, but p values show some statistically significant correlations
Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Detailed description of analysis is provided. The confounders used to adjust the OR models are clear and provided. Only the factor analysis of co-exposures correlation is insufficiently detailed to allow for replication, but this does not impact the outcome-exposure correlations.

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Study Citation:	Talbott, EO; Marshall, LP; Rager, JR; Arena, VC; Sharma, RK; Stacy, SL (2015). Air toxics and the risk of autism spectrum disorder: The results of a population based case-control study in southwestern Pennsylvania Environmental Health: A Global Access Science Source, 14 80
Data Type:	CaseControl_Childhood_PERC_AutismSpectrumDisorder_OR_Q4-Neurological/Behavior
HERO ID:	3007486

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression analysis used to compare interquartile ORs. Spearman correlation and principal component analysis were used to assess air toxics correlations. Model assumptions were met and the variables used were clearly stated and appropriate.
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 86: **Stingone et al. 2016: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Stingone, JA; Mcveigh, KH; Claudio, L (2016). Association between prenatal exposure to ambient diesel particulate matter and perchloroethylene with children's 3rd grade standardized test scores Environmental Research, 148 144-153
Data Type:	Cohort_Childhood_Neurodevelopment_ELA_Perc-Neurological/Behavior
HERO ID:	3223157

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	201,559 children born 1994 and 1998 enrolled in New York City public schools for 3rd grade before 2008. Maternal primary residence in New York City with successfully geocoded address on birth record. Inclusion/exclusion criteria clearly stated. Participants selected from NYC Department of Health and Mental Hygiene and NYC Department of Education. Children in private schools were not considered for this study.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Missing blood lead levels (potential confounder) in 22% of participants were imputed using single-chain Markov Chain Monte Carlo. Five imputation datasets were created and the separate analyses on each of these datasets weer then pooled to account for uncertainty. Imputation raised the percent children with levels >10 ug/dL from 4.4% to 6%. All other variables had < 5% missing data, and children with missing data on any other confounder were excluded from the analysis.
	Metric 3:	Comparison Group	Low	× 0.2	0.6	Low exposure group serves as reference group, but demographic details not provided according the exposure. Potential to introduce bias.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Geographic perchloroethylene levels based on EPA National Air Toxics Assessment (1996), a modeled ambient air concentrations by census tract with a "medium" overall confidence rating by EPA. Assigned based on maternal address at birth and divided into quartiles.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Adequate exposure ranges and sufficient number of subjects in each exposure category. Exposure divided into quartiles based on both perchloroethylene and diesel particulate matter levels: high both, high percerchloroethylene with low PM, high PM with low perchloroethylene, low both.

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Study Citation:	Stingone, JA; Mcveigh, KH; Claudio, L (2016). Association between prenatal exposure to ambient diesel particulate matter and perchloroethylene with children's 3rd grade standardized test scores Environmental Research, 148 144-153
Data Type:	Cohort_Childhood_Neurodevelopment_ELA_Perc-Neurological/Behavior
HERO ID:	3223157

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposure was estimated for the prenatal period and outcomes were assessed at 3rd grade, which is likely sufficient for neurological development. However, there is likely to be continuous exposure between these periods, which is not accounted for.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Achievement on 3rd grade standardized tests in math and English language arts (ELA) used as metric for academic outcomes and intelligence (reference provided). Details on the tests are provided. Scores standardized and dichotomized for this analysis.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Risk ratios with 95% confidence intervals reported in the text. All outlined statistical analyses, including sensitivity analyses, were reported in sufficient detail in text or supplemental material.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Models adjusted for important maternal and childhood factors, including race, lead exposure, tobacco/alcohol during pregnancy, and SES proxies (school lunch program and insurance type); neighborhood factors. Sensitivity analyses considered only children living in the same location at birth, 2-3 years and 3rd grade to account for differences in geographic location, and imputed data.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariate/confounder data obtained from birth records, school records and Lead Poisoning Prevention registry.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Diesel particulate matter exposure was also evaluated and strongly correlated (0.75) with perchloroethylene. The study adjusted for childhood lead exposure, an established neurotoxicant. For the extracted risk ratios, all participants had low diesel PM exposure (bottom 3 quartiles of exposure). Potential for residual confounding due to other air pollutants is mention as a potential limitation of the study.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A cohort study is appropriate for this type of exposure-outcome scenario and the research question. Appropriate statistical methods were used to analyze the data including quantile regression and multiple imputation.

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Study Citation:	Stingone, JA; Mcveigh, KH; Claudio, L (2016). Association between prenatal exposure to ambient diesel particulate matter and perchloroethylene with children's 3rd grade standardized test scores Environmental Research, 148 144-153
Data Type:	Cohort_Childhood_Neurodevelopment_ELA_Perc-Neurological/Behavior
HERO ID:	3223157

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	14,466 children (7.2%) had perchloroethylene exposure in 25th percentile and low diesel PM exposure. 35,818 children (17.8%) had high perchloroethylene and diesel PM exposure.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The methods are clear and reproducible of the risk ratios (quartiles of exposure and test scores) with access to the analytic data. Quantile regression is used to estimate the effects of PM and perchloroethylene exposure on dichotomized test scores, accounting for potential confounders.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Quantile regression models accounting for confounders were used in the analyses, and model selection was 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		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 87: **Bulka et al. 2016: Evaluation of Cancer Outcomes**

Study Citation:	Bulka, C; Nastoupil, LJ; Koff, JL; Bernal-Mizrachi, L; Ward, KC; Williams, JN; Bayakly, AR; Switchenko, JM; Waller, LA; Flowers, CR (2016). Relations between residential proximity to EPA-designated toxic release sites and diffuse large B-cell lymphoma incidence Southern Medical Journal, 109(10), 606-614
Data Type:	Toxic release sites (Perc-correlation)-Cancer
HERO ID:	3463478

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Exposure and disease data were aggregated at the census tract level. Individual-level data on exposure and disease status was not available, but analyses using data on the median years of residence in geographic areas included in the study suggested that selection bias was unlikely.
	Metric 2:	Attrition	High	× 0.4	0.4	It was noted that subjects in the database without age, sex, or race information were excluded. Although they did not provide numbers, it is not likely to be a high number.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Georgia census tract incidence rates were standardized by age, sex, and race with the U.S. National incidence rates as the reference group.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Geocoded data on toxic release sites in Georgia between 1988 and 1998 from the EPA's TRI. ArcGIS software was used to calculate distance from the census tract centroid to each TRI site. This is an ecological exposure assessment with neighborhood and distance from site used as measures of exposure. The magnitude of the releases from each TRI site was not taken into account in the analysis and varied by several orders of magnitude across TRI sites. A portion of the cases in the exposed group may have been exposed at very low levels, but this is not likely to have introduced bias.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	A Poisson regression was conducted based on distance from site.
	Metric 6:	Temporality	Low	× 0.4	1.2	Temporality is uncertain, but the study used TRI data from 1988 to 1998 and cancer registry data from 1999 to 2008. However, how long cases lived in the area is unknown.
Domain 3: Outcome Assessment						

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Study Citation:	Bulka, C; Nastoupil, LJ; Koff, JL; Bernal-Mizrachi, L; Ward, KC; Williams, JN; Bayakly, AR; Switchenko, JM; Waller, LA; Flowers, CR (2016). Relations between residential proximity to EPA-designated toxic release sites and diffuse large B-cell lymphoma incidence Southern Medical Journal, 109(10), 606-614
Data Type:	Toxic release sites (Perc-correlation)-Cancer
HERO ID:	3463478

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Diffuse large-B-cell lymphoma incidence was obtained from the Georgia Comprehensive Cancer Registry. This was used to obtain age-, sex-, and race-specific crude incidence rates for each census tract. This is considered an ecological way for assessing the outcome. Although it was noted that they used ICD codes they did not specify which ones and only used incidence rates instead of individual cancers.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Measured outcomes outlined are reported, but not in sufficient detail for detailed extraction (e..g., SIRs used were not reported nor were the observed and expected rates to calculate the SIRs). Standardized incidence ratio (SIR) was only provided by census tract and no data could be extracted from the figures as they are just color coded based on area. Only data available for extraction were Poisson regression results where no sample size or confidence intervals were provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, sex, and race were considered when creating the SIRs. SES was also taken into consideration.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained from registry databases and census tract data.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Results are based on TRI sites and distance from sites and there is no information provided on what other exposures may have occurred at those sites. Figures indicate that exposure could occur to several of the included chemicals in certain areas.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study is a preliminary evaluation linking geocoded cancer incidence data for specific periods with the EPA's Toxic Release Inventory data. The main purpose was to conduct cluster analyses and Poisson regression based on mean distance to a toxic release site.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Statistical power is not likely to be an issue as census tract data were used, which would include entire populations; however, the number of subjects included in the evaluation were not reported.

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Study Citation:	Bulka, C; Nastoupil, LJ; Koff, JL; Bernal-Mizrachi, L; Ward, KC; Williams, JN; Bayakly, AR; Switchenko, JM; Waller, LA; Flowers, CR (2016). Relations between residential proximity to EPA-designated toxic release sites and diffuse large B-cell lymphoma incidence Southern Medical Journal, 109(10), 606-614
Data Type:	Toxic release sites (Perc-correlation)-Cancer
HERO ID:	3463478

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient information is provided on how the data was obtained, how the spatial correlation of standardized incidence ratios were overlaid on the map with the toxic release data to evaluate clustering, use of global and local spatial statistics based on Monte Carlo simulations, and the use of Poisson regression models.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The clustering analysis and Poisson regression model appears appropriate and assumptions met as they were described.
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		2.2	
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 88: **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_Perc_HeadNeckCancer_OR_ContinuousCEI-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_Perc_HeadNeckCancer_OR_ContinuousCEI-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, perchloroethylene, and DCM. Insufficient data for carbon tetrachloride, so it was excluded from analysis beyond an ever/never OR.
	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.
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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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_Perc_HeadNeckCancer_OR_ContinuousCEI-Cancer
HERO ID:	3480125

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 89: **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 - Perc_high intensity T3 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 perchloroethylene 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 Perchloroethylene.
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 Perchloroethylene results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control study used to evaluate occupational TCE, Perchloroethylene, 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 statistically significant.
	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 - Perc_high intensity T3 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 90: **Lucas et al. 2015: Evaluation of Clinical Symptoms Outcomes**

Study Citation:	Lucas, D; Hervé, A; Lucas, R; Cabioch, C; Capellmann, P; Nicolas, A; Bodenes, A; Jegaden, D (2015). Assessment of exposure to perchloroethylene and its clinical repercussions for 50 dry-cleaning employees Journal of Occupational and Environmental Hygiene, 12(11), 767-773
Data Type:	France_TCE_exposed workers_clinical_symptoms-Other (please specify below)
HERO ID:	3488665

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Subjects' selection and inclusion/exclusion criteria are described in detail, for both exposed and unexposed subjects. However, 20 of the 70 exposed eligible subjects (29%) either refused to participate, or their employer refused to let them participate, or the occupational physician refused the establishment. There is no comparison of subjects characteristics for those 20 and those who participated. It's unlikely, however, that these refusals significantly biased the selection of participants.
	Metric 2:	Attrition	High	× 0.4	0.4	No attrition reported.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The inclusion/exclusion criteria are detailed for the exposed and control groups. It is unclear whether the medical history exclusion criteria applied to controls were also applied to exposed subjects. However, those criteria outline severe health symptoms unlikely to be present in a worker. Controls were matched to exposed subjects by age, sex, social and professional categories, and smoking status. The control group's lack of occupational perc exposure was verified.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure measured via levels of perchloroethylene in ambient air. Atmospheric sampling was performed using a passive diffusion badge worn by each employee with a detection limits of 2µg and quantification limits of 6µg. Blood samples also analyzed for a correlation analyses, but only in the exposed group. Years of employment were collected, but cumulative exposure not constructed.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range of air and blood samples in the exposed group are sufficient or adequate to develop an exposure-response estimate. An analysis with the control group and two exposure groups (based on years of employment) is briefly reported, but results not shown beyond lack of effects and p-value.

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Study Citation:	Lucas, D; Hervé, A; Lucas, R; Cabioch, C; Capellmann, P; Nicolas, A; Bodenes, A; Jegaden, D (2015). Assessment of exposure to perchloroethylene and its clinical repercussions for 50 dry-cleaning employees Journal of Occupational and Environmental Hygiene, 12(11), 767-773
Data Type:	France_TCE_exposed workers_clinical_symptoms-Other (please specify below)
HERO ID:	3488665

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Low	× 0.4	1.2	The list of clinical symptoms investigated include both acute and less acute symptoms. Therefore, the temporality of exposure and outcome is uncertain.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcome was assessed using well-established methods (health assessment was performed during a face to face interaction with a physician during a medical examination). Also, each subject completed a questionnaire assessing daytime drowsiness using Epworth's validated scale.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outlined statistical analyses, including sensitivity analyses, were reported in sufficient detail. Percent of groups with symptoms are reported with p-values for tests of differ.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	The analysis accounted for potential confounders including age, sex, social and professional categories, and smoking status.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Potential confounders (age, sex, social and professional categories, and smoking status were matching variables) were assessed using valid and reliable methodology (medical examination).
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Any co-exposures to pollutants that are not the target exposure that would likely bias the results were likely to be present in the dry-cleaning work place. Non-work related solvent exposure was reported in only 4% of the study group. In addition, matching variables such as social and professional categories, and smoking status might eliminate potential differential exposure to co-pollutants in the study groups.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design (cross-sectional) was appropriate for the research question. Statistical methods were appropriate although simple.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The 50 exposed and 95 matched controls were adequate to detect an effect.

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Study Citation:	Lucas, D; Hervé, A; Lucas, R; Cabioch, C; Capellmann, P; Nicolas, A; Bodenes, A; Jegaden, D (2015). Assessment of exposure to perchloroethylene and its clinical repercussions for 50 dry-cleaning employees Journal of Occupational and Environmental Hygiene, 12(11), 767-773
Data Type:	France_TCE_exposed workers_clinical_symptoms-Other (please specify below)
HERO ID:	3488665

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done (simple correlation analyses and Fisher's exact tests) and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Fisher's exact test was used for categorical analyses comparing symptoms by exposure group.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.167	0.17	Blood perchloroethylene levels have accurate and precise quantitative relationship with external exposure; and the biomarker is derived from exposure to one parent chemical.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	
	Metric 18:	Method Sensitivity	Medium	× 0.167	0.33	The detection limits was 2 µg/l and the quantification limits 5 µg/lL. Blood levels were analyzed on 49 subjects as one refused to have blood drawn. No measurement was below the limit of detection.. Analytical methods measuring biomarker are adequately reported.
	Metric 19:	Biomarker stability	High	NA	NA	Same-day analysis conducted, so biomarker stability is not a concern.
	Metric 20:	Sample contamination	Low	× 0.167	0.5	Samples were collected into EDTA tubes, transferred into plain glass tubes suitable for solvent analysis by pipette and then refrigerated during transport to the laboratory for same-day analysis There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable.
	Metric 21:	Method requirements	Medium	× 0.167	0.33	Blood perc levels were determined by gas chromatography using the DFG method
	Metric 22:	Matrix adjustment	Medium	× 0.167	0.33	No adjustments reported
Overall Quality Determination‡			Medium		1.7	
Extracted			Yes			

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Study Citation:	Lucas, D; Hervé, A; Lucas, R; Cabioch, C; Capellmann, P; Nicolas, A; Bodenes, A; Jegaden, D (2015). Assessment of exposure to perchloroethylene and its clinical repercussions for 50 dry-cleaning employees Journal of Occupational and Environmental Hygiene, 12(11), 767-773
Data Type:	France_TCE_exposed workers_clinical_symptoms-Other (please specify below)
HERO ID:	3488665

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 91: **Stewart et al. 1961: Evaluation of Clinical Chemistry/Biochemical Outcomes**

Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_clinicalchem-Clinical Chemistry/Biochemical
HERO ID:	58214

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	This case-study followed an accidental exposure to perchloroethylene. An adult male presented to the Dow Chemical medical center was examined after collapsing in work area with high perchloroethylene air concentrations without wearing personal protective equipment.
	Metric 2: Attrition	High	× 0.4	0.4	Only one subject was assessed in this study. He was followed for six weeks following treatment at the medical center and was not lost to follow-up during this period.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	The study was a case report of a single individual. No other individuals were included in the study. Some demographic details on the patient were provided. Previous medical history was predicted to be a factor in the outcomes assessed.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	The exposure was reported to be about 50 percent perchloroethylene and 50 percent Stoddard solvent. One study author recreated a simulated exposure using known information about the exposure episode. Information on the circumstances surrounding the exposure was reported in detail. Samples from the simulated exposure were collected in Saran bags and analyzed by infrared spectrometer (Perkin-Elmer Model 12C). Additionally, expired air samples from the patient were collected in saran bags and measured using the same method. The simulated exposure was not a validated method of exposure assessment, however, the patient's exposure was also directly assessed by perchloroethylene in expired air.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Simulated exposure levels varied by location in the recreated work environment. This was a case of a single exposure event of an individual and repeated exposure measurements in expired air were determined over a six-week interval. Average exposure during the 3.5 hour window of exposure was estimated to be 393 ppm.

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_clinicalchem-Clinical Chemistry/Biochemical
HERO ID:	58214

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established. The exposure preceded the symptoms presented by the patient. The patient's medical history was reviewed along with the symptoms and the study authors report there was no contributory pre-existing illness present.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Upon admittance to the hospital, a physical exam was conducted to evaluate acute effects (alterations in heart rate, blood pressure, respiration rate). During the six weeks of follow-up, clinical chemistry data (complete blood count and urinalysis) were collected. No further information was specified about outcome measurement, but it was presumably done in the medical clinic using the same methods each time.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	The abstract and introduction suggest statistical comparisons were intended to be made between clinical chemistry endpoints and perchloroethylene concentrations in expired air, however, this was not described. Clinical chemistry values from each follow-up visit are provided, along with the normal range.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates were not reported to be adjusted for in this analysis, however, adjustment in this case may not be appropriate.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Some covariates were discussed (previous physical health, occupational details), but these were not adjusted in the analysis. The sources were not provided, but assumed to be collected from medical and job records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The accidental solvent exposure was described as being 50 percent perchloroethylene and 50 percent Stoddard solvent (hydrocarbon mixture). This exposure was not accounted for in the statistical comparison, however, the study authors state Stoddard solvent was not detectable in the patient's expired air.
Domain 5: Analysis						

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_clinicalchem-Clinical Chemistry/Biochemical
HERO ID:	58214

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This case study reported the symptoms and effects from a single accidental exposure to a relatively high concentration of perchloroethylene. Only one individual was exposed from this event and was followed for six weeks post-exposure event. No statistical analysis was conducted, but clinical chemistry endpoints were compared with the normal ranges.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	In this case series study, only one person was exposed and followed for six weeks.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The exposure event was described in detail, however, some details on the simulated exposure were missing. Statistical comparisons were not adequately described and it is unclear what comparisons were to be made.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The abstract and introduction suggest statistical comparisons were intended to be made between clinical chemistry endpoints and perchloroethylene concentrations in expired air, however, this was not described. It is unclear if statistical methods were appropriate.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.167	0.17	Perchloroethylene in expired air is a direct measure of exposure to perchloroethylene.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarkers of effect.
	Metric 18:	Method Sensitivity	Medium	× 0.167	0.33	Perchloroethylene was detected in expired air for a majority of the follow-up period (21 days post exposure). The LOD was reported.
	Metric 19:	Biomarker stability	Low	× 0.167	0.5	Storage history of the expired air was not reported. Stability of perchloroethylene in the expired air is unclear.
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	No information was available on sample contamination, but there was no indication contamination occurred.
	Metric 21:	Method requirements	Low	× 0.167	0.5	This study utilized infrared spectroscopy to determine perchloroethylene concentrations.
	Metric 22:	Matrix adjustment	Low	× 0.167	0.5	Only one method of determination was reported and was not matrix-adjusted. It's unclear if matrix-adjustment is appropriate.
Overall Quality Determination‡			Medium		2.1	

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Study Citation:	R. D. Stewart, D. S. Erley, A. W. Schaffer, H. H. Gay (1961). Accidental vapor exposure to anesthetic concentrations of a solvent containing tetrachloroethylene Industrial Medicine and Surgery, 30(8,8), 327-330
Data Type:	Perchloroethylene_accidental_exposure_case_report_clinicalchem-Clinical Chemistry/Biochemical
HERO ID:	58214

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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.

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

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 92: **Mahalingaiah et al. 2016: Evaluation of Reproductive Outcomes**

Study Citation:	Mahalingaiah, S; Winter, MR; Aschengrau, A (2016). Association of prenatal and early life exposure to tetrachloroethylene (PCE) with polycystic ovary syndrome and other reproductive disorders in the cape cod health study: A retrospective cohort study Reproductive Toxicology, 65 87-94
Data Type:	Cape Cod Perc miscarriage low exp RR-Reproductive
HERO ID:	3488701

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Eligible participants were found through cross-referencing birth certificates and maternal residential addresses in the Cape Cod area 1969-1983. Initial exposures were determined based on maternal address and water pipe maps. Details on the participation rate and exclusionary reasons found in Aschengrau et al. 2011 (HERO ID 2127838). The participation rate of those selected is low (40.5%), but reasons for exclusion provided and similar across groups mitigating concern for selection bias.
	Metric 2: Attrition	High	× 0.4	0.4	There was some significant loss to follow-up from the original cohort (approximately 60%). Other reasons for exclusion include could not be located (6.6%), were deceased (2.2%), or refused to participate (3.7%). Detailed reasons for loss to follow-up can be found in Table 1 of Aschengrau et al., 2011 (HERO ID 2127838). The distribution of loss to follow-up was similar across exposure designations, mitigating some concern.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls or those initially designated as 'unexposed' were frequency matched to exposed individuals by birth month/year, taken from the same population of mothers bearing children between 1969 and 1983. These individuals were subject to the same inclusion/exclusion criteria and were geolocated and assigned exposure in the same manner as those initially designated as 'exposed'. Demographics and key risk factors were assessed by questionnaire and appeared similar or was adjusted for.
Domain 2: Exposure Characterization					

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Study Citation:	Mahalingaiah, S; Winter, MR; Aschengrau, A (2016). Association of prenatal and early life exposure to tetrachloroethylene (PCE) with polycystic ovary syndrome and other reproductive disorders in the cape cod health study: A retrospective cohort study Reproductive Toxicology, 65 87-94
Data Type:	Cape Cod Perc miscarriage low exp RR-Reproductive
HERO ID:	3488701

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	A leaching and transport model (Webler and Brown + EPANET) was utilized to determine exposure for all individuals from the prenatal period to age 5. The leaching model has been developed and used in previous studies (Gallagher et al. 2011; HERO ID 3490321). The model was also evaluated against samples taken from home in a validation study (Spence et al. 2008; HERO ID 758557). This represents a method that is not well-established, but is validated against a historical water samples.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	First, any exposure as determined by the leaching and transport model was determined and then compared to no exposure. This represents two levels of exposure--any or none--and would be classified accordingly as low. The second set of analyses looked at high exposure and low exposure, as determined by dividing exposed individuals into two groups at the median exposure level. These two high and low exposure groups were compared with the no exposure group which represents three levels of exposure. These results are accordingly rated as medium for this metric.
	Metric 6:	Temporality	High	× 0.4	0.4	This study investigates prenatal and early childhood exposure to Perc and the incidence of various reproductive effects (polycystic ovarian syndrome [PCOS], endometriosis, difficulty conceiving, and miscarriage) in adult women. The representation of prenatal and early life exposure is a particular strength of the study as these are critical developmental windows. This establishes a time order that exposure preceded disease.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	For all four outcomes analyzed in this study, women were asked by questionnaire if they had ever had difficulty conceiving or a miscarriage, or if their doctor had ever diagnosed them with PCOS or endometriosis. This represents a less-established method, but there is no evidence to suggest it has poor validity. It is self-reported information and is subject to recall or responder bias. This is likely to cause some non-differential misclassification, resulting in slight bias towards the null.

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Study Citation:	Mahalingaiah, S; Winter, MR; Aschengrau, A (2016). Association of prenatal and early life exposure to tetrachloroethylene (PCE) with polycystic ovary syndrome and other reproductive disorders in the cape cod health study: A retrospective cohort study Reproductive Toxicology, 65 87-94
Data Type:	Cape Cod Perc miscarriage low exp RR-Reproductive
HERO ID:	3488701

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes described in the abstract, introduction, and methods were provided in the results. Adjusted RR were provided in an easily extractable table. Number of participants (cases/N) per analysis was included an easily interpreted. Both crude and adjusted analyses are presented.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Information was collected via questionnaire for both mothers and their children (b. 1969-1983). To control for non-independent familial covariates, a generalized estimating equation analysis was performed for all outcomes. The authors state, "the log link was used while assuming equal correlation between birth outcomes from the same mother." Child's age was the only variable that had a meaningful impact (>10% change in crude) and was included in the model.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were collected by self-reported questionnaire. This represents a les-established method, but there is no evidence to suggest that this is an invalid or insensitive instrument. As this is self-reported information it is subject to recall or responder bias, potentially biasing the results towards the null.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposure to other solvents was collected via self-reported questionnaire about job history or hobbies. The amount of individuals with a history of occupational solvent exposure was quite low (9-12%) and was initially considered in the analysis, but was not included in the final model.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study investigates the association between prenatal and early childhood exposure to Perc. This was conducted as a part of a larger retrospective cohort for Cape Cod 1969-1983. The study design is appropriate for the research question. There were no apparent issues.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There was sufficient statistical power in the exposed population to detect an effect. There were 500 exposed women and 328 unexposed women in this study. There were no apparent issues.

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Study Citation:	Mahalingaiah, S; Winter, MR; Aschengrau, A (2016). Association of prenatal and early life exposure to tetrachloroethylene (PCE) with polycystic ovary syndrome and other reproductive disorders in the cape cod health study: A retrospective cohort study Reproductive Toxicology, 65 87-94
Data Type:	Cape Cod Perc miscarriage low exp RR-Reproductive
HERO ID:	3488701

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to reproduce the results of this study given access to original data. There were no apparent issues.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method of calculating risk in this population (risk ratio, RR) is transparent and states how they determined what covariates were included in the final adjusted 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	
	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 93: **Ruckart et al. 2015: Evaluation of Cancer Outcomes**

Study Citation:	Ruckart, PZ; Bove, FJ; Shanley, E; Maslia, M (2015). Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: A case control study Environmental Health: A Global Access Science Source, 14 74
Data Type:	CampLejeune_MaleMarines_Perc_BreastCancerAge_HazardRatio_HighCumulativeExposure-Cancer
HERO ID:	3489298

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Case-control study 71 cases and 373 controls. Male marines born before 1969, diagnosed/treated 1995-2013 with identifiable tour dates/locations. Inclusion/exclusion criteria not detailed at every stage. No information is provided on how the number of controls was reduced from 663 to 400.
	Metric 2:	Attrition	High	× 0.4	0.4	Excluded 9% of cases and 7% of controls, because to attain personnel files used to classify exposure. Demographic data for those excluded provided and does not suggest bias.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were selected from incident cancer cases not associated with solvents (skin, mesothelioma, and bone). Controls were randomly selected within skin to obtain 5 controls/case. Control characteristics were similar to cases and considered as variables (race, Vietnam service). Controls were diagnosed earlier than cases.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	This study constructed residential cumulative exposure to PCE and TCE through drinking water. The National Personnel Record Center (NPRC) identified those stationed at Camp Lejeune before 1986 (sole source of exposure considered). Historical reconstruction (ASTDR) of monthly average contamination in drinking water was based on 1980-1985 measurements at 3 contaminated water treatment plants. Estimated exposure was based on likely residence and duration of tour.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	There was sufficient exposure to determine an effect. Exposures were reported as not exposed, low and high. Some endpoints showed dose-response.
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure occurred 10+ year before diagnosis, which is appropriate for this outcome (breast cancer).
Domain 3: Outcome Assessment						

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Study Citation:	Ruckart, PZ; Bove, FJ; Shanley, E; Maslia, M (2015). Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: A case control study Environmental Health: A Global Access Science Source, 14 74
Data Type:	CampLejeune_MaleMarines_Perc_BreastCancerAge_HazardRatio_HighCumulativeExposure-Cancer
HERO ID:	3489298

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Department of Veteran's Affairs Central Cancer Registry (VACCR) has information on eligible veterans diagnosed with or treated for cancer, which covers ~28% of US veterans (generally with service-connected disabilities or low income). At least a portion were histologically confirmed. VACCR identified cases based on primary diagnosis and histological confirmation.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of breast cancer outcomes were provided and extractable. Odds ratios were reported with confidence interval and number of cases and controls were reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for age at diagnosis, race, service in Vietnam. Several other potential confounders were evaluated rank [surrogate for SES], diabetes and gynecomastia) and did not impact OR.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Socio-demographic information, and relevant medical conditions identified through VACCR and VA Patient Treatment Files; medical information was missing for 7% of cases and 13% of controls. Vietnam service, rank, Military Occupational Specialty (MOS) codes were from NPRC.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Service related co-exposure to solvents and electromagnetic fields were determined from MOS codes. Neither Perc or TCE were isolated exposures in the drinking water, however, exposures outside of Camp Lejeune are not anticipated to be significantly different between cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate for the research questions. Logistic regression was used to estimate odds ratios, hazard ratios and their 95% confidence intervals.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sufficient sample size (71 male breast cancer cases) to detect an effect, but have wide confidence intervals. No information provided on statistical power in terms of sample size.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Exact logistic regression and conditional logistic regression were used to determine odds ratios. Sufficient detail was provided to understand and reproduce results.

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Study Citation:	Ruckart, PZ; Bove, FJ; Shanley, E; Maslia, M (2015). Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: A case control study Environmental Health: A Global Access Science Source, 14 74
Data Type:	CampLejeune_MaleMarines_Perc_BreastCancerAge_HazardRatio_HighCumulativeExposure-Cancer
HERO ID:	3489298

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression was used to calculated OR, adjusted OR and 95% confidence intervals for breast cancer. Similar models were used to calculate hazard ratio for age of diagnosis. Models were appropriate and 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‡			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 94: **Aschengrau et al. 2016: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Aschengrau, A; Janulewicz, PA; White, RF; Vieira, VM; Gallagher, LG; Getz, KD; Webster, TF; Ozonoff, DM (2016). Long-term neurotoxic effects of early-life exposure to tetrachloroethylene-contaminated drinking water 82(1), 169-179
Data Type:	Cape Cod Perc drinking teen RR-Neurological/Behavior
HERO ID:	3489677

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Eligible participants were found through cross-referencing birth certificates and maternal residential addresses in the Cape Cod area 1969-1983. Detailed elements of the study design were provided in a prior publication (Aschengrau et al., 2011; HERO ID 2127838). Participation rates across initial exposure designations indicate low probability of selection bias.
	Metric 2: Attrition	Medium	× 0.4	0.8	The prior publication (HERO ID 2127838) indicates there were 1698 eligible participants, but Table 1 provides a total participant count of 1378. There is no explanation for this exclusion from the analysis.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls or those initially designated as 'unexposed' were frequency matched to exposed individuals by birth month/year, taken from the same population of children. These individuals were subject to the same inclusion/exclusion criteria and were geolocated and assigned exposure in the same manner as those initially designated as 'exposed'. The present study provides a table of participant characteristics, revealing little difference between exposed and unexposed.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	A leaching and transport model (Webler and Brown + EPANET) was utilized to determine exposure for all individuals from the prenatal period to age 5. The leaching model has been developed and used in previous studies (Gallagher et al. 2011; HERO ID 3490321). The model was also evaluated against samples taken from home in a validation study (Spence et al. 2008; HERO ID 758557). This represents a method that is not well-established, but is validated against a historical water samples.

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Study Citation:	Aschengrau, A; Janulewicz, PA; White, RF; Vieira, VM; Gallagher, LG; Getz, KD; Webster, TF; Ozonoff, DM (2016). Long-term neurotoxic effects of early-life exposure to tetrachloroethylene-contaminated drinking water 82(1), 169-179
Data Type:	Cape Cod Perc drinking teen RR-Neurological/Behavior
HERO ID:	3489677

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Results for behavioral outcomes and mental health outcomes were reported as the RR for those in the highest tertile. This represents three levels of exposure. Additionally, the authors note that the range of cumulative (prenatal to 5 years) exposure to Perc for this population was 11 mg to 4668 g, showing a sufficient range of exposure to detect an effect.
	Metric 6:	Temporality	High	× 0.4	0.4	Cumulative exposure measures assessed the exposure of individuals from the prenatal period through 5 years of age, which is a strength of this study. Several of the behavioral outcomes analyzed in this study correspond to life events in the teenage years. In this case, there was appropriate temporality for the exposure preceding the disease in both behavioral and mental health outcomes.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The risky behavior outcomes and mental health and behavior outcomes assessed in this study were determined through self-reported questionnaires. Outcomes for risky behavior included age at initiation of smoking, smoking habits, drinking habits, and drug use habits. Outcomes for mental health and behavior included age at initiation of smoking, smoking habits, drinking habits, and drug use habits. Both sets of outcomes relied on self-reported data and may be subject to recall or responder bias.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	The study's measured outcomes reported in the abstract, introduction, and methods were mostly provided in the results. Some results are presented as RRs for those participants in the highest exposure tertile and others are presented as RRs for ever/never exposed. Results for the middle tertile of exposure are not presented making it difficult to assess trend. The results are also presented in-text, making the comparisons being made slightly unclear. Additionally, the number included in each analyses was not presented clearly.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Aschengrau, A; Janulewicz, PA; White, RF; Vieira, VM; Gallagher, LG; Getz, KD; Webster, TF; Ozonoff, DM (2016). Long-term neurotoxic effects of early-life exposure to tetrachloroethylene-contaminated drinking water 82(1), 169-179
Data Type:	Cape Cod Perc drinking teen RR-Neurological/Behavior
HERO ID:	3489677

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The study authors mention demographic characteristics, key risk factors for the relevant outcomes, and occupational/hobby-related solvent exposure were assessed as potential confounders, included if they changed the crude model by greater than 10%. This provides indirect evidence of adjustment for the final model results presented. There is no clear indication of which variables were included in the final model for all outcomes.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed by self-reported questionnaire. This is not a well-established method, but there is no evidence that this method is not valid.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposure to solvents was assessed through questionnaire responses, listing jobs or hobbies that may have resulted in solvent exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate for the research question. This study used maternal addresses to assess both prenatal and early childhood exposures to Perc. The ability to recreate historical exposures, especially early childhood and prenatal is a strength of the study.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were enough participants included in the analysis of behavioral and mental health outcomes to detect an effect in the population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to reproduce the study results given availability of the original data. Depending on the outcome, confounding variables that changed the crude estimate by >10% to 30% were included in final multivariate models.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Mean differences were used for assessing relationships with continuous outcomes (eg, color confusion index). Ninety-five percent confidence intervals (95% CI) and p-values were used to measure the precision of the associations.
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	

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Study Citation:	Aschengrau, A; Janulewicz, PA; White, RF; Vieira, VM; Gallagher, LG; Getz, KD; Webster, TF; Ozonoff, DM (2016). Long-term neurotoxic effects of early-life exposure to tetrachloroethylene-contaminated drinking water 82(1), 169-179
Data Type:	Cape Cod Perc drinking teen RR-Neurological/Behavior
HERO ID:	3489677

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	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 95: **Aschengrau et al. 2016: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Aschengrau, A; Gallagher, LG; Winter, MR; Vieira, VM; Janulewicz, PA; Webster, TF; Ozonoff, DM (2016). No association between unintentional head injuries and early-life exposure to tetrachloroethylene (PCE)-contaminated drinking water Journal of Occupational and Environmental Medicine, 58(10), 1040-1045
Data Type:	Cape Cod Perc Head Injury Dich RR-Neurological/Behavior
HERO ID:	3489895

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Eligible participants were found through cross-referencing birth certificates and maternal residential addresses in the Cape Cod area from the period 1969 to 1983. Initial exposure designations were determined based on this cross-reference of maternal addresses and detailed water pipe installation maps. Detailed elements of the study design including comparisons of participants and nonparticipants were provided in a prior publication (Aschengrau et al., 2011; HERO ID 2127838). Although loss to follow-up bias is of concern due to the large attrition among both exposed and unexposed subjects, the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2: Attrition	Unacceptable	× 0.4	0.16	There was significant loss to follow-up from the original cohort (approximately 60%). Others could not be located (6.6%), were deceased (2.2%), or refused to participate (3.7%). Detailed reasons for loss to follow-up can be found in Table 1 of Aschengrau et al., 2011 (HERO ID 2127838) or Table 1 of the present study. The distribution of loss to follow-up was similar across exposure designations, mitigating some concern. The results indicate all those who participated were included in the main analysis of head injury. There was some exclusion from detailed head injury analyses due to missing data, but the impact was likely not appreciable. Missing data/exclusion from these detailed head injury analyses would likely bias the results towards the null.

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Study Citation:	Aschengrau, A; Gallagher, LG; Winter, MR; Vieira, VM; Janulewicz, PA; Webster, TF; Ozonoff, DM (2016). No association between unintentional head injuries and early-life exposure to tetrachloroethylene (PCE)-contaminated drinking water Journal of Occupational and Environmental Medicine, 58(10), 1040-1045
Data Type:	Cape Cod Perc Head Injury Dich RR-Neurological/Behavior
HERO ID:	3489895

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls or those initially designated as 'unexposed' were frequency matched to exposed individuals by birth month/year, taken from the same population of mothers bearing children between 1969 and 1983. These individuals were subject to the same inclusion/exclusion criteria and were geolocated and assigned exposure in the same manner as those initially designated as 'exposed'. Demographics and key risk factors were assessed by questionnaire in both those initially designated as 'exposed' and those designated as 'unexposed'. The present study provides a table of participant characteristics, revealing little difference between exposed and unexposed.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A leaching and transport model was utilized to determine exposure for all individuals from the prenatal period to age 5. The leaching model has been developed and used in previous studies (Gallagher et al. 2011; HERO ID 3490321). The transport model takes into account flow rates and direction. To assign cumulative exposure, the Webler and Brown leaching algorithm was incorporated with EPANET water distribution modeling software (U.S. EPA). The model was also evaluated against samples taken from home in a validation study (Spence et al. 2008; HERO ID 758557). This represents an indirect method of exposure that is not well-established, but is validated against a historical water samples. It was assumed that all water users drew the same amount of water. This could lead to some non-differential exposure misclassification due to bottled water use or water use outside the home, but is not of great concern. Residences with private wells or served by non-Perc leaching pipes were considered unexposed (records of these water sources agree).

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Study Citation: Aschengrau, A; Gallagher, LG; Winter, MR; Vieira, VM; Janulewicz, PA; Webster, TF; Ozonoff, DM (2016). No association between unintentional head injuries and early-life exposure to tetrachloroethylene (PCE)-contaminated drinking water Journal of Occupational and Environmental Medicine, 58(10), 1040-1045

Data Type: Cape Cod Perc Head Injury Dich RR-Neurological/Behavior

HERO ID: 3489895

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Two analyses were conducted to investigate the association between prenatal/early childhood exposure to Perc and head injuries. The first compared tertiles of cumulative exposure and those with no exposure. This represents 4 levels of exposure (none and Q1-Q3). Another analysis was conducted for dichotomous exposure (any or none). This represents two levels of exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Cumulative exposure to Perc is measured from the prenatal period to 5 years of age. Approximately 41% of reported head injuries occurred after 18 years of age and the median age was 15, suggesting most head injuries likely occurred after 5 years of age which helps establish temporality between exposure and outcome.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The outcome investigated by this study was head injuries. Incidence of head injuries was assessed through self-reported questionnaires. Other details of the head injury were included in the questionnaire responses. This does not represent a well-established method for assessing head injury. Reliance on self-reported outcome information allows for recall or responder bias, with a potential bias towards the null. Due to this, the rating for this metric remains at low.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes described in the abstract, introduction, and methods were presented in the results. The table of results (Table 2) clearly provides full tabulation of participants included in each analysis, accompanied by a confidence interval.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted analyses were used to determine potential confounders from relevant demographic characteristics, head injury risk factors, or other solvent exposures. Covariates altering the crude RR by greater than 10% were included in the final model. Authors state that no covariates fit these criteria, so unadjusted results are presented.

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Study Citation:	Aschengrau, A; Gallagher, LG; Winter, MR; Vieira, VM; Janulewicz, PA; Webster, TF; Ozonoff, DM (2016). No association between unintentional head injuries and early-life exposure to tetrachloroethylene (PCE)-contaminated drinking water Journal of Occupational and Environmental Medicine, 58(10), 1040-1045
Data Type:	Cape Cod Perc Head Injury Dich RR-Neurological/Behavior
HERO ID:	3489895

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders (excluding co-exposures) were assessed. The paper did not describe if the self-administered survey used to gather demographic characteristics, medical and occupational histories, lifestyle factors, residential addresses from birth through early childhood, and history of head injuries was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Other sources of solvents were considered a potential confounder, but did not alter crude RR by at least 10% to be included in the final analyses.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study investigates the association between prenatal and early childhood chronic exposure to Perc and head injuries. This retrospective cohort study design was appropriate for investigating the effects of long-term PCE exposure. The authors state this study was conducted due to concerns about neurological impairments (such as impairments in cognition, vision, attention, and motor skills) found in other studies examining occupational exposure to Perc. Head injury was chosen as an outcome as neurological impairments "plausibly increase the likelihood of unintentional injuries." Appropriate statistical methods (i.e., generalized estimating equations) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There is a sufficient number of participants to detect an effect in the exposed population. The total analysis sample included 544 unexposed individuals and 828 exposed individuals.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The 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 method (generalized estimating equations) for calculating risk ratios 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	
	Metric 18:	Method Sensitivity		NA	NA	

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Study Citation:	Aschengrau, A; Gallagher, LG; Winter, MR; Vieira, VM; Janulewicz, PA; Webster, TF; Ozonoff, DM (2016). No association between unintentional head injuries and early-life exposure to tetrachloroethylene (PCE)-contaminated drinking water Journal of Occupational and Environmental Medicine, 58(10), 1040-1045
Data Type:	Cape Cod Perc Head Injury Dich RR-Neurological/Behavior
HERO ID:	3489895

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‡		~~Unacceptable~~⋆⋆ ⟶ Low§		~~2.0~~	
Extracted		Yes			

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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: "In consideration of the reasons provided by the authors that the high attrition in the study population is unlikely to result in selection bias (see 'additional comments' field above), recommend upgrading the overall study quality rating to low."

Table 96: **Hadkhale et al. 2017: Evaluation of Cancer Outcomes**

Study Citation:	Hadkhale, K; Martinsen, JI; Weiderpass, E; Kjaerheim, K; Sparen, P; Tryggvadottir, L; Lynge, E; Pukkala, E (2016). Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries International Journal of Cancer, 140(8), 1736-1746
Data Type:	NOCCA project (perc-high exposure group)-Cancer
HERO ID:	3489952

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	This is based on a large cohort of 14.9 million individuals from four of five Nordic countries who participated in one or more population censuses from 1960-1990 (individual data was not available for Denmark). All subjects were selected from the same general population during the same time frame using the same methods.
	Metric 2:	Attrition	High	× 0.4	0.4	There is little if any attrition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	For each case, 5 controls were randomly selected matched by birth year and sex among individuals who were alive and free from bladder cancer at the date of diagnosis of the case. Table of characteristics indicates that there was a similar distribution by country in the cases and controls.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Occupation information was obtained from computerized census records. Exposure was qualitatively estimated based on linkage between occupational codes and the NOCCA-JEM, which was developed from the Finnish JEM. Some details were provided. Exposure was assumed to start at age 20 and end at the index date or at 65 years. If occupation codes changed on the census, it was assumed that individuals changed occupations at the mid-point of the census years. Cumulative exposures were estimated by summing up the product of proportion and level of exposure based on occupational code and employment period.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range was sufficient enough to break the exposure into 4 groups from unexposed to >87.55 ppm.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established by reporting 10-year lag results, but it is unclear if exposure falls in the relevant exposure window.
Domain 3: Outcome Assessment						

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Study Citation:	Hadkhale, K; Martinsen, JI; Weiderpass, E; Kjaerheim, K; Sparen, P; Tryggvadottir, L; Lynge, E; Pukkala, E (2016). Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries International Journal of Cancer, 140(8), 1736-1746
Data Type:	NOCCA project (perc-high exposure group)-Cancer
HERO ID:	3489952

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Incident bladder cancer cases were obtained from the NOCCA cancer registries. No further information was provided.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All relevant information is provided. Number of cases and controls in the different exposure levels and hazard ratios with 95% confidence intervals and p-values for trends were all provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, sex, and country were addressed. Smoking information was unknown, but they addressed why they did not consider it an issue. SES could not be addressed.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained from registry and census databases. However, it is unclear how much of the potential confounding information is gathered from the self-administered questionnaire and if this questionnaire was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Although many different jobs were assessed and not all exposures to all chemicals in each job could be addressed, they did adjust for those that would be potentially related to bladder cancer and included benzene, toluene, aliphatic and alicyclic hydrocarbon solvents as well as other solvents.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design is appropriate. The study is a nested case-control study based on the Nordic Occupational Cancer project cohort with all incidence cases of bladder cancer included. This study design is appropriate to study the effects of several different agents on bladder cancer.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants is adequate for statistical power with total number of cases over 100,000 and controls over 500,000. Even when broken down into exposure groups there were more than 150 subjects for any given group.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The study describes the use of conditional logistic regression for estimating hazard ratios and 95% confidence intervals and the Pearson's chi-square test for linear trends. Details were also provided for the different lag times used.

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Study Citation:	Hadkhale, K; Martinsen, JI; Weiderpass, E; Kjaerheim, K; Sparen, P; Tryggvadottir, L; Lynge, E; Pukkala, E (2016). Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries International Journal of Cancer, 140(8), 1736-1746
Data Type:	NOCCA project (perc-high exposure group)-Cancer
HERO ID:	3489952

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Medium	× 0.2	0.4	The study is transparent on the methods used including conditional logistic regression for estimating hazard ratios and 95% confidence intervals and the Pearson's chi-square test for linear trends. Details were also provided for the different lag times used.
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 97: **Gallagher 2011: Evaluation of Cancer Outcomes**

Study Citation:	Gallagher, LG; Vieira, VM; Ozonoff, D; Webster, TF; Aschengrau, A (2011). Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: Reanalysis of a case-control study using a modified exposure assessment Environmental Health: A Global Access Science Source, 10 47
Data Type:	Perc breast cancer adult women cumulative exposure ever-exposed 19-year latency-Cancer
HERO ID:	3490321

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Study subjects were participants in two prior case-control studies and were permanent residents in eight towns in the Cape Cod region of MA. Incident breast cancer cases between 1983-1993 were obtained from the Massachusetts Cancer Registry. 1,192 cases were identified. Exclusion criteria are detailed, and participation rates are reported at the various stages of the study. Demographic characteristics are discussed (quantitative data are not presented for all covariates), but covariates were similar and there is no indication of biased sampling.
	Metric 2: Attrition	Medium	× 0.4	0.8	There was moderate exclusion of subjects, but exclusions were adequately addressed. Overall 1,192 cases and 7,869 controls were selected for inclusion in the analysis. However, subjects were excluded if they could not be located or contacted (87 cases and 1,125 controls), did not meet residential eligibility criteria (31 cases and 4,404 controls), consent could not be obtained from their physician or subject refused to participate (136 cases and 338 controls), or had unknown PCE exposure status (8 cases and 34 controls). The majority of excluded controls were identified using random digit dialing. Additionally, another 666 eligible random digit dial controls were not interviewed after the target number of control interviews was reached. An additional 19 subjects (10 cases, 9 controls) were excluded because they had missing information that was needed for the EPANET exposure model. 920 cases and 1293 controls were ultimately included in analysis.

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Study Citation:	Gallagher, LG; Vieira, VM; Ozonoff, D; Webster, TF; Aschengrau, A (2011). Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: Reanalysis of a case-control study using a modified exposure assessment Environmental Health: A Global Access Science Source, 10 47
Data Type:	Perc breast cancer adult women cumulative exposure ever-exposed 19-year latency-Cancer
HERO ID:	3490321

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Controls were selecting using multiple methods during the same timeframe to ensure efficient identification of participants of both vital statuses and various ages. Living controls 64 years old and younger were selected by random digit dialing and controls 65 years old and older were randomly selected from Medicare records. Deceased controls were randomly selected from records of deceased residents of the eight towns provided by the Massachusetts Bureau of Health, Statistics, Research, and Evaluation. Authors do not provide a table of results indicating case and control demographics, but they describe controls as "demographically similar to cases" and state that participants were "predominantly white, over 60 years old, postmenopausal at diagnosis or index year, and having attained an educational level of at least 12 years." Occupational perc exposures and bathing habits were similar between the two groups.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Exposure was assessed using the same method for all participants. Authors used a modified version of EPANET to model each town's water distribution system, geocode each residents address, and map each residence to a node in the pipe network. A perc/vinyl resin liner was applied to some pipes in 1980 and the model considered leaching rates, distribution directions, flow rates, and other variables that would impact the magnitude of residents' perc exposures. Residential histories were considered in this cumulative exposure assessment. Authors also conducted validation testing against the manual model used in their previous studies as well as a small number of historical measurements taken in 1980. Statistical analysis considered ever-never exposure as well as quartiles of exposure at 9 latency periods (0, 5, 7, 9, 11, 13, 15, 17 and 19 years) and each leaching rate constant (0.025, 0.75, 2.25, 5 and 10 years). Duration of exposure was examined in intervals of 1-5 years, 5-10 years, and greater than 10 years. The referent group for all analyses was always comprised of women who were unexposed during the entire study period.

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Study Citation:	Gallagher, LG; Vieira, VM; Ozonoff, D; Webster, TF; Aschengrau, A (2011). Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: Reanalysis of a case-control study using a modified exposure assessment Environmental Health: A Global Access Science Source, 10 47
Data Type:	Perc breast cancer adult women cumulative exposure ever-exposed 19-year latency-Cancer
HERO ID:	3490321

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	For some cohorts, ever-never exposure assessments used only two levels of exposure. For othe cohorts, peak exposure analyses were conducted comparing (1) 4 exposure levels to the never-exposed reference, <median, >median, >75th percentile and >90th percentile or (2) 3 exposure levels to the never-exposed reference, 1-5 years exposure, 5-10 years exposure, 10+ years exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure was retrospectively determined through the diagnosis date for cases or a randomly assigned year for controls, so exposure preceded cancer incidence for cases. Several duration periods (up to 15 years) and latencies (up to 19 years) were considered.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cases and controls were followed for the same amount of time. Cancer cases were obtained from the Massachusetts Cancer Registry, and there is no indication of poor validity.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	A description of all statistical analyses is reported in detail in the methods section. Depending on cohort, some differences were noted. Quantitative results were reported for all latency periods as ORs and 95% CIs but not in a way that would allow for detailed extraction. Categorical cumulative exposure duration analyses are reported for all latency periods and report the number of cases and controls included in each analysis. Both crude and adjusted model results are presented. The number of cases and controls included in each latency analysis is not indicated. Peak exposure and exposure duration analyses were not reported in results tables and only some noteworthy results were quantified in the in-text discussion.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Gallagher, LG; Vieira, VM; Ozonoff, D; Webster, TF; Aschengrau, A (2011). Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: Reanalysis of a case-control study using a modified exposure assessment Environmental Health: A Global Access Science Source, 10 47
Data Type:	Perc breast cancer adult women cumulative exposure ever-exposed 19-year latency-Cancer
HERO ID:	3490321

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The study included females only by design. Age, and race were not considered as potential confounding variables in the statistical model, but participants were stated to be primarily white women over the age of 60. Education was tested for model inclusion, but was ultimately removed as it did not alter the estimates sufficiently to be included. The final statistical model included: family history of breast cancer, personal history of prior breast cancer, age at first live birth or stillbirth, occupational PCE exposure, and study of origin (first study or second expanded study).
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Trained personnel conducted interviews to obtain demographic characteristics, risk factors for breast cancer, occupational exposure to PCE and a 40- year residential history. No further details are provided about the interview or study questionnaire. This method used for confounder assessment is an insensitive method of unknown validity.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures are not anticipated in this general population study.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design was appropriate for the research question, and appropriate statistical analyses (i.e., multivariate logistic regression) were conducted.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	920 cases and 1293 controls should be sufficient to detect an effect. Authors do not specifically discuss statistical power, and although none of the results achieved statistical significance, a number of results were borderline statistically significant.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Statistical methods used to calculated odds ratios are described in sufficient detail to reproduce these analyses with the number of subject and incidence of breast cancer in each exposure category provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratios (OR) and 95% confidence intervals calculated using multiple logistic regression and adjusted for covariates. The model building process was appropriate, and model assumptions were met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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Study Citation:	Gallagher, LG; Vieira, VM; Ozonoff, D; Webster, TF; Aschengrau, A (2011). Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: Reanalysis of a case-control study using a modified exposure assessment Environmental Health: A Global Access Science Source, 10 47
Data Type:	Perc breast cancer adult women cumulative exposure ever-exposed 19-year latency-Cancer
HERO ID:	3490321

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 98: **Desrosiers et al. 2015: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Desrosiers, TA; Lawson, CC; Meyer, RE; Stewart, PA; Waters, MA; Correa, A; Olshan, AF (2015). Assessed occupational exposure to chlorinated, aromatic and Stoddard solvents during pregnancy and risk of fetal growth restriction Occupational and Environmental Medicine, 72(8), 587-593
Data Type:	Cohort_Childhood_Neurodevelopment_Perc_TCE_DCM_CCL4-Growth (early life) and Development
HERO ID:	3490931

Domain	Metric	Rating†	MWF*	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	High	× 0.4	0.4	Participants are a subset of the National Birth Defects Prevention Study, which is a US Centers for Disease Control case-control study for major congenital malformations. Participants taken from the controls (live births with no malformation) born 1997-2002 identified based on birth certificates and hospital records. Inclusion/exclusion criteria and participation rates provided and reasonable.
Metric 2:	Attrition	Medium	× 0.4	0.8	Moderate attrition: 68% of eligible mothers of control infants participated in the telephone interview. Minimal exclusion of participants due to pregestational diabetes (20) or multiples (97).
Metric 3:	Comparison Group	High	× 0.2	0.2	Differences in maternal age and education considered in logistic regression models (includes maternal age, education, BMI, smoking).
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	Self-reported job histories (computer-assisted telephone interview) were used by industrial hygienists and occupational epidemiologists, who developed solvent-specific job databases to assess probability of occupational exposure. No detailed employment records were reviewed. Exposed defined as holding any job with an exposure probability >0 during pregnancy or the month proceeding conception. Participants were considered exposed or unexposed to chlorinated solvents. It was shown that participants were exposed to chlorinated solvents other than Perc.
Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	Insufficient distribution of exposure to detect an exposure-response relationship. Individual chemical exposure (probability >0) presented by outcome. Due to correlation between solvents of the same class risk estimates were assessed only for a group of chlorinated solvents (carbon tetrachloride, chloroform, methylene chloride, perchloroethylene, trichloroethylene, and 1,1,1-trichloroethane).

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Study Citation:	Desrosiers, TA; Lawson, CC; Meyer, RE; Stewart, PA; Waters, MA; Correa, A; Olshan, AF (2015). Assessed occupational exposure to chlorinated, aromatic and Stoddard solvents during pregnancy and risk of fetal growth restriction Occupational and Environmental Medicine, 72(8), 587-593
Data Type:	Cohort_Childhood_Neurodevelopment_Perc_TCE_DCM_CCL4-Growth (early life) and Development
HERO ID:	3490931

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Occupational exposure assessed from one month prior to conception throughout gestation. Weight determined at birth. Temporality is established and should cover the relevant window, although no stratification given with respect to sensitive developmental periods.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Fetal growth restriction was quantified using well established methods, namely by determining infants that were small for gestational age (SGA, <10th percentile of birthweight by gestational age in a national reference). Specific for sex, parity, and race for infants >37 weeks gestation.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	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	Adjusted for maternal age, education, race, BMI, tobacco and alcohol use, multivitamins, pregnancy intention, number of previous live births, gestational diabetes, infant sex and maternal residence. Several of these factors varied greatly with relation to birthweight (outcome).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Less established method used to assess confounders (i.e., all covariates assessed from a phone interview) without presenting data on method validation, but little to no evidence method had poor validity and little to no evidence of confounding.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	85% of exposed had mixed exposure (largely with other chlorinated solvents). Estimated effects based on solvent class. Methylene chloride had a 98% correlation with trichloroethane exposure. No direct evidence of an unbalanced provision of additional co-exposures across the primary study groups.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate study design (i.e. cohort) and use of statistical methods (i.e. regression) were employed to analyze the association between solvent classes and SGA. For chemical-specific analyses, prevalence of SGA and non-SGA in mothers exposed to CCl4, DCM, PCE, TCE was reported.

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Study Citation:	Desrosiers, TA; Lawson, CC; Meyer, RE; Stewart, PA; Waters, MA; Correa, A; Olshan, AF (2015). Assessed occupational exposure to chlorinated, aromatic and Stoddard solvents during pregnancy and risk of fetal growth restriction Occupational and Environmental Medicine, 72(8), 587-593
Data Type:	Cohort_Childhood_Neurodevelopment_Perc_TCE_DCM_CCL4-Growth (early life) and Development
HERO ID:	3490931

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants are adequate to detect an effect for participants exposed to PCE, TCE, and DCM. There were 10 and 7 infants with SGA and exposure to PCE and TCE, respectively. DCM had slightly more exposed participants with SGA (n=15). Insufficient number of subjects with CCl4 exposure and SGA (n=1).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of logistic regression sufficient for chlorinated solvent analysis as a group. No statistical analysis conducted on single chemical exposure.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression used to estimate ORs for group of chlorinated solvents. Rationale for variable selection is stated. Model assumptions do not appear to be violated. No statistical analysis conducted on single chemical exposure.
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‡			Unacceptable⋆⋆		1.7	
Extracted			No			

⋆⋆ Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 99: **Zhao et al. 2016: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Zhao, JH; Duan, Y; Wang, YJ; Huang, XL; Yang, GJ; Wang, J (2016). The influence of different solvents on systemic sclerosis: An updated meta-analysis of 14 case-control studies 22(5), 253-259
Data Type:	Zhao_Perc_exposed workers_metaanalysis_SSc-Hematological and Immune
HERO ID:	3503809

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.667	1.33	Selection criteria for cases and controls was rated according to the Newcastle-Ottawa Scale (4 stars is the highest, 1 star lowest. A study was issued 4 stars if met all of the following criteria: adequacy of case definition, representativeness of the cases, selection of controls, and definition of controls). A total of 5 studies evaluated TCE exposures, of which 2 also evaluated perc exposure. In addition, 1 study evaluated perc exposure and not TCE. Among the 5 studies with TCE data, 2 received the highest rating (4 stars), 2 studies received 2 stars, and 1 study received 1 star for selection. Among the 3 studies with perc data, 1 received the highest rating (4 stars), and 2 studies received 2 stars. Overall, some key elements of the study design were not present for 4 studies, but available information indicates a low risk of selection bias.
	Metric 2: Attrition	Not Rated	NA	NA	N/A for meta-analysis (participation rate was not reported).

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Study Citation:	Zhao, JH; Duan, Y; Wang, YJ; Huang, XL; Yang, GJ; Wang, J (2016). The influence of different solvents on systemic sclerosis: An updated meta-analysis of 14 case-control studies 22(5), 253-259
Data Type:	Zhao_Perc_exposed workers_metaanalysis_SSc-Hematological and Immune
HERO ID:	3503809

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 3:	Comparison Group	Medium	× 0.333	0.67	Comparability for cases and controls was rated according to the Newcastle-Ottawa Scale. A study was issued a maximum of 2 stars: 1 for the most important factor for comparability and 1 for any additional factor. The study authors selected matching by age and sex as the most important factor and matching by smoking and/or residency area as the other important factors. A total of 5 studies evaluated TCE exposures, of which 2 also evaluated perc exposure. In addition, 1 study evaluated perc exposure and not TCE. Among the 5 studies with TCE data, 3 studies received 2 stars, 1 studies received 1 star, and 1 study received zero stars for comparability. Among the 3 studies with perc data, 1 study receive 2 stars, 1 study received 1 star, and 1 study received zero stars. Since 4 of 6 studies matched by at least the most important factor, an overall rating of medium is assigned for this metric.
Domain 2: Exposure Characterization						

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Study Citation:	Zhao, JH; Duan, Y; Wang, YJ; Huang, XL; Yang, GJ; Wang, J (2016). The influence of different solvents on systemic sclerosis: An updated meta-analysis of 14 case-control studies 22(5), 253-259
Data Type:	Zhao_Perc_exposed workers_metaanalysis_SSc-Hematological and Immune
HERO ID:	3503809

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A total of 5 studies evaluated TCE exposures, of which 2 also evaluated perc exposure. In addition, 1 study evaluated perc exposure and not TCE. Exposure for cases and controls was rated according to the Newcastle-Ottawa Scale. The exposure item is rated over a maximal number of 3 stars, 1 for ascertainment of exposure, 1 for same method of ascertainment for cases and controls, and 1 if there was the same nonresponse rate in cases and controls. Among the 5 studies with TCE data, 4 studies received 2 stars and 1 study received 1 stars for exposure. Among the 3 studies with perc data, 1 study receive 2 stars and 2 studies received 1 star. In addition, exposure was assessed with a JEM for 1 study, experts in 3 studies , and self-reported in 2 study. High likelihood of for misclassification of exposure based on professional judgement or self-reporting in 4 of 6 studies.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Study reports 2 levels of exposure: exposed vs. unexposed.
	Metric 6:	Temporality	Low	× 0.4	1.2	The temporality of exposure and outcome is uncertain. There was only 1 study that evaluated TCE and perc exposure (Goldman 1996) reported on the duration of exposure.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed using well-established methods: in the 6 studies with TCE and/or perc data, SSc was diagnosed according to definitions in the 1980 revision of the American College of Rheumatology criteria or the consultant's criteria.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Assessed publication bias for meta-analysis. Publication bias was 1st observed by visual inspection of a funnel plot, then assessed with a Beggs test. Results from the Beggs test did not reveal any statistical evidence of publication bias. In addition, all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of cases and controls reported for each analysis.

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Study Citation:	Zhao, JH; Duan, Y; Wang, YJ; Huang, XL; Yang, GJ; Wang, J (2016). The influence of different solvents on systemic sclerosis: An updated meta-analysis of 14 case-control studies 22(5), 253-259
Data Type:	Zhao_Perc_exposed workers_metaanalysis_SSc-Hematological and Immune
HERO ID:	3503809

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 1	1	Explicit considerations were made for potential confounders through the use of matching on important factors (age and sex) in 4 of the 6 studies with TCE and/or perc data.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	No description was provided on the covariate characterization in the studies included in meta-analysis.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	No description was provided on co-exposure confounding in meta-analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., case-control for assessment of a rare disease in relation to TCE and perc exposure) and appropriate statistical methods (i.e., Mantel-Haenszel random-effect model) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls are adequate to detect an effect in the exposed population. The perc studies included 714 cases and 2479 controls. The TCE studies included 1029 cases and 2884 controls.
	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	Mantel-Haenszel random-effect model was used to combine pooled ORs if studies indicated heterogeneity, and then by fixed effects model under the condition of the heterogeneity (tested non-significant). 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‡			Medium		1.8	
Extracted			Yes			

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Study Citation:	Zhao, JH; Duan, Y; Wang, YJ; Huang, XL; Yang, GJ; Wang, J (2016). The influence of different solvents on systemic sclerosis: An updated meta-analysis of 14 case-control studies 22(5), 253-259
Data Type:	Zhao_Perc_exposed workers_metaanalysis_SSc-Hematological and Immune
HERO ID:	3503809

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 100: **Dow 1976: Evaluation of Irritation Outcomes**

Study Citation:	Dow Chemical Company (1976). Repeated insult patch test on fabrics treated with golden CS solvent - perchloroethylene
Data Type:	Patch test_perc-Irritation
HERO ID:	4214209

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Methods of recruitment were not reported. It was noted that 58 panelists from St. Petersburg, Fl area were enrolled in the study.
	Metric 2:	Attrition	High	× 0.4	0.4	Minimal attrition: 5 of the 58 (9%) dropped out for personal reasons, but there was no indication of when they dropped out (i.e., before the test began or after it began). Individual scores indicate that subjects dropped out before and after study began (3 apparently before and 2 during), but there results do not indicate that they dropped out due to excessive irritation.
	Metric 3:	Comparison Group	High	× 0.2	0.2	One part was stated to be untreated. So all subjects would have been their own control.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A less-established method was used and no method validation was conducted against well-established methods, but there was little to no evidence that the method had poor validity and little to no evidence of significant exposure misclassification. Specifically, it was noted that six patches (i.e., test materials) were applied to the upper arms. Test materials were untreated material or material treated with perchloroethylene or a new drycleaning fluid (perchloroethylene is the principal ingredient). The test patch consisted of a square of the test fabric. No specific level of exposure or ascertainment of chemical presence on test materials was provided. No information was provided on how recent the samples had been treated.
	Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	There is no information to indicate that the treated material had any remaining perc present when applied in testing.
	Metric 6:	Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure and outcome (i.e. the exposure precedes the disease).
Domain 3: Outcome Assessment						

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Study Citation: Dow Chemical Company (1976). Repeated insult patch test on fabrics treated with golden CS solvent - perchloroethylene
Data Type: Patch test_perc-Irritation
HERO ID: 4214209

Domain		Metric	Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Insult patch test is a well-established method for assessing sensitization and allergic response. Patch site was scored by an experienced staff member just prior to the patch applications at the second through the ninth visit and on the tenth visit. The challenge application site was scored at 48 and 96 hours after application. Scale was provided, but there is no indication that the outcome assessors were blind to the treatment.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Individual scores were provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.667	1.33	No covariates were considered, but subjects would have been their own control so would have accounted for differences in potential confounders between the subjects.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates were not assessed.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	There are no co-exposures that would have been present to bias the results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	Appropriate prospective cohort study design chosen for assessing irritative properties of test materials arising from chronic exposure.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	Power should have been sufficient if there was any irritation related to exposure to test materials.
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	No data analyses were conducted. Authors provided a brief summary of the results, which is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Not Rated	NA	NA	No statistics were conducted.
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‡			Unacceptable**		1.8	

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Study Citation:	Dow Chemical Company (1976). Repeated insult patch test on fabrics treated with golden CS solvent - perchloroethylene
Data Type:	Patch test_perc-Irritation
HERO ID:	4214209

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Extracted		No			

** Consistent with our *Application of Systematic Review in TSCARisk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency.

⋆ 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 101: **Aschengrau et al. 1993: Evaluation of Cancer Outcomes**

Study Citation:	HSIA (Halogenated Solvents Industry Alliance) (1993). Initial submission: Cancer risk and tetrachloroethylene (pce) contaminated drinking water in Massachusetts with cover letter dated 032493
Data Type:	perc leukemia adults >90% exposure 5-yr latency-Cancer
HERO ID:	4214428

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Study subjects were permanent residents in five towns in the Cape Cod region of MA. Incident bladder cancer, kidney cancer, and leukemia cases between 1983-1986 were obtained from the Massachusetts Cancer Registry. 79 bladder cancer cases, 42 kidney cancer cases, and 44 leukemia cases were identified. Exclusion criteria are detailed, and participation rates are reported at the various stages of the study. Demographic characteristics presented in Table 3, and differences were controlled for in statistical analyses.

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Study Citation:	HSIA (Halogenated Solvents Industry Alliance) (1993). Initial submission: Cancer risk and tetrachloroethylene (pce) contaminated drinking water in Massachusetts with cover letter dated 032493
Data Type:	perc leukemia adults >90% exposure 5-yr latency-Cancer
HERO ID:	4214428

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 2:	Attrition	Medium	× 0.4	0.8	There was moderate exclusion, but acceptable reasons (individuals could not be contacted, did not meet eligibility criteria, doctor refused to participate) for exclusions were detailed. 44 incident leukemia cases were identified in the Massachusetts Cancer Registry in 1983-1986; 35 were interviewed, and 34 were ultimately included in the statistical analyses. Outcome-specific details for controls were not reported, but overall 611 living controls >65 years old and 918 deceased controls were identified., though only 464 and 732, respectively, were interviewed. 737 controls were included in the leukemia-specific analyses. 79 incident bladder cancer cases were identified in the Massachusetts Cancer Registry in 1983-1986; 63 were interviewed, and 61 were ultimately included in the statistical analyses. Outcome-specific details for controls were not reported, but overall 611 living controls >65 years old and 918 deceased controls were identified., though only 464 and 732, respectively, were interviewed. 852 controls were included in the bladder cancer-specific analyses. 42 incident kidney cancer cases were identified in the Massachusetts Cancer Registry in 1983-1986; 35 were interviewed and ultimately included in the statistical analyses. Outcome-specific details for controls were not reported, but overall 611 living controls >65 years old and 918 deceased controls were identified., though only 464 and 732, respectively, were interviewed. 777 controls were included in the kidney cancer-specific analyses.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were selected using multiple methods during the same timeframe to ensure efficient identification of participants of both vital statuses and various ages. Living controls 64 years old and younger were selected by random digit dialing and controls 65 years old and older were randomly selected from Medicare records. Deceased controls of similar age were randomly selected from death certifications of Upper Cape residents who had died subsequent to 1983. Demographic characteristics presented in Table 3, and differences were controlled for in statistical analyses.
Domain 2: Exposure Characterization						

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Study Citation:	HSIA (Halogenated Solvents Industry Alliance) (1993). Initial submission: Cancer risk and tetrachloroethylene (pce) contaminated drinking water in Massachusetts with cover letter dated 032493
Data Type:	perc leukemia adults >90% exposure 5-yr latency-Cancer
HERO ID:	4214428

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was assessed using the same method for all participants, though a number of assumptions were required, and validation was not reported. Perc exposure was estimated using a model developed by Webler and Brown to predict the dose delivered to individual households by the public water distribution system. Authors created maps that identified affected pipes (those that had a perc/vinyl resin liner applied in 1980, as reported by the water utility companies), determined water flow, and to plotted participants' households. Pipe installation dates, length, location, and load were also considered. Residential histories were factored into the cumulative exposure assessment. Exposure was analyzed in two different ways: (1) considering ever vs. never exposure and (2) unexposed, low exposure, and high exposure. Additional analyses also explored the effect of latent exposures, considering a 5-year latency period for leukemia and a 15-year latency period for bladder and kidney cancers. The reference group was always the unexposed participants.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Some exposure analyses were assessed using 3 levels: unexposed, low (through the 90th percentile of exposure), and high exposure (>90th percentile).; others were assessed using 2 levels: ever vs. never exposed.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality of exposure and outcome is established, but it is unclear whether the exposures fall within the relevant window. Exposure was retrospectively determined through the diagnosis date for cases or the index year for controls, and only exposures occurring before diagnosis/index year were considered. Leukemia analyses considered both 0- and 5-year latency periods. Bladder and kidney cancer analyses considered only a 0-year latency period, as there was an insufficient number of cases to conduct the 15-year latency period analyses.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Incident bladder cancer, kidney cancer, and leukemia cases in 1983-1986 were obtained from the Massachusetts Cancer Registry, which was reported to be nearly complete for the specific cancers and geographic areas under study.

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Study Citation:	HSIA (Halogenated Solvents Industry Alliance) (1993). Initial submission: Cancer risk and tetrachloroethylene (pce) contaminated drinking water in Massachusetts with cover letter dated 032493
Data Type:	perc leukemia adults >90% exposure 5-yr latency-Cancer
HERO ID:	4214428

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 8: Reporting Bias	Low	× 0.333	1.0	Analyses are outlined in the methods section, and quantitative results are reported for most planned analyses. The number of cases and controls included in each analysis is included in the results table. Dichotomous (ever-never analyses) and categorical (unexposed, low, high) analyses with and without latency periods are reported, though bladder and kidney cancer case numbers were insufficient to conduct the 15-year latency period analyses. Crude ORs and 95% CIs are reported in Table 4. A number of analyses had sufficient case numbers (as defined by the authors in the methods section) to conduct adjusted analyses, but these results were not reported in full. Adjusted results for the ever-never exposure and >90 percentile exposure groups in the 5-year latency period are presented in-text for leukemia. Adjusted results for the low exposure level were not reported for the 5-year or 0-year latency periods for leukemia. Adjusted results were not presented for the low exposure group in the 0-year latency period analyses for either bladder or kidney cancer.
Domain 4: Potential Counfounding/Variable Control					
	Metric 9: Covariate Adjustment	High	× 0.5	0.5	Control sampling stratified by age, gender, and year of death (if applicable). All statistical analyses considered sex, age at diagnosis or index year, vital status at interview, educational level, and occupational exposure to PCE, benzene, and other solvents. Leukemia analyses additionally adjusted for prior medical treatment with irradiation. Smoking rates appear to differ between some groups, but this is not factored into the analysis. Participants were described as "predominantly white [and] elderly." Distributions of covariates for cases and outcome-specific control groups are reported in Table 3. Leukemia analyses additionally adjusted for prior medical treatment with irradiation. Bladder cancer analyses additionally adjusted for usual number of cigarettes smoked, history of urinary tract infection of stone, and history of cancer-associated job. Kidney cancer analyses additionally adjusted for usual number of cigarettes smoked and history of urinary tract infection of stone.

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Study Citation:	HSIA (Halogenated Solvents Industry Alliance) (1993). Initial submission: Cancer risk and tetrachloroethylene (pce) contaminated drinking water in Massachusetts with cover letter dated 032493
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Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Trained personnel conducted interviews to obtain demographic characteristics, confounding variables such as smoking and occupational exposure to PCE, and a 40- year residential history. No further details are provided about the interview or study questionnaire.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Authors discuss other suspected environmental contamination in the Upper Cape region in the introduction, but there is no evidence to suggest these potential co-exposures would be unbalanced across the various groups in this analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design was appropriate for the research question, and appropriate statistical analyses (i.e., multivariate logistic regression) were conducted.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Authors do not specifically discuss statistical power. Although the case numbers in specific analyses are small, statistically significant results were achieved in some of the analyses with the smallest number of cases (e.g., adjusted analysis of high exposure vs. unexposed after 5-year latency for leukemia) so the number of cases appears to be adequate.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Statistical methods are described in sufficient detail to reproduce these analyses.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The model building process was appropriate, and 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		1.8	
Extracted			Yes			

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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