United States
Environmental Protection Agency

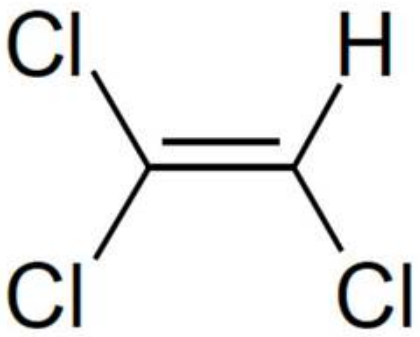
Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for Trichloroethylene

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Data

CASRN: 79-01-6



November 2020

Table Listing

1 **Ruijten et al. 1991: Evaluation of Neurological/Behavior Outcomes** . . . 3
2 **Greenland et al. 1994: Evaluation of Cancer Outcomes** . . . 6
3 **Wang et al. 2009: Evaluation of Cancer Outcomes** . . . 10
4 **Antilla et al. 1995: Evaluation of Cancer Outcomes** . . . 14
5 **Chia et al. 1996: Evaluation of Reproductive Outcomes** . . . 18
6 **Hansen et al. 2001: Evaluation of Cancer Outcomes** . . . 21
7 **Miligi et al. 2006: Evaluation of Cancer Outcomes** . . . 25
8 **Lagakos et al. 1986: Evaluation of Cancer Outcomes** . . . 28
9 **Lagakos et al. 1986: Evaluation of Respiratory Outcomes** . . . 31
10 **Morgan et al. 1998: Evaluation of Cancer Outcomes** . . . 34
11 **Moore et al. (2010): Evaluation of Cancer Outcomes** . . . 37
12 **Seiji et al. 1990: Evaluation of Genotoxicity Outcomes** . . . 41
13 **Boice et al. 1999: Evaluation of Cancer Outcomes** . . . 43
14 **Radican et al. 2008: Evaluation of Cancer Outcomes** . . . 47
15 **Gold et al. 2010: Evaluation of Cancer Outcomes** . . . 50
16 **Purdue et al. (2011): Evaluation of Cancer Outcomes** . . . 53
17 **Ikbal et al. 2004: Evaluation of Genotoxicity Outcomes** . . . 57
18 **Green et al. 2004: Evaluation of Renal Outcomes** . . . 59
19 **Axelson et al. 1994: Evaluation of Cancer Outcomes** . . . 62
20 **Brüning et al. 2003: Evaluation of Cancer Outcomes** . . . 65
21 **Goldberg et al. 1990: Evaluation of Growth (Early Life) And Development Outcomes** . . . 67
22 **Hardell et al. 1994: Evaluation of Cancer Outcomes** . . . 69
23 **Pesch et al. 2000: Evaluation of Cancer Outcomes** . . . 72
24 **Raaschou-Nielsen et al. 2003: Evaluation of Cancer Outcomes** . . . 74
25 **Yauck et al. 2004: Evaluation of Growth (Early Life) And Development Outcomes** 77
26 **Zhao et al. 2005: Evaluation of Cancer Outcomes** . . . 80
27 **Nagaya et al. 1989: Evaluation of Genotoxicity Outcomes** . . . 83
28 **Boice et al. (2006): Evaluation of Cancer Outcomes** . . . 86
29 **Nordstrom et al. 1998: Evaluation of Cancer Outcomes** . . . 89
30 **Persson and Fredrikson, 1999: Evaluation of Cancer Outcomes** . . . 93
31 **Charbotel et al. 2006: Evaluation of Cancer Outcomes** . . . 96
32 **Cocco et al. 2010: Evaluation of Cancer Outcomes** . . . 98
33 **Barry et al. 2011: Evaluation of Cancer Outcomes** . . . 101
34 **Windham et al. 2006: Evaluation of Neurological/Behavior Outcomes** . . . 104
35 **Billionnet et al. 2011: Evaluation of Hematological And Immune Outcomes** . . . 108
36 **Billionnet et al. 2011: Evaluation of Respiratory Outcomes** . . . 112
37 **Kalkbrenner et al. 2010: Evaluation of Neurological/Behavior Outcomes** . . . 116
38 **Forand et al. 2012: Evaluation of Cardiovascular Outcomes** . . . 120
39 **Lipworth et al. 2011: Evaluation of Cancer Outcomes** . . . 123
40 **Zhang et al. 2013: Evaluation of Hematological And Immune Outcomes** . . . 127
41 **Charbotel et al. 2013: Evaluation of Cancer Outcomes** . . . 130
42 **Roberts et al. 2013: Evaluation of Neurological/Behavior Outcomes** . . . 133
43 **Bahr et al. 2011: Evaluation of Cancer Outcomes** . . . 136
44 **Bassig et al. 2013: Evaluation of Hematological And Immune Outcomes** . . . 139
45 **Siemiatycki 1991: Evaluation of Cancer Outcomes** . . . 143
46 **Christensen et al. 2013: Evaluation of Cancer Outcomes** . . . 146
47 **Cordier et al. 2012: Evaluation of Growth (Early Life) And Development Outcomes** 149
48 **Gilboa et al. 2012: Evaluation of Growth (Early Life) And Development Outcomes** 153
49 **Goldman et al. 2012: Evaluation of Neurological/Behavior Outcomes** . . . 156
50 **Hansen et al. 2013: Evaluation of Cancer Outcomes** . . . 160
51 **Jia et al., 2012: Evaluation of Hematological And Immune Outcomes** . . . 163

52 **Murata et al. 2010: Evaluation of Neurological/Behavior Outcomes** . . . 166
53 **Neta et al. 2012: Evaluation of Cancer Outcomes** . . . 169
54 **Ruder et al. 2013: Evaluation of Cancer Outcomes** . . . 172
55 **Vermeulen et al. 2012: Evaluation of Renal Outcomes** . . . 175
56 **Heineman et al. 1994: Evaluation of Cancer Outcomes** . . . 182
57 **Vizcaya et al. 2013: Evaluation of Cancer Outcomes** . . . 186
58 **Vlaanderen et al. 2013: Evaluation of Cancer Outcomes** . . . 189
59 **Zungun et al., 2013: Evaluation of Neurological/Behavior Outcomes** . . . 193
60 **Zungun et al., 2013: Evaluation of Hepatic Outcomes** . . . 196
61 **Hosgood et al. 2012: Evaluation of Hematological And Immune Outcomes** . . . 199
62 **Cocco et al. 2013: Evaluation of Cancer Outcomes** . . . 203
63 **Morales-Suárez-Varela et al. 2013: Evaluation of Cancer Outcomes** . . . 206
64 **Ruckart et al. 2013: Evaluation of Growth (Early Life) And Development Outcomes** 209
65 **Ruckart et al. 2013: Evaluation of Cancer Outcomes** . . . 212
66 **Heck et al. 2013: Evaluation of Cancer Outcomes** . . . 215
67 **Seidler et al. 2007: Evaluation of Cancer Outcomes** . . . 219
68 **von Ehrenstein et al. 2014: Evaluation of Neurological/Behavior Outcomes** . . . 222
69 **Bove et al. 2014: Evaluation of Cancer Outcomes** . . . 225
70 **Bove et al. 2014: Evaluation of Neurological/Behavior Outcomes** . . . 228
71 **Talibov et al. 2014: Evaluation of Cancer Outcomes** . . . 231
72 **Mattei et al. 2014: Evaluation of Cancer Outcomes** . . . 236
73 **Brender et al. 2014: Evaluation of Growth (Early Life) And Development Outcomes** 239
74 **Ruckart et al. 2014: Evaluation of Reproductive Outcomes** . . . 242
75 **Singthong et al. 2015: Evaluation of Respiratory Outcomes** . . . 246
76 **Singthong et al. 2015: Evaluation of Genotoxicity-Micronucleus Frequency Outcomes** . . . 249
77 **Singthong et al. 2015: Evaluation of Skin And Connective Tissue Outcomes** . . . 252
78 **Dosemeci et al. 1999: Evaluation of Cancer Outcomes** . . . 255
79 **Silver et al. 2014: Evaluation of Renal Outcomes** . . . 258
80 **Silver et al. 2014: Evaluation of Neurological/Behavior Outcomes** . . . 261
81 **Silver et al. 2014: Evaluation of Cancer for all cancers outcomes other than testicular cancer Outcomes** . . . 264
82 **Silver et al. 2014: Evaluation of Cancer for testicular cancer outcome Outcomes** . 267
83 **Bove et al. 2014: Evaluation of Neurological/Behavior Outcomes** . . . 270
84 **Swartz et al. 2015: Evaluation of Growth (Early Life) And Development Outcomes** 273
85 **Chaigne et al 2015: Evaluation of Hematological And Immune Outcomes** . . . 276
86 **Alanee et al. 2015: Evaluation of Cancer Outcomes** . . . 279
87 **Talbott et al 2015: Evaluation of Neurological/Behavior Outcomes** . . . 282
88 **Bassig et al. 2016: Evaluation of Hematological And Immune Outcomes** . . . 286
89 **Bove et al. 1995: Evaluation of Growth (Early Life) And Development Outcomes** 289
90 **Bulka et al. 2016: Evaluation of Cancer Outcomes** . . . 292
91 **Carton et al. 2017: Evaluation of Cancer Outcomes** . . . 295
92 **Purdue et al. 2016: Evaluation of Cancer Outcomes** . . . 298
93 **Ruckart et al. 2015: Evaluation of Cancer Outcomes** . . . 300
94 **Hadkhale et al. 2017: Evaluation of Cancer Outcomes** . . . 303
95 **Buhagen et al. 2016: Evaluation of Cancer Outcomes** . . . 306
96 **Montani et al. 2015: Evaluation of Respiratory Outcomes** . . . 308
97 **Zhao et al. 2016: Evaluation of Hematological And Immune Outcomes** . . . 313
98 **Wright et al. 2017: Evaluation of Cardiovascular Outcomes** . . . 318
99 **Thiokol Corp 1986: Evaluation of Genotoxicity Outcomes** . . . 321

Table 1: **Ruijten et al. 1991: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Ruijten, MW; Verberk, MM; Sallé, HJ (1991). Nerve function in workers with long term exposure to trichloroethene British Journal of Industrial Medicine, 48(2), 87-92
Data Type:	Ruijten_TCE_exposed workers_sensory NCV-Neurological/Behavior
HERO ID:	65298

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Male printers exposed to TCE for 6 years or more and non-exposed workers from the same printing works were contacted. It was noted that 68 workers agreed to participate, but it was not reported how many were asked from each group (exposed vs control). Exclusion criteria were reported.
	Metric 2:	Attrition	Low	× 0.4	1.2	68 initial volunteers; 7 excluded due to other risk factors for neuropathy or alcohol consumption >50 glasses per week. Certain endpoints evaluated a lower number of subjects to "strict criteria" for acceptable measures. The masseter reflex was for 14 exposed and 15 controls. The sensory nerve analysis was for 20 exposed and 23 controls. It is not clear if other tests used all subjects or not. Additionally, there is no explanation as to why 50 glasses per week was chosen as the cutoff for alcohol consumption, and the "other risk factors for neuropathy" were not explained.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Cases and controls matched based on physical job activity, education, nationality, and age. They had all been employed for at least 6 years at the print works.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Periodic exposure measurements at plant from 1966-1981 (methods not reported); exposure over past 3 years was estimated based on previous measurements and ":half-time" use without other major changes in processes. All exposed subjects worked in the printing process where up to 3 years prior to investigation the ink used contained TCE as the solvent.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Cumulative exposure was calculated and evaluated on a continuous basis. Range of cumulative exposures were not reported. Results were also evaluated as just exposed compared to unexposed. Exposure data did not allow for differentiation of exposure with respect to different jobs.
	Metric 6:	Temporality	High	× 0.4	0.4	All subjects employed 6 years or longer.

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Data Type: Ruijten_TCE_exposed workers_sensory NCV-Neurological/Behavior
HERO ID: 65298

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Measurements of autonomic nerve function, trigeminal nerve function, and peripheral nerve function were completely described and were standard methods.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Effect estimates reported with 90% CIs (not 95% CIs); mean values only reported for controls with exposed results reported as difference from controls with 90% CI. Although title indicates number of subjects, text indicated this was different for at least two of the tests. Results were provided for all measurements noted to be obtained in the methods.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates included age, alcohol consumption, and nationality ; cases and controls were matched. The alcohol consumption was calculated as a cumulative measure (years x glasses/week). The Quetelet-index was included for autonomic nerve parameters and body length and skin temp for peripheral nerve parameters.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	No information was provided on how the covariates were obtained, but it is assumed that the information was obtained via a questionnaire during recruitment.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Study authors state that no exposure to neurotoxicants other than TCE occurred in exposed group. Some controls were exposed occasionally (<1 hr/wk) to terpentine-like organic solvents.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design (comparing exposed to unexposed subjects) and methods is appropriate for the research question regarding the effects of TCE on the nervous system.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The sample size was small (total 31 exposed and 28 controls) with some tests limited to 14-23 subjects, but significant results were observed indicating that it was likely of sufficient power to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis of covariance and multiple linear regression analysis were sufficiently described.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	When data were not normally distributed, the data were log or square root transformed.

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Data Type:	Ruijten_TCE_exposed workers_sensory NCV-Neurological/Behavior
HERO ID:	65298

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure		NA	NA	
	Metric 17: Effect biomarker		NA	NA	
	Metric 18: Method Sensitivity		NA	NA	
	Metric 19: Biomarker stability		NA	NA	
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		1.7	
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 2: **Greenland et al. 1994: Evaluation of Cancer Outcomes**

Study Citation:	Greenland, S; Salvan, A; Wegman, DH; Hallock, MF; Smith, TJ (1994). A case-control study of cancer mortality at a transformer-assembly facility International Archives of Occupational and Environmental Health, 66(1), 49-54
Data Type:	TCE_KidneyCancer-Cancer
HERO ID:	202292

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Participants were restricted to white males that were employed long enough to receive pension benefits (about 10-15 years) at General Electric plant in Pittsfield, MA . Site-specific cancer deaths among active or retired employees were cases. The size of the underlying cohort was not known due to the absence of work history records. The exclusion of non-pensioned employees could play a role if the likelihood of being pensioned is not similar for all types of deaths and/or related to exposure.
	Metric 2: Attrition	Medium	× 0.4	0.8	Outcome and exposure data were largely complete. A number of subjects were excluded from analysis owing to large periods in work history of unrated exposure. Reasons for exclusion were documented. In included subjects, less than 2% of employment periods were based on imputed exposure levels.
	Metric 3: Comparison Group	High	× 0.2	0.2	Cases and controls were recruited from the same population. Controls were noncancer deaths from the same underlying cohort as the cases, with the exclusion of certain diagnoses based on their possible associations with the exposure under study. One hundred and seven noncancer deaths were excluded from the control group The remaining 1202 controls were 78 % circulatory, 10 % respiratory, 6 % injury, and 6 % other causes of death.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	The work histories of cases and controls generated over 1000 job titles from 50 separate departments occupying approximately 100 buildings Materials used and industrial hygiene records were of limited use, because they did not go back far enough in time. Instead, job-exposure matrices were based on interviews on long-term employees and rated by an industrial hygienist. For TCE, exposure was classified as = no exposure; 1 = any exposure.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Reports two levels of exposure (exposed vs. non-exposed).

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Data Type:	TCE_KidneyCancer-Cancer
HERO ID:	202292

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	The temporality of exposure and outcome likely adequate. Criteria for inclusion was employment before 1984 (with subjects stopping work in 1946 or later), and death between 1969 (time when pension records became available) to 1984.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes were assessed based on death certificate diagnoses. A subset of these diagnoses was validated. To reduce the false-positive rate, hospital records for those cancer diagnoses that were reported to have less than a 90 % confirmation rate in a previous study by Percy et al were requested. Among the 1911 subjects with job history, 257 required validation; 75 % of the validation inquiries yielded responses Among the responses, 94 % confirmed or adjusted the cancer diagnosis from the death certificate, with 87 % of diagnoses validated by means such as histology, imaging, surgery, or autopsy Individual diagnoses were corrected according to the validation substudy
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Effects estimates for the outcomes described in the methods section are presented, with confidence intervals (ORs and 95% CIs). However, the number of cases and controls in each cancer/exposure category are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age and death year were entered into all regressions, however, other covariates (not explicitly specified) were entered only when they altered an estimate by 20%. Based on data in the paper (Table 2), there were few differences between cases and controls, so that adjustments did not appreciably affect the results.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Potential confounders were presumably obtained from pension documentation and/or death certificates; however, not all covariates were described in adequate detail.

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Study Citation:	Greenland, S; Salvan, A; Wegman, DH; Hallock, MF; Smith, TJ (1994). A case-control study of cancer mortality at a transformer-assembly facility International Archives of Occupational and Environmental Health, 66(1), 49-54
Data Type:	TCE_KidneyCancer-Cancer
HERO ID:	202292

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Workers were exposed to > 250 chemicals, including 30 potential mutagens or carcinogens. Exposure to 7 substances were evaluated in the study. Co-exposures to other substances (in addition to TCE) that could influence the results were present.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study used an appropriate design (case-control study). Logistic regression analyses were used to address the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants in the study was adequate (512 cases and 1202 controls). However, statistical power may not have been sufficient to detect effects with respect to some site-specific cancer type (but it is unclear which)
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The description of analyses is provided in limited detail to easily facilitate reproduction of the results .For each exposure score and cancer site involving more than eight cases, crude and age-stratified contingency table of the two variables were examined, along with Mantel test for trend. However, it is unclear which cancer sites had more than 8 cases. The selection for covariates selection is reported, but not which covaraites were under consideration .
	Metric 15:	Statistical models	Medium	× 0.2	0.4	A description of the method (logistic regression, Mantel test for trend) used to calculate ORs was presented.
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			

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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

Table 3: **Wang et al. 2009: Evaluation of Cancer Outcomes**

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

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

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

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

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

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

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 4: **Antilla et al. 1995: Evaluation of Cancer Outcomes**

Study Citation:	Anttila, A; Pukkala, E; Sallmen, M; Hernberg, S; Hemminki, K (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons Journal of Occupational and Environmental Medicine, 37(7), 797-806
Data Type:	TCE-Workers_Stomach cancer-Cancer
HERO ID:	630313

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	3974 male and female workers were selected from Finland, were regularly exposed to solvents, and were part of the biological monitoring cohort from 1967-1992. There were 2050 men (avg age 32.8) and 1924 women (avg age 37.7) included in the study. Only persons with full identification were included in the cancer study. Comparison group sourced from Finnish cancer registry between 1967-1992. Person years calculated at time of last referred measurement and ended at time of death, emigration or in 1992 - 26 year follow up only possible for TCE.
	Metric 2:	Attrition	High	× 0.4	0.4	No losses occurred among the originally identified cohort members, however 2 persons died prior to 1967 and were therefore excluded from cancer incidence study; therefor of the 3976 Finnish workers which were monitored, only 3974 were included in this study
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The worker cohort was compared to the corresponding average incidence in Finland. The breakdowns of males and females included in the exposed worker cohort were presented in Table 1. Expected number of cases was calculated by multiplying the gender and age-specific PY in each group by the corresponding average incidence in Finland. Not adjusted for race; study was conducted in Finland on residents in 1967-1992.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	TCE: Urine collected to measure trichloroacetic acid (U-TCA) as a biomarker of TCE exposure from 1965-1982; no method of quantitation described Perc: blood perchloroethylene measured from 1974-1983 DCM: methylene chloride was measured from 1975-1983 via concentration of 1,1,1-trichloroethane from the blood
	Metric 5:	Exposure levels	Low	× 0.2	0.6	exposed vs. unexposed groupings

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Study Citation: Anttila, A; Pukkala, E; Sallmen, M; Hernberg, S; Hemminki, K (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons Journal of Occupational and Environmental Medicine, 37(7), 797-806
Data Type: TCE-Workers_Stomach cancer-Cancer
HERO ID: 630313

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	TCE: Person years calculated at time of last referred measurement and ended at time of death, emigration or in 1992 - 26 year follow up only possible for TCE. No duration of exposure discussed; database only stated to contain measures from workers "regularly exposed to solvent" (medium) Perc & DCM: not reported in this study (low)
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The follow up for death was automatically done in the Population Register Center and cancer incidence data was drawn the average cancer incidence in Finland during the period of observation
	Metric 8:	Reporting Bias	High	× 0.333	0.33	TCE: SIR with 95% CI (high) Perc & DCM: not reported (low)
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Expected number of cases calculated by multiplying gender and age-specific number of person-years in each age group by corresponding average cancer incidence in Finland during the period of observation: further division was made by the time elapsed from fist personal measurement. Standardized incidence ratio (SIR) calculation was not adjusted for race. Indirect evidence SIR was adjusted for age and gender.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	age and sex were collected using personal identification code from the Finnish Institute of Occupational Health. SIRs among men and women were found to not differ
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Halogenated hydrocarbon solvent exposure was assessed namely for TCE, perchloroethylene and DCM metabolites from urine or blood. Not all subjects had measurements of all hydrocarbons taken and the levels were not adjusted for in calculating the SIR.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This is a cohort study analyzing for correlations between exposure to halogenated hydrocarbons by measuring biomarkers and SIR of cancer incidence in an exposed population

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Study Citation:	Anttila, A; Pukkala, E; Sallmen, M; Hernberg, S; Hemminki, K (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons Journal of Occupational and Environmental Medicine, 37(7), 797-806
Data Type:	TCE-Workers_Stomach cancer-Cancer
HERO ID:	630313

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	TCE: Of the 237 cancer cases, 208 were monitored for a urinary product of TCE exposure (U-TCA) and is high enough to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	To calculate the standardized incidence ratio (SIR), the observed number of cases were divided by the expected number.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Statistical significance was tested by Mantel-Haenszel chi squared test assuming a Poisson distribution
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.167	0.17	TCE: levels of trichloroacetic acid in the urine (U-TCA) for TCE from 1965-1982; Perc: tetrachloroethylene (Perc) in the blood from 1974-1983 DCM: 1,1,1-trichloroethane in the blood from 1975-1983 Concentration to exposure relationship not discussed, however as these are biomarkers of exposure to these halogenated hydrocarbons it is assumed they reliable as a measure of exposure
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarker of effect.
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	Method and LOD were not reported
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	It is unknown if samples were collected similarly and the half-lives are known to be short and measures are known to only be representative of a few days. There was no discussion of stability in the matrix; however, differences between exposure levels were assessed (quartiles).
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	No QA measures were described, no known contamination discussed
	Metric 21:	Method requirements	Medium	× 0.167	0.33	Methods of analysis were not described.
	Metric 22:	Matrix adjustment	Low	× 0.167	0.5	Urine specific gravity was measured, but adjusted values were not presented.
Overall Quality Determination‡			Medium		1.9	
Extracted			Yes			

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Study Citation:	Anttila, A; Pukkala, E; Sallmen, M; Hernberg, S; Hemminki, K (1995). Cancer incidence among Finnish workers exposed to halogenated hydrocarbons Journal of Occupational and Environmental Medicine, 37(7), 797-806
Data Type:	TCE-Workers_Stomach cancer-Cancer
HERO ID:	630313

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 5: **Chia et al. 1996: Evaluation of Reproductive Outcomes**

Study Citation:	Chia, SE; Ong, CN; Tsakok, MF; Ho, A (1996). Semen parameters in workers exposed to trichloroethylene Reproductive Toxicology, 10(4), 295-299
Data Type:	Occupational - evaluation of semen parameters - uTCA 75-<100 mg/g creatinine-Reproductive
HERO ID:	630432

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Workers were recruited from an electronics factory in Singapore, using TCE as a degreaser. Men were recruited during a voluntary free medical visit. Response rates (79.8%) are detailed int he current reference. All workers were recruited using the same eligibility criteria and in the same manner.
	Metric 2: Attrition	High	× 0.4	0.4	14 of 99 men were excluded from the analysis.with sufficient explanation. Reasons for exclusion were due to medical histories identifying potential confounding conditions as reported by WHO (e.g., diabetes, STIs, etc.) and clinical conditions related to the testes. Exposure and outcome data were otherwise complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	All men were recruited from the same population. Demographic and lifestyle characteristics were considered in the analysis. Referent group was the lowest quartile of exposure.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Urine was collected on the same day or week of semen collection. Concentrations of TCE urine metabolite tetrachloroacetic acid were measured using spectrophotometry as detailed in Ogata, Takasuka, and Tomokuni (1970). All men's urine was reported to be collected in this way.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	There were four quartiles of exposure used in this logistic regression analysis. These include <25, 25 to < 75, 75 to <100, and 100 mg/g creatinine TCA.
	Metric 6: Temporality	Medium	× 0.4	0.8	Urine and semen samples were collected in the same time window (the same day). Semen parameters are generally sensitive to recent exposure, but there is still some uncertainty on the relevant exposure window. This is not expected to appreciably bias the results.
Domain 3: Outcome Assessment					

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Study Citation: Chia, SE; Ong, CN; Tsakok, MF; Ho, A (1996). Semen parameters in workers exposed to trichloroethylene Reproductive Toxicology, 10(4), 295-299
Data Type: Occupational - evaluation of semen parameters - uTCA 75-<100 mg/g creatinine-Reproductive
HERO ID: 630432

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Semen samples were evaluated blindly at the Infertility Clinic of the Singapore General Hospital within an hour of receiving the sample. Outcomes were reported to be assessed according to WHO semen evaluation guidelines. This is a well-established method of assessing semen parameters.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods were provided in the results. The number of men in each exposure/outcome group is detailed in the tables. There is sufficient information for a full extraction.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Marital status was the only potential confounder included in the final analysis. The study authors state they evaluated potential confounders by "stratified analyses and Mantel-Haenszel procedures." Age, smoking, and alcohol use were considered, but not included in the final model which may impact the results.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed by self-reported questionnaire. This was not reported to be validated, but there is no reason to suggest this is not a valid instrument.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Occupational exposure to other potentially toxic substances was asked in the questionnaire. Co-exposures were not discussed further, and there is no evidence to suggest co-exposures would impact the results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study was designed as a cross-sectional analysis of an occupational cohort. Semen measures and sperm parameters are generally sensitive to recent exposures, making this an appropriate design.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 85 subjects in this analysis. This was sufficient to detect an effect on semen parameters.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Cutoff points for quantiles were described. Other details on the logistic regression analysis were provided such that the analysis could be reproduced.

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Study Citation:	Chia, SE; Ong, CN; Tsakok, MF; Ho, A (1996). Semen parameters in workers exposed to trichloroethylene Reproductive Toxicology, 10(4), 295-299
Data Type:	Occupational - evaluation of semen parameters - uTCA 75-<100 mg/g creatinine-Reproductive
HERO ID:	630432

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression was used to determine the relationship between sperm density and exposure to TCE. Sperm density data was appropriately log transformed to normalize the data.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.167	0.33	This study looked at urinary trichloroacetic acid. This metabolite may be derived from exposure to multiple chlorinated compounds, including TCE.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	Biomarkers of effect were not used.
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	LOD/LOQ not stated. The methods only make reference to a validation paper (Ogata, Takasuke, and Tomokuni, 1970) which is not found in HERO.
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	Storage/stability was not discussed; however, differences between exposure levels could be demonstrated.
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	Samples were stated to be collected in a "plastic bottle that had been pre-washed with deionized water." No other steps or procedures were described to ensure contamination did not occur.
	Metric 21:	Method requirements	Low	× 0.167	0.5	Urinary tetrachloroacetic acid concentrations were determined using spectrophotometry as described in Ogata, Takasuke, and Tomokuni (1970). This paper was not found in HERO, but is available on PubMed.
	Metric 22:	Matrix adjustment	Medium	× 0.167	0.33	Study provides creatinine adjusted values only.
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 =≥ 1 to < 1.7; Medium =≥ 1.7 to < 2.3; Low =≥ 2.3 to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

Table 6: **Hansen et al. 2001: Evaluation of Cancer Outcomes**

Study Citation:	Hansen, J; Raaschou-Nielsen, O; Christensen, JM; Johansen, I; Mclaughlin, JK; Lipworth, L; Blot, WJ; Olsen, JH (2001). Cancer incidence among Danish workers exposed to trichloroethylene Journal of Occupational and Environmental Medicine, 43(2), 133-139
Data Type:	TCE_NHL_Males-Cancer
HERO ID:	630590

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Participants were identified from the Danish National Institute of Occupational Health records on occupational TCE exposures occurring in 275 workplaces since 1947 (urine samples) and 1974 (individual breathing zone samples). A total of 2397 urine samples and 472 breathing zone samples were available. Records indicated measurement concentration, date, and conditions; information about the company where the sample was taken; and demographic information about the individual (name, sex, birth date, address, work tasks). 36% of the urinary TCE measurements and 48% of the air TCE measurements could not be linked using the unique 10-digit personal identification numbers assigned to Danish residents by the Central Population Registry.
	Metric 2: Attrition	Medium	× 0.4	0.8	There was moderate subject loss to follow up. Of 2397 available urine samples and 472 available breathing zone samples, Table 1 indicates that 1519 (63%) urine samples and 245 (52%) breathing zone samples were included. Imputations were made in two situations. (1) Workers with measurements of TCE below the level of detection were assigned a level at one-half of the detection limit. (2) If workers were already employed when the Pension Fund was started (1964), the starting date of the program was considered the starting date at the job (excluded in dose-response analyses stratified by duration).
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Baseline characteristics were not discussed. Site-specific SIRs were calculated from Danish national incidence rates by sex, 5-year age group, and calendar year. Participants were categorized according to period of first known employment, duration of employment, median air concentration, and cumulative exposure.
Domain 2: Exposure Characterization					

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Study Citation: Hansen, J; Raaschou-Nielsen, O; Christensen, JM; Johansen, I; Mclaughlin, JK; Lipworth, L; Blot, WJ; Olsen, JH (2001). Cancer incidence among Danish workers exposed to trichloroethylene Journal of Occupational and Environmental Medicine, 43(2), 133-139
Data Type: TCE_NHL_Males-Cancer
HERO ID: 630590

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was directly measured on an individual basis. Urine measurements were quantified using the Fujiwara method (as described in Christensen 1990, but not detailed in this publication or described as validated). Air sampling methods are not described.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Primary results evaluated cancer incidence in exposed vs. non-exposed individuals only. Additional analyses (of esophogeal cancer and NHL in men, and cervical cancer in women) were performed according to period of first exposure, duration of employment, calculated individual mean measurement level, and cumulative exposure (referent +2 exposure groups).
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established in this cohort, but latency may be insufficient for individuals with the latest-occurring exposures. Exposure between 1947 and 1989 was considered. Follow up for cancer incidence ended on the date of death, emigration, or December 31, 1996.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cancer incidence data were obtained using the Danish Cancer Registry and personal identification numbers. Information on the type of cancer and date of diagnosis was abstracted. Tumors were classified acording to a modified version of the ICD-7. Follow up for cancer began on April 1, 1968 and ended on the date of death, emigration, or December 31, 1996. Non-Hodgkin's Lymphoma and esophageal cancer cases were histologically confirmed.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	SIRs and 95% CIs stratified by genders are presented for 26 cancers, which were not outlined in the abstract or methods section but are assumed to be a complete list. Table 3 explores exposure by period of first employment, duration of employment, individual mean exposre, and cumulative exposure for a subset of 3 cancer types.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjustments were described, and were age- and sex-adjusted. The study authors noted that information on individual alcohol intake and socioeconomic influences (papilloma virus infection) were not available.

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Study Citation: Hansen, J; Raaschou-Nielsen, O; Christensen, JM; Johansen, I; Mclaughlin, JK; Lipworth, L; Blot, WJ; Olsen, JH (2001). Cancer incidence among Danish workers exposed to trichloroethylene Journal of Occupational and Environmental Medicine, 43(2), 133-139
Data Type: TCE_NHL_Males-Cancer
HERO ID: 630590

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Confounders were assessed using a reliable methodology (data pulled from National Institute of Occupational Health and Danish Cancer Registry records).
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	There is no evidence that there was an unbalanced provision of additional co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The retrospective cohort design was appropriate to investigate incidence of multiple types of cancer among TCE-exposed workers.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants (n = 803) and person-years (16,730 P-Y) was adequate to detect an effect of TCE exposure.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Authors describe the population against which the occupational cancer incidence rates were standardized against in addition to the adjustments made (age, sex, calendar year), so the analyses would be reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The SIR calculations are transparent.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.167	0.33	The biomarker (urinary TCA) is derived from multiple parent chemicals.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarker of effect was measured.
	Metric 18:	Method Sensitivity	Medium	× 0.167	0.33	Limits of detection are low enough to detect the chemical in a sufficient number of samples (675 of 712 participants) to address the research question. The limit of detection was specified in the report (5 mg/L before 1979; 1 mg/L thereafter).
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	The storage/stability of the biomarker was not likely to bias the results (few details were provided). Differences in exposure levels could be demonstrated.
	Metric 20:	Sample contamination	Low	× 0.167	0.5	No documentation of the steps taken to ensure data reliability (if available) were provided in the study report.
	Metric 21:	Method requirements	Medium	× 0.167	0.33	Analysis of urinary TCA using Fujiwara method
	Metric 22:	Matrix adjustment	Medium	× 0.167	0.33	Urinary measures are assumed to be unadjusted for both creatinine and specific gravity.
Overall Quality Determination‡			Medium		1.9	

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Study Citation:	Hansen, J; Raaschou-Nielsen, O; Christensen, JM; Johansen, I; Mclaughlin, JK; Lipworth, L; Blot, WJ; Olsen, JH (2001). Cancer incidence among Danish workers exposed to trichloroethylene Journal of Occupational and Environmental Medicine, 43(2), 133-139
Data Type:	TCE_NHL_Males-Cancer
HERO ID:	630590

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 7: **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 TCE_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	High rating: key elements of study design were reported, and the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2:	Attrition	High	× 0.4	0.4	High rating: 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	High rating: cases and controls were similar; controls randomly 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	Low rating: Occupational study population with exposure 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 blinded to disease status.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Medium rating: range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported

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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 TCE_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	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	High rating: appropriate adjustments or explicit considerations were made for potential confounders in the final analyses through the use of statistical models for covariate adjustment
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Medium rating: Primary confounders (excluding co-exposures) were assessed. The paper did not describe if the questionnaire used to collect information on education, smoking, etc. has been previously validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Medium rating: co-exposures were measured and modeled separately, and the authors noted that '...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						

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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 TCE_exposure intensity level-Cancer
HERO ID:	630788

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Medium rating: 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.
	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	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: logistic regression models were used to generate Odds Ratios. Rationale for variable selection is stated. Model assumptions are met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		1.6	
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 8: **Lagakos et al. 1986: Evaluation of Cancer Outcomes**

Study Citation:	Lagakos, SW; Wessen, BJ; Zelen, M (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts Journal of the American Statistical Association, 81(395), 583-596
Data Type:	Retrospective cohort, childhood leukemia incidence-Cancer
HERO ID:	632483

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cases were identified by a hospital cancer registry; diagnosed in Woburn, MA between 1964 and 1983
	Metric 2:	Attrition	High	× 0.4	0.4	Any exclusion of subjects from analyses was adequately addressed, and reasons were documented.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis. "Table 8 summarizes the results and indicates that the risks to unexposed individuals are similar in East and West Woburn. Thus it does not appear as though the positive associations with G and H exposure were caused by a difference in baseline rates between East and West Woburn."
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Wells G&H were know to have been contaminated with directly measured TCE. Individual-level exposure assessed as cumulative # of years of water received from those wells.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There were two exposure metrics. One was never exposed vs. some exposure; the other was the number of years exposed to the TCE contaminated wells.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Childhood leukemia has a short latency. The overwhelming majority of the leukemia cases were ALL, which is most common <5 years of age. Most cases would have had sufficient latency so their temporality is sufficient, however, exposures within the latent periods were not excluded which would cause an underestimation of effect.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Hospital-based childhood leukemia diagnosis.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Analyses tested hypothesis of no effect and rejected using p-value based on the observed and expected values and the var(expected) - see Table 2. Since the variance is the square of the standard error, this meets the criterion.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Lagakos, SW; Wessen, BJ; Zelen, M (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts Journal of the American Statistical Association, 81(395), 583-596
Data Type:	Retrospective cohort, childhood leukemia incidence-Cancer
HERO ID:	632483

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis. "Table 8 summarizes the results and indicates that the risks to unexposed individuals are similar in East and West Woburn. Thus it does not appear as though the positive associations with G and H exposure were caused by a difference in baseline rates between East and West Woburn."
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed using the questionnaire and census records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	No adjustment for co-exposures was provided. Perc, a known cause of lyphohematopoetic cancer, was also detected - but at more than 10-fold lower concentrations.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design directly assesses the effect of well water predominantly contaminated with TCE.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Small number of cases, but apparently large enough to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Association between childhood cancer, disorder or pregnancy outcomes and cumulative and binary TCE exposure evaluated with hazard functions and Cox models. Equations outlined in the text and number of cases clear.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Hazard estimated using incidence ratios. Cox models and simple regression equations used. Analysis is transparent and acceptable.
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:	Lagakos, SW; Wessen, BJ; Zelen, M (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts Journal of the American Statistical Association, 81(395), 583-596
Data Type:	Retrospective cohort, childhood leukemia incidence-Cancer
HERO ID:	632483

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 9: **Lagakos et al. 1986: Evaluation of Respiratory Outcomes**

Study Citation:	Lagakos, SW; Wessen, BJ; Zelen, M (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts Journal of the American Statistical Association, 81(395), 583-596
Data Type:	Retrospective cohort, childhood respiratory tract disorder TCE-Respiratory
HERO ID:	632483

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cases were identified by a hospital cancer registry; diagnosed in Woburn, MA between 1964 and 1983
	Metric 2:	Attrition	High	× 0.4	0.4	Any exclusion of subjects from analyses was adequately addressed, and reasons were documented.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis. "Table 8 summarizes the results and indicates that the risks to unexposed individuals are similar in East and West Woburn. Thus it does not appear as though the positive associations with G and H exposure were caused by a difference in baseline rates between East and West Woburn."
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Wells G&H were know to have been contaminated with directly measured TCE. Individual-level exposure assessed as cumulative # of years of water received from those wells.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There were two exposure metrics. One was never exposed vs. some exposure; the other was the number of years exposed to the TCE contaminated wells.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Childhood leukemia has a short latency. The overwhelming majority of the leukemia cases were ALL, which is most common <5 years of age. Most cases would have had sufficient latency so their temporality is sufficient, however, exposures within the latent periods were not excluded which would cause an underestimation of effect.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Hospital-based childhood leukemia diagnosis.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Analyses tested hypothesis of no effect and rejected using p-value based on the observed and expected values and the var(expected) - see Table 2. Since the variance is the square of the standard error, this meets the criterion.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Lagakos, SW; Wessen, BJ; Zelen, M (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts Journal of the American Statistical Association, 81(395), 583-596
Data Type:	Retrospective cohort, childhood respiratory tract disorder TCE-Respiratory
HERO ID:	632483

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Any differences in baseline characteristics of groups were considered as potential confounding or stratification variables and were thereby controlled by statistical analysis. "Table 8 summarizes the results and indicates that the risks to unexposed individuals are similar in East and West Woburn. Thus it does not appear as though the positive associations with G and H exposure were caused by a difference in baseline rates between East and West Woburn."
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed using the questionnaire and census records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	No adjustment for co-exposures was provided. Perc, a known cause of lyphohematopoetic cancer, was also detected - but at more than 10-fold lower concentrations.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design directly assesses the effect of well water predominantly contaminated with TCE.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Small number of cases, but apparently large enough to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Association between childhood cancer, disorder or pregnancy outcomes and cumulative and binary TCE exposure evaluated with hazard functions and Cox models. Equations outlined in the text and number of cases clear.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Hazard estimated using incidence ratios. Cox models and simple regression equations used. Analysis is transparent and acceptable.
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:	Lagakos, SW; Wessen, BJ; Zelen, M (1986). An analysis of contaminated well water and health effects in Woburn, Massachusetts Journal of the American Statistical Association, 81(395), 583-596
Data Type:	Retrospective cohort, childhood respiratory tract disorder TCE-Respiratory
HERO ID:	632483

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 10: **Morgan et al. 1998: Evaluation of Cancer Outcomes**

Study Citation:	Morgan, RW; Kelsh, MA; Zhao, K; Heringer, S (1998). Mortality of aerospace workers exposed to trichloroethylene Epidemiology, 9(4), 424-431
Data Type:	TCE_KidneyCancerMortality_CumulativeHigh_RR-Cancer
HERO ID:	646937

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	All workers employed for at least 6 months between 1950 and 1985 at the Hughes Aircraft manufacturing site in Arizona were included in the study (n =20,508). Of these eligible participants, 27 employees were excluded owing to missing information. Therefore, selection is not likely to be biased.
	Metric 2: Attrition	High	× 0.4	0.4	There was minimal loss to follow-up (112 death certificates not found of over 4000 deaths); exposure and outcome data were largely complete.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	All subject recruited from the same factory using the same inclusion and exclusion criteria. Exposed workers had higher proportion of females, and non-white workers. Although effects estimates were adjusted for age and sex, the study authors indicated that they did not control for race because data were too sparse. Data were analyzed compared to national averages for US population and within the cohort (stratified by exposure status).
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Industrial hygiene measurement data were limited prior to 1975. Therefore, a master exposure matrix was developed by industrial hygienists using experienced employees to rate TCE exposure by job classification as high, medium, low or none. Cumulative TCE exposure was calculated from months worked in each job exposure category. To have a classification of "none," participants were estimated to have <6 months working in any TCE exposed job. The highest exposure jobs involved work on degreaser machines using TCE, with exposure estimated to be 50 ppm by industrial hygienists. Exposure via drinking water or wash water (from contaminated well water before 1981) was not considered in classifying exposure.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	Risk estimates determined based on cumulative exposure, ever/never, and peak exposures. Only 23% of the study population was TCE-exposed.

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Study Citation:	Morgan, RW; Kelsh, MA; Zhao, K; Heringer, S (1998). Mortality of aerospace workers exposed to trichloroethylene Epidemiology, 9(4), 424-431
Data Type:	TCE_KidneyCancerMortality_CumulativeHigh_RR-Cancer
HERO ID:	646937

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	TCE exposure from working at aerospace facility preceded mortality with an adequate follow up. Participants hired from 1950-1989 and followed up through 1993.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The outcome (death) was ascertained using records from the Social Security Administration and National Death Index; death certificates were obtained and coded according to ICD guidelines. Not stated who performed this coding and no links between these death certificates and cancer registries.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	Standardized mortality ratios (SMRs) with 95% confidence intervals were provided for most causes of deaths. Data based on the internal cohort were limited to selected outcomes. Both Cox models and Mantel-Haenszel procedures were used for proportional hazard, but only Cox results were presented as these results were stated to be similar. Additionally, the results of the ever/never assessment were not reported, but stated to be similar to the cumulative and peak assessments.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The study noted that analyses based on the internal cohort took into account exposure classification, age at hire, and gender. Data for race were not suitable for stratification. Final models did not include decade of hire because this covariate did not appreciably change the results.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Data obtained from the Social Security Administration and/or National Death Index included DOB, sex, race, date of hire, job title and termination date.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures not evaluated, but not anticipated to bias the results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Mortality data for a cohort of aerospace factory workers used to determine standardized mortality ratios (relative to US population) and relative risk (based on exposure level within the cohort) for a variety of cancers and respiratory diseases.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants in the study is adequate (4733 of 20,508 employees were TCE-exposed).

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Study Citation:	Morgan, RW; Kelsh, MA; Zhao, K; Heringer, S (1998). Mortality of aerospace workers exposed to trichloroethylene Epidemiology, 9(4), 424-431
Data Type:	TCE_KidneyCancerMortality_CumulativeHigh_RR-Cancer
HERO ID:	646937

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Standardized mortality ratios (SMRs) and relative risk (RR) calculated in transparent method with all adjustments and number of cases reported.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Standardized mortality ratios (SMRs) determined using OCMAP software. Relative risk calculated using the Cox proportional hazard model. All adjustments and number of cases reported. Race and hire date not adjusted, due to sparse data and lack of impact, respectively.
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 11: **Moore et al. (2010): Evaluation of Cancer Outcomes**

Study Citation:	Moore, LE; Boffetta, P; Karami, S; Brennan, P; Stewart, PS; Hung, R; Zaridze, D; Matveev, V; Janout, V; Kollarova, H; Bencko, V; Navratilova, M; Szeszenia-Dabrowska, N; Mates, D; Gromiec, J; Holcatova, I; Merino, M; Chanock, S; Chow, WH; Rothman, N (2010). Occupational trichloroethylene exposure and renal carcinoma risk: Evidence of genetic susceptibility by reductive metabolism gene variants Cancer Research, 70(16), 6527-6536
Data Type:	Case control study of renal cell carcinoma incidence-any exposure to TCE-Cancer
HERO ID:	679709

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Setting, participation rate, inclusion and exclusion criteria, and methods of case ascertainment were described. The study was a hospital-based case-control study of renal cell carcinoma conducted between 1999 and 2003 in seven centers in four countries (Moscow, Russia; Bucharest, Romania; Lodz, Poland; and Prague, Olomouc, Ceske-Budejovice and Brno, Czech Republic). All newly diagnosed and histologically confirmed cases were identified from participating hospitals. Inclusion and exclusion criteria were provided. Controls were selected from the same hospitals with inclusion and exclusion criteria provided. Participation rates were not reported. The study indicated how many cases and controls were included, but not how many were asked or participation rates to determine if there were differences in the two groups. This information may be available in cited references (Brennan 2008 and Hung 2007), but neither were available in HERO.
	Metric 2:	Attrition	Medium	× 0.4	0.8	825 of 1097 cases and 1184 of 1476 controls were included in the Any TCE analysis. There was no explanation for the attrition, but it is assumed to be related to the ability to evaluate the exposure. Similar attrition occurred in both cases and controls.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were matched by sex, age and study center and were recruited during the same time period as cases. Table of characteristics was provided. Prevalence of smoking was similar. A higher proportion of cases (i.e., 33.2) than controls (27.2) reported a first degree relative with cancer. Characteristics were tested in the model and adjusted for if necessary.
Domain 2: Exposure Characterization						

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Study Citation:	Moore, LE; Boffetta, P; Karami, S; Brennan, P; Stewart, PS; Hung, R; Zaridze, D; Matveev, V; Janout, V; Kollarova, H; Bencko, V; Navratilova, M; Szeszenia-Dabrowska, N; Mates, D; Gromiec, J; Holcatova, I; Merino, M; Chanock, S; Chow, WH; Rothman, N (2010). Occupational trichloroethylene exposure and renal carcinoma risk: Evidence of genetic susceptibility by reductive metabolism gene variants Cancer Research, 70(16), 6527-6536
Data Type:	Case control study of renal cell carcinoma incidence-any exposure to TCE-Cancer
HERO ID:	679709

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Occupational exposure was assessed using expert judgement. A general questionnaire was given for each job held for at least a year with detailed description on tasks performed. Specialized occupational questionnaires were used in cases of employment in specific jobs or industries. Exposure assessment teams from each center with extensive knowledge of the industries in the region with additional training from the NCI industrial hygienist evaluated the frequency and intensity of exposure for every job in each subjects history. This was done blind to the case status.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Initially there were two groups with yes or no exposure, then the yes exposure was broken down further into additional categories to look at cumulative or average intensity, which were compared to the reference of no exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established as all jobs held for at least one year were included. The analysis also included a 20-year lag, in which jobs held in the last 20 years before diagnosis in cases or interview in controls were excluded.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histologically confirmed cases of renal cell carcinoma were identified by participating hospitals.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All relevant information include number of cases and controls in the different exposure categories along with the odds ratios and confidence intervals were provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Analyses adjusted for sex, age, and study center. Other characteristics including place of residence, tobacco smoking, BMI, and self-reported history of hypertension were also considered, but were not included in the final model because they did not change the estimate by more than 10%.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data collected by interviewers trained at each center via a standard questionnaire. There is no information provided to indicate that the questionnaire was validated or were done the same in each center.

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Study Citation:	Moore, LE; Boffetta, P; Karami, S; Brennan, P; Stewart, PS; Hung, R; Zaridze, D; Matveev, V; Janout, V; Kollarova, H; Bencko, V; Navratilova, M; Szeszenia-Dabrowska, N; Mates, D; Gromiec, J; Holcatova, I; Merino, M; Chanock, S; Chow, WH; Rothman, N (2010). Occupational trichloroethylene exposure and renal carcinoma risk: Evidence of genetic susceptibility by reductive metabolism gene variants Cancer Research, 70(16), 6527-6536
Data Type:	Case control study of renal cell carcinoma incidence-any exposure to TCE-Cancer
HERO ID:	679709

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Several chlorinated organic solvents were included. It was noted that there was no significant co-exposures identified with TCE exposure except for chlorinated and organic solvents, which could not be controlled for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design is appropriate as it is the best way to address outcomes such as cancer especially when evaluating different exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants are adequate to detect an effect. For any TCE exposure there were 825 cases (48 with TCE exposure) and 1184 controls (40 with TCE exposure). Average intensity and cumulative exposures had far fewer subjects (10-31 cases or controls in each exposure), based on breaking down the 48 exposed subjects, but number of subjects were likely sufficient as significant effects were identified,
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Details of the analysis including categorical exposure metric, statistical methods, covariates considered, and lagged analysis were detailed.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The study clearly stated use of unconditional logistic regression model and methods were 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			Yes			

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Study Citation:	Moore, LE; Boffetta, P; Karami, S; Brennan, P; Stewart, PS; Hung, R; Zaridze, D; Matveev, V; Janout, V; Kollarova, H; Bencko, V; Navratilova, M; Szeszenia-Dabrowska, N; Mates, D; Gromiec, J; Holcatova, I; Merino, M; Chanock, S; Chow, WH; Rothman, N (2010). Occupational trichloroethylene exposure and renal carcinoma risk: Evidence of genetic susceptibility by reductive metabolism gene variants Cancer Research, 70(16), 6527-6536
Data Type:	Case control study of renal cell carcinoma incidence-any exposure to TCE-Cancer
HERO ID:	679709

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.

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

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 12: **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:	TCE_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 69.8 to 120 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: TCE_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 $=\geq 1$ 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: **Boice et al. 1999: Evaluation of Cancer Outcomes**

Study Citation:	Boice, JD, Jr; Marano, D; Fryzek, J; Sadler, C; Mclaughlin, JK (1999). Mortality among aircraft manufacturing workers Occupational and Environmental Medicine, 56(9), 581-597
Data Type:	TCE_NHL_>5YEARS-Cancer
HERO ID:	699183

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	The study included all workers employed at the Lockheed Martin aircraft manufacturing factories in California for at least 1 year on or after January 1, 1960.
	Metric 2: Attrition	High	× 0.4	0.4	Only workers employed < 1 year, with missing work histories, or incorrect dates were excluded. There was minimal loss to follow-up, and reasons for attrition were adequately addressed. Mortality follow up was estimated to be 99% complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	The key elements of the study design were reported. Worker population identified from work history (Kardex), cards, personnel files and retirement records. Detailed personnel listings were available for three calendar periods ending in 1972, 1975, and 1997. SMRs and/or RRs were adjusted by age and race; the choice of a reference population was justified. The general population of California for white workers. General population rates of the United States were used for the smaller number of non-white workers because their racial composition was more similar to that of the United States than that of the state of California.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Exposure assessment was comprehensive, including detailed job descriptions, interviews of long-term workers, walk-through visits of aircraft manufacturing plants, review of detailed environmental assessments and industrial hygiene surveys, and experience from previous assessments of similarly exposed workers. An actual exposure level (in ppm) could not be realistically assigned to individual workers (in the absence of historical air sampling data). However lack of direct measurements of exposure levels could result in misclassification of exposure that could bias the risk towards the null.

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Study Citation:	Boice, JD, Jr; Marano, D; Fryzek, J; Sadler, C; Mclaughlin, JK (1999). Mortality among aircraft manufacturing workers Occupational and Environmental Medicine, 56(9), 581-597
Data Type:	TCE_NHL_>5YEARS-Cancer
HERO ID:	699183

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reported two levels of exposure (exposed [routinely or routinely + intermittently compared to unexposed). Duration of potential exposure reported also with three levels.
	Metric 6:	Temporality	High	× 0.4	0.4	The study presents an appropriate temporality (i.e. exposure precedes outcome). The follow-up period was adequate (average > 20 years per worker).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome (mortality) was assessed using national, state, and company records. Mortality follow up was estimated as 99% complete. Cause of death, coded according to the ICD code in use at the time of death, was obtained from the California death tape for those dying in California after 1959 and from the national death index for non-California residents dying after 1978. For all other deaths, death certificates were obtained from company sources or state vital statistics departments and then coded by a trained nosologist for the underlying cause of death. Of the 20 236 deaths, 342 (1.7%) had a missing cause of death.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Statistical analyses are reported in sufficient detail. Effects estimates (SMRs or RRs) and and 95% CIs were provided for measured outcomes.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SMRs for routine TCE exposure were sex- and race-adjusted; however, initial analyses indicated few differences in mortality patterns among factory workers by sex or race (i.e. considered not to appreciably bias the results). RRs for selected cancers by duration of TCE exposure were adjusted for sex, race, and several other factors.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Three overlapping sources were used to identify the worker population: work history cards, personnel files, and retirement records. Available data included date of birth, sex, and race.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Potential co-exposures to Perchloroethylene and mixed solvents were adjusted for. RRs for routine or intermittent exposure compared to workers not exposed to solvents.
Domain 5: Analysis						

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Study Citation:	Boice, JD, Jr; Marano, D; Fryzek, J; Sadler, C; Mclaughlin, JK (1999). Mortality among aircraft manufacturing workers Occupational and Environmental Medicine, 56(9), 581-597
Data Type:	TCE_NHL_>5YEARS-Cancer
HERO ID:	699183

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design (retrospective cohort) was appropriate to address the research question (i.e., evaluate the risk of cancer and other diseases among workers exposed to TCE).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants (77 965 workers who accrued nearly 1.9 million person-years of follow up) was adequate to detect an effect in the exposed population (although statistical power may not have been sufficient to detect effects for all site-specific cancers and duration of exposure combinations).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to be conceptually reproducible.The regression model computed relative risks over four categories of years of potential exposure (0, <1, 1–4, >5 years), excluding the small percentage with unknown years of exposure. For all analyses, the non-exposed referent category consisted of 11 097 factory workers who had no or only incidental exposure to solvents or chromate. Date of birth, date of starting employment, date of finishing employment, sex and race (white or non-white) were included in the model.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The methods used to calculate SMRs and RRs were adequately described. Relative risks were estimated by Poisson regression techniques with trend tests conducted to learn whether there were significant increases in risk with increasing years of potential exposure to specific 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	
	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:	Boice, JD, Jr; Marano, D; Fryzek, J; Sadler, C; Mclaughlin, JK (1999). Mortality among aircraft manufacturing workers Occupational and Environmental Medicine, 56(9), 581-597
Data Type:	TCE_NHL_>5YEARS-Cancer
HERO ID:	699183

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 14: **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_TCE_KidneyCancer-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	Medium	× 0.2	0.4	For 21 chemicals (including TCE, Perc, CCl4 and DCM), exposure was classified as yes/no. For additional analyses, four categories of TCE exposure were developed for workers considering frequency and pattern of exposure based on the job tasks: low intermittent, low continuous, high intermittent, and high continuous. Also, based on estimates of frequency and intensity of exposure, cumulative exposure scores for TCE were developed. No quantitative assessment of exposure was conducted.

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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_TCE_KidneyCancer-Cancer
HERO ID:	699234

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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						
	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 TCE and various other chemicals. Exposures were not mutually exclusive; therefore, it was not possible to evaluate the risk of death from exposure to a singular chemical while controlling for exposure to other chemicals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cohort design and calculation of hazard ratios were appropriate for determining the association between exposure to TCE, Perc, CCl4 and DCM, and all-cause, cancer, and non-cancer mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort was large (adequate for statistical analyses). Despite the relatively large size of the cohort, the number of cases for many causes of death was small to evaluate associations.

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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_TCE_KidneyCancer-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, Perc, CCl4 and DCM and all-cause and cause-specific mortality (hazard ratios) are clearly described in the study report.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 15: **Gold et al. 2010: Evaluation of Cancer Outcomes**

Study Citation:	Gold, LS; Stewart, PA; Milliken, K; Purdue, M; Severson, R; Seixas, N; Blair, A; Hartge, P; Davis, S; De Roos, AJ (2010). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents Occupational and Environmental Medicine, 68(6), 391-399
Data Type:	Gold_TCE_exposed workers_cancer_10yrlag_1-415 CE score-Cancer
HERO ID:	699241

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

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Study Citation:	Gold, LS; Stewart, PA; Milliken, K; Purdue, M; Severson, R; Seixas, N; Blair, A; Hartge, P; Davis, S; De Roos, AJ (2010). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents Occupational and Environmental Medicine, 68(6), 391-399
Data Type:	Gold_TCE_exposed workers_cancer_10yrlag_1-415 CE score-Cancer
HERO ID:	699241

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

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Study Citation:	Gold, LS; Stewart, PA; Milliken, K; Purdue, M; Severson, R; Seixas, N; Blair, A; Hartge, P; Davis, S; De Roos, AJ (2010). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents Occupational and Environmental Medicine, 68(6), 391-399
Data Type:	Gold_TCE_exposed workers_cancer_10yrlag_1-415 CE score-Cancer
HERO ID:	699241

Domain	Metric	Rating†	MWF⋆	Score	Comments††

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

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

where High $=\geq 1$ to < 1.7; Medium $=\geq 1.7$ to < 2.3; Low $=\geq 2.3$ to ≤ 3.0. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.
†† This metric met the criteria for high confidence as expected for this type of study
§ Evaluator's explanation for rating change: "The number of exposed cases and controls in the different subgroups is small and results should be interpreted with caution."

Table 16: **Purdue et al. (2011): Evaluation of Cancer Outcomes**

Study Citation:	Purdue, MP; Bakke, B; Stewart, P; De Roos, AJ; Schenk, M; Lynch, CF; Bernstein, L; Morton, LM; Cerhan, JR; Severson, RK; Cozen, W; Davis, S; Rothman, N; Hartge, P; Colt, JS (2011). A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma Environmental Health Perspectives, 119(2), 232-238
Data Type:	Case-control study TCE-exposed workers and NHL (cumulative exposure >234,000 ppm-hr)-Cancer
HERO ID:	699921

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Case-control study of occupational exposure to TCE in 4 US areas (State of Iowa, LA county, CA, Seattle, WA, and Detroit, MI). Cases (20-74 years of age; 76% participation rate) were enrolled from the National Cancer Institute–Surveillance, Epidemiology, and End-Results (NCI-SEER) registry, and were diagnosed with incident non-Hodgkin lymphoma (NHL) between July 1998 and June 2000 (n=1,891;). Controls were taken from the general population matched by age, sex, race and geographical area (n=982; 52% participation rate).
	Metric 2: Attrition	Medium	× 0.4	0.8	There was moderate subject withdrawal from the study (participation rate of 76% in cases and 52% in controls), given different reasons reported in the study.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls were selected from the general population in the same SEER registry areas as the cases by random digit dialing (RDD; < 65 years of age) and from residents listed in Medicare files (65–74 years of age), and were matched by age (5-year intervals), sex, race and SEER geographical area.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Probability, frequency and intensity of exposure were estimated by an industrial hygienist, based on participants' responses to questionnaires (mailed residential and occupational history calendar and CAPI, administered during in-person interview), together with a literature review and exposure matrices. Job modules focused on solvent exposures were incorporated into the CAPI when data collection was ongoing and administered to 682 cases and 640 controls. No employer records were used.

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Study Citation:	Purdue, MP; Bakke, B; Stewart, P; De Roos, AJ; Schenk, M; Lynch, CF; Bernstein, L; Morton, LM; Cerhan, JR; Severson, RK; Cozen, W; Davis, S; Rothman, N; Hartge, P; Colt, JS (2011). A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma Environmental Health Perspectives, 119(2), 232-238
Data Type:	Case-control study TCE-exposed workers and NHL (cumulative exposure >234,000 ppm-hr)-Cancer
HERO ID:	699921

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Five categories of probability of exposure to TCE (0%, < 10%, 10–49%, 50–89%, or = 90%), four categories of exposure frequency (< 2, 2–9, 10–19, or = 20 hr/week) and five categories of exposure intensity (< 1, 1–19, 20–99, 100–199, or = 200 estimated ppm) were assigned to participants based on their job history, and were integrated to develop several metrics of TCE exposure. Based on probability, subjects were defined as unexposed, possibly exposed, and probably exposed. The authors considered that the "possibly exposed" category was unrealistically high among controls thus "suggesting poor specificity", and this group was not used in further analyses. For those "probably exposed" (2.8% of controls and 3.8% of cases), additional metrics were determined: duration of exposure (years), cumulative exposure (ppm-hours), average weekly exposure, and average exposure intensity.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposure was assessed taking into account occupational history, but it is unclear whether exposures fall within relevant exposure windows for NHL. The study evaluated latency periods of 5 and 15 years in sensitivity analyses (detailed results not shown).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Incident NHL (including histologic types) was obtained from the NCI-SEER registry.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Odds ratios and 95% Confidence Intervals were reported for different exposure metrics of estimated occupational exposure to TCE and NHL incidence (Table 1). Results from sensitivity analyses, including the evaluation of 5 and 15-year latency periods, were not fully reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Models were adjusted for age (< 45, 45–64, = 65 years), sex, race (Caucasian, African American, other/unknown), education level (< 12, 12–15, = 16 years), and SEER area (Detroit, Iowa, Los Angeles, Seattle).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariate characterization is reported in Table 2. Validation of the questionnaire used to obtain the underlying data is not reported.

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Study Citation:	Purdue, MP; Bakke, B; Stewart, P; De Roos, AJ; Schenk, M; Lynch, CF; Bernstein, L; Morton, LM; Cerhan, JR; Severson, RK; Cozen, W; Davis, S; Rothman, N; Hartge, P; Colt, JS (2011). A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma Environmental Health Perspectives, 119(2), 232-238
Data Type:	Case-control study TCE-exposed workers and NHL (cumulative exposure >234,000 ppm-hr)-Cancer
HERO ID:	699921

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposure confounding was not evaluated and there may have been potential confounding, related to use of other degreasers and/or other exposures not captured in the occupational history of some participants.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design (case control) was appropriate to assess the association between occupational exposure to TCE and NHL (a rare disease). The statistical method (logistic regression modeling) was appropriate for this study design.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study showed enough power to detect an effect for some exposure metrics, but there was a small number of subjects estimated to be highly exposed to TCE.
	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 for estimating the association between occupational exposure to TCE and NHL (odds ratios) are clearly 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		1.8	
Extracted			Yes			

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Study Citation:	Purdue, MP; Bakke, B; Stewart, P; De Roos, AJ; Schenk, M; Lynch, CF; Bernstein, L; Morton, LM; Cerhan, JR; Severson, RK; Cozen, W; Davis, S; Rothman, N; Hartge, P; Colt, JS (2011). A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma Environmental Health Perspectives, 119(2), 232-238
Data Type:	Case-control study TCE-exposed workers and NHL (cumulative exposure >234,000 ppm-hr)-Cancer
HERO ID:	699921

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 17: **Ikbal et al. 2004: Evaluation of Genotoxicity Outcomes**

Study Citation:	M. Ikbal, A. Tastekin, H. Dogan, I. Pirim, R. Ors (2004). The assessment of genotoxic effects in lymphocyte cultures of infants treated with chloral hydrate Mutation Research, 564(2,2), 159-164
Data Type:	SCE and MN in peripheral blood lymphocytes-Other (please specify below)
HERO ID:	700424

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	The study indicated that 18 infants were included (including sex, mean/range of ages). The exclusion criteria specified were prior chemotherapy, radiotherapy, or phototherapy, and/or concurrent drug use. Other details with respect to setting, inclusion criteria, and methods of participant selection were not reported.
	Metric 2:	Attrition	High	× 0.4	0.4	No samples from any of the subjects were excluded from analysis.
	Metric 3:	Comparison Group	High	× 0.2	0.2	The genotoxicity assays were performed pre- and post-exposure; therefore, the comparison and exposure groups were the same infants.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposures were consistently administered to the study subjects. Chloral hydrate was mixed in breast milk or formula and administered orally as a single dose of 50 mg/kg.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Two levels of exposure are reported (before and after exposure).
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established, as genotoxicity assays were performed before and one hour after CH exposure;however, it is unclear whether the duration between exposure and outcome assessment (1 h) was sufficient for the outcomes of interest.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes (SCE and MN determinations) were assessed using well-established methods and the methods described in detail.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The measured outcomes (SCE and MN) were reported before and after exposure. The raw data for the 18 subjects as well as the mean +/- SE were provided in the report.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 1	1	Comparison between pre and post exposure results in the same group of infants minimizes need for covariate assessment

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Study Citation:	M. Ikbal, A. Tastekin, H. Dogan, I. Pirim, R. Ors (2004). The assessment of genotoxic effects in lymphocyte cultures of infants treated with chloral hydrate Mutation Research, 564(2,2), 159-164
Data Type:	SCE and MN in peripheral blood lymphocytes-Other (please specify below)
HERO ID:	700424

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Covariates were not assessed.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	Same subjects were unexposed and exposed, and the exposure was controlled.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	The study design was appropriate to address the research question (i.e., the effect of CH exposure on SCE/MN frequency in peripheral lymphocytes); appropriate statistical methods were used.
	Metric 13:	Statistical power	Medium	× 0.25	0.5	The sample size was sufficient to detect a biological effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.25	0.5	The description of the analysis is sufficient and conceptually reproducible.
	Metric 15:	Statistical models	Not Rated	NA	NA	The study does not use a statistical 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~~ ⟶ Medium§		~~1.5~~	
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

§ Evaluator's explanation for rating change: "The study evaluates SCE and MN in 18 infants before and 1 hr after administration of chloral hydrate. It is not clear that 1 hr is sufficient time for the effects to be manifested."

Table 18: **Green et al. 2004: Evaluation of Renal Outcomes**

Study Citation:	Green, T; Dow, J; Ong, C; Ng, V; Ong, H; Zhuang, Z; Yang, X; Bloemen, L (2004). Biological monitoring of kidney function among workers occupationally exposed to trichloroethylene Occupational and Environmental Medicine, 61(4), 312-317
Data Type:	Green_TCE_exposed workers_NAG control-Renal
HERO ID:	700447

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Participants included 70 workers (58 males, 12 females) in electronic and related industries from several factories with occupational TCE exposure. 54 (50 males, 4 females) age-matched hospital and administrative staff with no known history of exposure to organic solvents or heavy metals were recruited as controls. Details regarding recruitment and participation rates were not reported, though inclusion criteria are.
	Metric 2:	Attrition	High	× 0.4	0.4	One exposed subject was excluded for duration analysis because years of exposure data were unavailable.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Age- and sex-matched comparison group; same exclusion criteria. Mean age 32.6 and 30.3 in exposed and controls, respectively.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Only current exposure measured in exposed group. It does not appear that urinary biomarkers of exposure were measured in control subjects.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Two analyses conducted - exposed/unexposed AND exposure-response analysis conducted in exposed group. Also contained four different levels of exposure (years of exposure).
	Metric 6:	Temporality	High	× 0.4	0.4	Measured exposure at a single time-point, but median duration of exposure was 4.1 years. Duration analysis was conducted.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Used markers of renal disease, some of which are not well-established.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All renal markers outlined in the methods section were reported. Table 1 presents means, SD, significance and sample sizes, though Tables 2 and 3 report only mean and significance.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Green, T; Dow, J; Ong, C; Ng, V; Ong, H; Zhuang, Z; Yang, X; Bloemen, L (2004). Biological monitoring of kidney function among workers occupationally exposed to trichloroethylene Occupational and Environmental Medicine, 61(4), 312-317
Data Type:	Green_TCE_exposed workers_NAG control-Renal
HERO ID:	700447

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.667	1.33	Controls were age- and sex-matched, and toxicity markers were normalized for urinary creatinine, but no additional mention of covariate adjustments were discussed. Potential confounding variables were exclusion criteria (e.g., high BP or diabetes)
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	Exposed workers were matched to unexposed participants based on age and sex. The source of age and sex data was not reported, but these covariates are not suspected to require sensitive instruments.
	Metric 11:	Co-exposure Confounding	Medium	× 0.333	0.67	Study authors state that TCE was the only organic solvent that subjects in exposed group were exposed to. Controls had no history of exposure to organic solvents or heavy metals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cross-sectional study design was appropriate to determine differences in mean renal toxicity markers between TCE-exposed and unexposed participants.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sample size (n=74 exposed, 50 unexposed) was sufficient to detect an effect of TCE exposure.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of correlation tests and chi-square tests for difference in means was sufficient. Authors provide cut-points in the results tables for categorical analyses.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for determining correlations and differences in means was transparent.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.143	0.29	Urinary trichloroacetic acid levels have been shown to correlate well with exposure, a concentration of 100 mg/l equating to a TRI exposure of 50 ppm over several shifts. Unclear if it is derived from other parent chemicals. Trichloroethanol was also evaluated.
	Metric 17:	Effect biomarker	Medium	× 0.143	0.29	"Conventional" renal toxicity markers - urinary albumin and N-acetyl glucosaminidase (NAG) "Early" renal toxicity markers - urinary glutathione S-transferase a activity and urinary concentrations of b-2-microglobulin, a-1-microglobulin, and retinol binding protein (reportedly more sensitive than conventional markers) Renal toxicity markers based on proposed MOA - formic acid and methylmalonic acid

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Study Citation:	Green, T; Dow, J; Ong, C; Ng, V; Ong, H; Zhuang, Z; Yang, X; Bloemen, L (2004). Biological monitoring of kidney function among workers occupationally exposed to trichloroethylene Occupational and Environmental Medicine, 61(4), 312-317
Data Type:	Green_TCE_exposed workers_NAG control-Renal
HERO ID:	700447

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Method Sensitivity	Medium	× 0.143	0.29	Biomarker of exposure identified in all 70 exposed cases. LOQ reported
	Metric 19:	Biomarker stability	Medium	× 0.143	0.29	No data on stability, but extensive methods.
	Metric 20:	Sample contamination	Low	× 0.143	0.43	Study authors do not provide documentation of steps to prevent contamination or otherwise provide assurance that study data are reliable.
	Metric 21:	Method requirements	Medium	× 0.143	0.29	GC-MS (trichloroacetic acid); protein spectroscopy (trichloroethanol)
	Metric 22:	Matrix adjustment	Medium	× 0.143	0.29	creatinine-adj reported
Overall Quality Determination‡			Medium		1.8	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 19: **Axelson et al. 1994: Evaluation of Cancer Outcomes**

Study Citation:	Axelson, O; Seldén, A; Andersson, K; Hogstedt, C (1994). Updated and expanded Swedish cohort study on trichloroethylene and cancer risk Journal of Occupational Medicine, 36(5), 556-562
Data Type:	TCE exposed workers - Cancer incidence and mortality - Liver-Cancer
HERO ID:	701067

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Details on study participation can be found in Axelson et al. 1978 (HERO ID 75070). Participants were drawn from a free consumer surveillance database. In the parent reference, it was mentioned that some of the database was deleted and some remained from which the first part of the cohort was derived. The second part of the cohort was drawn from later records as they had reached sufficient latency time. There is some uncertainty with differences in recruiting between the first and second cohort from the database as it was mentioned that some records were deleted in the first, but not in the second. This is not expected to appreciably bias the results.
	Metric 2:	Attrition	High	× 0.4	0.4	Minimal loss to follow up (96.7% participation). Details on reasons for loss to follow-up are provided in the current reference and included name mismatches and emigration.
	Metric 3:	Comparison Group	High	× 0.2	0.2	The referent population was the general population of Sweden over the same time period, stratified into 5-year age blocks. Male and female estimates were presented separately, however, the female cohort only had 249 participants.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Urinary trichloroacetic acid concentrations were measured and reported to the surveillance system between 1955 and 1975. Individual participants had their urine measured and values reported by employers. There is little detail on the method, amount, or timing of samples which introduces uncertainty into using this database as a measure of exposure. In this study, mean TCE exposure values are used.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The study authors created 3 levels of exposure using urinary trichloroacetic acid levels in order to investigate dose-response relationships, however, the reported effect estimate is an SIR compared to the general population which represents two levels of exposure.

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Study Citation:	Axelson, O; Seldén, A; Andersson, K; Hogstedt, C (1994). Updated and expanded Swedish cohort study on trichloroethylene and cancer risk Journal of Occupational Medicine, 36(5), 556-562
Data Type:	TCE exposed workers - Cancer incidence and mortality - Liver-Cancer
HERO ID:	701067

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	11 years of follow for subject entering at the end of the study (1975). It should also be noted the mean urinary TCE metabolite concentration was used for this analysis. Samples were not necessarily analyzed at the same time.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The Swedish cause-of-death and cancer registries were searched for each participant. This represents a well-established method of ascertaining cancer and/or vital status.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods is provided in the results. The number of observed cases is provided along with SIR/SMRs to allow for easily tabulation and inclusion in a meta-analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.667	1.33	Results are adjusted for age and stratified by sex. No other covariate information was identified. This represents a partial list of potential confounders and those not included are not expected to appreciably bias the results.
	Metric 10:	Covariate Characterization	High	× 0.333	0.33	Covariates were drawn from employment records submitted to the TCE-use surveillance database. There is no evidence to suggest this is an invalid method of determining covariate information.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	Co-exposures were not assessed.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study appropriately investigated long-term effects of exposure to TCE by calculating SIRs and SMRs comparing a cohort of workers with known exposure to TCE with rates of cancer incidence and mortality in the general population.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	This study looked at cancer incidence and mortality in a cohort of 1421 men. This is a sufficient number of individuals to detect elevated rates of cancer incidence or mortality.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis was described sufficiently that it could be reproduced given original data. The cut points for dose-response analysis was described as well as the method of determining TCE exposure (average exposure or highest).

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Study Citation:	Axelson, O; Seldén, A; Andersson, K; Hogstedt, C (1994). Updated and expanded Swedish cohort study on trichloroethylene and cancer risk Journal of Occupational Medicine, 36(5), 556-562
Data Type:	TCE exposed workers - Cancer incidence and mortality - Liver-Cancer
HERO ID:	701067

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The study authors described the cohort, its origins, and its limitations. The choice of exposure categorization and comparisons was described in the current reference.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.167	0.33	The study utilized urinary tetrachloroacetic acid concentrations, submitted to a surveillance database. This urinary metabolite may have more than one parent compound.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No effect biomarker was used.
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	LOD/LOQ was not provided.
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	No stability data was presented; however, differences between exposure groups was evident.
	Metric 20:	Sample contamination	Low	× 0.167	0.5	No documentation of steps to prevent contamination. Samples were not processed by a central facility or team of technicians, but rather values were reported to a database..
	Metric 21:	Method requirements	Low	× 0.167	0.5	No information on methods of measurement. Samples may have been analyzed with different quantitative methods.
	Metric 22:	Matrix adjustment	Low	× 0.167	0.5	No matrix adjustment was indicated.
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 =≥ 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 20: **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 TCE-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 Perc 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 (self-assessed) or 4-3 levels (length of occupational exposure).
	Metric 6:	Temporality	High	× 0.4	0.4	Data provided for Time Period 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
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						

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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 TCE-Cancer
HERO ID:	701363

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	Small number of cases; number of controls was increased to increase power.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The study design using case-control and conditional logistic regression was appropriately described to be reproduced.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The conditional logistic regression model was well described. risk estimation was conditional on 10 strata resulting from gender and five age groups (<50, 50–<60, 60–<70, 70–<80, 80+ years). Smoking was implemented as a confounder by smoking status (never smoker, ex-smoker, current smoker).
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 21: **Goldberg et al. 1990: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Goldberg, SJ; Lebowitz, MD; Graver, EJ; Hicks, S (1990). An association of human congenital cardiac malformations and drinking water contaminants Journal of the American College of Cardiology, 16(1), 155-164
Data Type:	Case control study; offspring of residents exposed to contaminated drinking water-Growth (early life) and Development
HERO ID:	702148

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Participant selection, inclusion/exclusion criteria and case ascertainment were described.
	Metric 2:	Attrition	Low	× 0.4	1.2	707 families were included; 1,362 were originally identified as candidates. Reasons for exclusion were provided. Missing data for 218 subjects.
	Metric 3:	Comparison Group	High	× 0.2	0.2	3 control groups; cases and controls were similar in many respects except for potential exposure
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Method used to quantify exposure were not provided. Only one part of the contaminated water area was used for the investigation without details provided on why a specific area was selected except to indicate that the other areas were minimally populated during the period of contamination. Exposure in 9 public wells ranged from 6-239 ppb. Exposure was measured only once in 1981, but the study period began 12 years earlier. Determination of exposure levels was not possible from this study design due to changing contamination level, varying usage and changes in water flow patterns. The study authors indicate that it was impossible to determine the boundaries of the contamination.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Only evaluated as exposed and unexposed with levels in exposed ranging from 6 to 239 ppb without any measurement in the unexposed subjects; therefore, making it impossible to distinguish between the two groups or make any determination on exposure levels.
	Metric 6:	Temporality	Low	× 0.4	1.2	Temporality is uncertain, because exposure was measured 12 years after the beginning of the study period (1969).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Case registry and cardiologists' records were used to identify patient with cardiac outcomes.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Fold increase in OR was reported. The actual value and confidence intervals were not reported.

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Study Citation:	Goldberg, SJ; Lebowitz, MD; Graver, EJ; Hicks, S (1990). An association of human congenital cardiac malformations and drinking water contaminants Journal of the American College of Cardiology, 16(1), 155-164
Data Type:	Case control study; offspring of residents exposed to contaminated drinking water-Growth (early life) and Development
HERO ID:	702148

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Covariates that were controlled for are listed in Table 1.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Potential confounders were assessed from questionnaire data.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposure to DCE and chromium were not accounted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design and the statistical method was appropriate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls seem adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Full details of the analyses were not provided.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Full details of the statistical analyses were not provided.
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			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 22: **Hardell et al. 1994: Evaluation of Cancer Outcomes**

Study Citation:	Hardell, L; Eriksson, M; Degerman, A (1994). Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma Cancer Research, 54(9), 2386-2389
Data Type:	occupational TCE_ NHL-Cancer
HERO ID:	702305

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Few details were provided, but the basic elements of the study design were reported. The information provided suggests that selection into the study was not likely to be biased.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Exclusion from the study/analyses were not discussed in the study report. The study indicates that all 105 NHL cases were evaluated, and 335 (control) respondents to the questionnaire were used (information on response rate not provided).
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls (n = 335) were matched to cases by sex, place, and area of residence (living controls; from the National Population Register); or by these factors and including the year of death (deceased controls; from the National Registry for Causes of Death).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was assessed via a self-administered questionnaire (with telephone interview follow-up, when applicable). While the information obtained from the questionnaire included a complete work history (leisure activities, etc). the study does not indicate how job titles were used to assign TCE exposure. However, it appears through the Nordic Working Classification system. Although recall bias is possible, the study authors suggested that the validity of self-reported exposures was shown by another study using a similar questionnaire in the same area (Hardell et al. 1979).
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reports two levels of TCE exposure only (exposed or unexposed).
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established, but it is unclear when exposure occurred relative to NHL incidence.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The outcome (NHL incidence) was assessed using a different classification system (Rappaport classification). The study authors indicated that this classification is comparable to that used in Europe and the United States.

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Study Citation:	Hardell, L; Eriksson, M; Degerman, A (1994). Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma Cancer Research, 54(9), 2386-2389
Data Type:	occupational TCE_ NHL-Cancer
HERO ID:	702305

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Data for NHL incidence are reported in a way that is amenable to data extraction (number of exposed cases and controls; OR with CIs).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Other than the criteria used for matching (sex, age, and other demographic information), other potential confounders were not analyzed statistically.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information on sex and age was presumably obtained from registries (National Population Registry and/or National Registry for Causes of Death). Limited information on other covariates (evaluated in the questionnaire) were reported.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Exposure to other substances was assessed in the study (chlorophenols, organic solvents). There was no indication of an unbalanced provision of additional exposures across groups. Potential confounding between exposures of interest was evaluated using multivariate analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate to address the research question. The case-control study design is appropriate for studying cancer especially when evaluating multiple possible exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were few numbers of exposed cases and controls, limiting the statistical power of the analyses; however, a statistical increase was observed.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Although descriptions of the analyses performed were not provided in detail, the methods indicate the method of statistical analysis used and stratification variables considered.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Mantel-Haenszel methods were used, stratified by age and vital status. The method for calculating risk 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	

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Study Citation:	Hardell, L; Eriksson, M; Degerman, A (1994). Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma Cancer Research, 54(9), 2386-2389
Data Type:	occupational TCE_ NHL-Cancer
HERO ID:	702305

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	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 23: **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-TCE males 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 urotheial 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
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.

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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-TCE males medium exp.-Cancer
HERO ID:	85973

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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.
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 24: **Raaschou-Nielsen et al. 2003: Evaluation of Cancer Outcomes**

Study Citation:	Raaschou-Nielsen, O; Hansen, J; Mclaughlin, JK; Kolstad, H; Christensen, JM; Tarone, RE; Olsen, JH (2003). Cancer risk among workers at Danish companies using trichloroethylene: A cohort study American Journal of Epidemiology, 158(12), 1182-1192
Data Type:	TCE_Occupational_EsophagealAdenocarcinoma_SIR-Cancer
HERO ID:	707487

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	347 small (<200 employees) Danish companies in a variety of industries (e.g. iron/metal, dry cleaning, electronics) using TCE were identified from Danish National Institute for Occupational Health, Danish Product Registry, a dry cleaning survey, and company archives. Large companies (n=110) were excluded, due to relatively low exposure to TCE. Workers at these companies were identified from records in the national Supplementary Pension Fund (mandatory, unique IDs after 1968). Included blue-collar workers with employment > 3 months (n = 40, 049).
	Metric 2: Attrition	Medium	× 0.4	0.8	White-collar workers and those with an unknown status were excluded (~60 of workers). Blue-collar workers with less than 3 months at a company were also excluded (30% of blue-collar workers). An additional 4 worker were excluded, due to an unverified personal identification number. 80% of the blue-collar cohort, was followed for 10+ years.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Expected numbers of cancers were based on the Danish population as a whole; blue-collar workers (and associated socioeconomic considerations) may be higher in the cohort examined in the study than in the general population. Danish national incidence rates of site-specific cancers by sex, 5-year age group, and calendar year were used.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	All participants worked at companies with a verified TCE use. Although the blue-collar status was not anticipated to change over careers, only the most recent job titles were available. Participants were assigned an exposure solely on the basis of a blue-collar job in an company with a document TCE usage. Citations (Raaschou-Nielsen et al. 2001, 2002) for TCE exposure estimates were provided to show that TCE exposure in Danish work environments decreased from the 1960s to 1980s (urinary metabolite 58 mg/L and 14 mg/L, respectively), but are not linked to specific industries or positions.

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Study Citation:	Raaschou-Nielsen, O; Hansen, J; Mclaughlin, JK; Kolstad, H; Christensen, JM; Tarone, RE; Olsen, JH (2003). Cancer risk among workers at Danish companies using trichloroethylene: A cohort study American Journal of Epidemiology, 158(12), 1182-1192
Data Type:	TCE_Occupational_EsophagealAdenocarcinoma_SIR-Cancer
HERO ID:	707487

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The study compared any potential exposure to TCE (blue-collar job at TCE using company) to the general population. For some analyses, 3 surrogates of TCE exposure levels (duration of employment, year of first employment, and number of employees) were used to predict high, medium and low exposure.
	Metric 6:	Temporality	High	× 0.4	0.4	Occupational TCE exposure estimated beginning in 1968. Follow-up occurred though 1997 (or through death or emigration). This follow-up period for most workers (~80%) was 10 years or more (adequate latency).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cancer incidence was determined through the Danish Cancer Registry linked through the personal identification number. Type of cancer classified according to a Danish modified version of the ICD 7 codes (subdivide kidney cancers and identify esophageal adenocarcinomas).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Risk estimates for various cancers were provided for subset of exposure and the cohort as standardized incidence ratios (SIRs) with confidence intervals.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	The major covariates were accounted for. Cancer incidence rates by sex, age, and calendar year were used. There is the possibility that other (weaker) factors (e.g., smoking, alcohol consumption) may have been more common in the exposed cohort than in the general population. Limiting the cohort to blue-collar workers could lead to differences in SES relative to the general population comparison group, that were not accounted for in the analysis.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Data on potential confounders was obtained from Danish Central Population registry.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures to pollutants other than TCE (that could appreciably bias the results) were not known to be present.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	An occupational cohort from companies using TCE was used to evaluate risk to cancers using a 10 year lag.

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Study Citation:	Raaschou-Nielsen, O; Hansen, J; Mclaughlin, JK; Kolstad, H; Christensen, JM; Tarone, RE; Olsen, JH (2003). Cancer risk among workers at Danish companies using trichloroethylene: A cohort study American Journal of Epidemiology, 158(12), 1182-1192
Data Type:	TCE_Occupational_EsophagealAdenocarcinoma_SIR-Cancer
HERO ID:	707487

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Cohort of 40,049 blue-collar workers at Danish TCE-using companies sufficient to detect changes in cancer incidence.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Standardized incidence ratios (SIRs) determined for several cancers and surrogates of exposure, with relevant data provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Standardized incidence ratios (SIRs) 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		1.8	
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 25: **Yauck et al. 2004: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Yauck, JS; Malloy, ME; Blair, K; Simpson, PM; Mccarver, DG (2004). Proximity of residence to trichloroethylene-emitting sites and increased risk of offspring congenital heart defects among older women Birth Defects Research, Part A: Clinical and Molecular Teratology, 70(10), 808-814
Data Type:	Developmental toxicity- CHD in infants born (exposed mothers > 38 years)-Growth (early life) and Development
HERO ID:	708515

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Most key elements of the study design are reported, including inclusion/exclusion criteria, methods of participant selection, case ascertainment, and matching procedures. Participation rate among cases and controls who were approached for recruitment not reported and, but no direct evidence of bias.
	Metric 2: Attrition	High	× 0.4	0.4	There was no to minimal exclusion of data from analysis, and outcome data were complete.
	Metric 3: Comparison Group	Low	× 0.2	0.6	The key elements as described indicate that cases and controls were similar based on recruitment from the same population, using the same eligibility criteria, with the number of controls reported, and within the same time frame. Cases and controls are described only qualitatively (e.g. no difference) for some key elements rather than quantitatively (e.g. percentages not reported). Exposure of controls and cases characterized by matching by year during which the 5th week of gestation occurred (timing of cardiac development). Exposed group seems to draw mainly from residents of a single neighborhood or subsection of the overall study area, thus exposed and referents may differ by key elements associated with neighborhood (e.g. socioeconomic status).
Domain 2: Exposure Characterization					

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Study Citation:	Yauck, JS; Malloy, ME; Blair, K; Simpson, PM; Mccarver, DG (2004). Proximity of residence to trichloroethylene-emitting sites and increased risk of offspring congenital heart defects among older women Birth Defects Research, Part A: Clinical and Molecular Teratology, 70(10), 808-814
Data Type:	Developmental toxicity- CHD in infants born (exposed mothers > 38 years)-Growth (early life) and Development
HERO ID:	708515

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	There was no direct/independent measurement of TCE exposure. A less-established method to estimate exposure was used. Proximity of maternal residence to source of TCE emissions was used as a surrogate of exposure. Classification trees were used to determine a distance delineating exposure from nonexposure. The exposure characterization method accounts for some, but not all spatial and temporal variability in TCE concentrations in the study area, thus nondifferential exposure misclassification is likely. Although the study did not account for occupational exposure or changes in residence, there is no reason to believe that misclassification was differential.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The study reports two levels of exposure (exposed and unexposed). Concentration of TCE in the exposed and unexposed group were not measured or reported, so magnitude, range, or variability of the exposures is unknown.
	Metric 6:	Temporality	High	× 0.4	0.4	The study presents an appropriate temporality between exposure (during pregnancy) and outcome (after birth).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome (congenital heart defects) was assessed in cases and controls using well-established methods (medical records, surgical findings, and/or autopsy reports).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Effects estimates (ORs) are reported with 95% confidence intervals and numbers of cases/controls evaluated.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Various confounders were considered in the analyses; others for which no data were available (e.g., multivitamin intake, pregnancy terminations) are not expected to be different among groups. Due to low population density near all but a few exposure sources, the exposed group seems to draw mainly from residents in a subsection of the overall study area; for this reason, lack of adjustment for a neighborhood factors such as socioeconomic status is a potential source of bias.

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Study Citation:	Yauck, JS; Malloy, ME; Blair, K; Simpson, PM; Mccarver, DG (2004). Proximity of residence to trichloroethylene-emitting sites and increased risk of offspring congenital heart defects among older women Birth Defects Research, Part A: Clinical and Molecular Teratology, 70(10), 808-814
Data Type:	Developmental toxicity- CHD in infants born (exposed mothers > 38 years)-Growth (early life) and Development
HERO ID:	708515

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Potential confounders for both cases and controls were acquired from birth record data.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	There is no direct evidence that there was an unbalanced provision of additional exposures across cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate to evaluate the association between TCE exposure and congenital heart defects; appropriate statistical methods were used.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls are adequate to detect exposure-related effects.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Details regarding analyses were sufficiently descriptive (i.e., reproducible). Forward stepwise logistic regression was used to estimate the risk of congenital heart defects associated with residential proximity to TCE-emitting sites.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The methods for calculating ORs were 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		1.8	
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 26: **Zhao et al. 2005: Evaluation of Cancer Outcomes**

Study Citation:	Zhao, Y; Krishnadasan, A; Kennedy, N; Morgenstern, H; Ritz, B (2005). Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers American Journal of Industrial Medicine, 48(4), 249-258
Data Type:	TCE_KidneyCancer_HighExposure-Cancer
HERO ID:	708570

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. The selection of subjects into/out of the study seems to be appropriate. Although all details were not provided, it seems that all workers who fit the inclusion criteria were included in the study.
	Metric 2: Attrition	High	× 0.4	0.4	With respect to exposure, an exposure score was imputed for 210 members of the cohort who had a record that reported a single job title without a job description; the study authors validated that imputation methods did not bias the results. With respect to outcome, the number of incidence cases was incomplete, because cancer incidence was followed-up only from 1988 to 2000 (and not before 1988). 63 subjects were excluded because company records contained no job title or code information. Of the 6107 male workers included in the study, 6044 had available exposure assessments and were included in the cancer deaths from 1950-2001, 5149 were included in the cancer death subcohort from 1988-2000, and 5049 were included in the cancer incidence between 1988-2000.
	Metric 3: Comparison Group	High	× 0.2	0.2	Elements of the study design were reported. Subjects were selected for the study based on the same inclusion/exclusion criteria, and were selected from the same eligible population. The comparison group consisted of non-exposed workers at the same company.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Exposure was assessed from a job exposure matrix (JEM) based on data from walk-through visits, interviews, and reviews of historical reports covering the entire work history. Exposure was rated by an industrial hygienist and reviewed by two of the investigators. Assessments were made blind to the cancer status. Each job title was assigned a 1 to 4 category reflecting relative intensity of exposure over three time periods. A time-dependent intensity score was generated with the JEM for each chemical exposure and worker.

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Study Citation:	Zhao, Y; Krishnadasan, A; Kennedy, N; Morgenstern, H; Ritz, B (2005). Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers American Journal of Industrial Medicine, 48(4), 249-258
Data Type:	TCE_KidneyCancer_HighExposure-Cancer
HERO ID:	708570

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Each job was categorized as to exposure level (none, low, medium, or high). Cumulative exposure levels were determined by multiplying the exposure score of the job by the duration of time at that job (low, medium, and high categories).
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure to TCE (1950 to 1993) preceded cancer incidence (1988 to 2000) and mortality (1950 to 2001).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes were assessed using well-established methods (i.e. consultation of registries). Cancer incidence data were obtained from the California cancer registry and from registries from other select states (1988 to 2000 only). Cancer mortality data were obtained from company records, the Social Security Administration, vital statistics files for California, and/or the U.S. National Death Index (NDI). Cancer mortality data were verified (when applicable) by reviewing information on death certificates.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	A description of measured outcomes is presented in the methods section. Effects estimates are presented with confidence intervals and the number of subjects.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments were made for potential confounders (including SES, time since first employment, etc). Race was not controlled for, but according to death certificates, 96% of decreased workers were white. Smoking status was not available for most of the subjects, but the authors assessed the potential for confounding in the small subset of subjects with the information available. Only a weak association was observed between smoking and exposure to TCE.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Personnel record information was used to obtain data on covariates (e.g., SES). No data on race were available. Data on tobacco smoking (limited in scope) were determined from medical questionnaires. There was no evidence of confounding.

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Study Citation:	Zhao, Y; Krishnadasan, A; Kennedy, N; Morgenstern, H; Ritz, B (2005). Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers American Journal of Industrial Medicine, 48(4), 249-258
Data Type:	TCE_KidneyCancer_HighExposure-Cancer
HERO ID:	708570

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures to pollutants were adjusted for (i.e., PAH, hydrazine, mineral oil). Benzene exposure was not associated with any of the cancers and was stated not to appear to confound the estimates of other chemicals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate to address the research question. The retrospective cohort design was appropriate to study multiple outcomes based on exposures occurring in a specific occupational population.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants is adequate to detect an effect in the exposed population. There were 6107 subjects included with at least 5000 subjects for any given analysis.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to be conceptually reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Methods for calculating effects estimates 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		1.3	
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 27: **Nagaya et al. 1989: Evaluation of Genotoxicity Outcomes**

Study Citation:	T. Nagaya, N. Ishikawa, H. Hata (1989). Sister-chromatid exchanges in lymphocytes of workers exposed to trichloroethylene Mutation Research, 222(3,3), 279-282
Data Type:	TCE_exposed workers_SCE_lymphocytes-Other (please specify below)
HERO ID:	724723

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	The setting (location), participation rate, inclusion and exclusion criteria, and methods of participant selection were not reported.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of individuals at stages of study and reasons for non participation were not provided .
	Metric 3:	Comparison Group	Unacceptable	× 0.2	0.04	Sources and methods of selection of participants in all exposure groups were not reported. Controls were matched on sex, age, and smoking habits; however, the population(s) sampled for controls and exposed persons was not described except that "controls were various workers who had not used TCE or any other organic solvents". The paper does not specify whether the exposed and control groups were from the same facility/type of facility, area, etc.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	Exposure was assessed by employment and by urinary total trichloro compound levels. Exposure characterization was limited to "workers had constantly used TCE in their jobs" and "controls were various workers who had not used TCE or any other organic solvents". No details of facility type, degree or frequency of TCE exposure, etc. were provided. Urinary total trichloro compound concentration was also reported but for exposed subjects only; this metric was not clearly defined (except as analyzed by alkaline-pyridine method) and may not be specific to TCE exposure.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reports 2 levels exposure (exposed/not exposed) by employment characterization, and reports urinary total trichloro concentration per person for exposed persons only (not controls)
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposed participants had worked with TCE "constantly" for an average of 9.7 yrs before blood samples taken for SCE determination. However, the range of employment durations was wide (0.7-34 yrs) and the number of exposed subjects was small (22) suggesting a potential for misclassification of exposure.

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Study Citation:	T. Nagaya, N. Ishikawa, H. Hata (1989). Sister-chromatid exchanges in lymphocytes of workers exposed to trichloroethylene Mutation Research, 222(3,3), 279-282
Data Type:	TCE_exposed workers_SCE_lymphocytes-Other (please specify below)
HERO ID:	724723

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	SCEs were evaluated with well-established method. Number of cells evaluated/person appeared to be appropriate (25 cells containing 46 chromosomes each/person)
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Description of the measured outcomes is reported, and outcome is reported for each individual (exposed and control) as well as in summary form (mean and SD, by smoking status and across all exposed and control).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Matching was used to control for age, sex, and smoking status; data were also presented after stratification by smoking status. However, other potential confounders (workplace co-exposures, health conditions/medications, etc.) were neither evaluated nor controlled for.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Matching was used to control for age, sex, and smoking status. Smoking/nonsmoking was defined "subjects referred to as 'nonsmokers' in both groups had not smoked for at least the last 2 years. Each 'smoker' smoked 10-50 cigarettes per day". There was no attempt to characterize other potential covariates (workplace co-exposures, health conditions/medications, etc.).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	No information was reported on co-exposures. Controls were described as "workers who had not used TCE or any other organic solvents", while no information was provided on potential exposure to other organic solvents among the exposed participants, suggesting the possibility/likelihood of unbalanced provision of co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.5	1	Data analyzed by student's t-test and linear correlation analysis.
	Metric 13:	Statistical power	Unacceptable	× 0.25	0.06	There were 22 exposed and 22 control participants; this number is unlikely to be adequate to detect an effect.
	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

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Study Citation:	T. Nagaya, N. Ishikawa, H. Hata (1989). Sister-chromatid exchanges in lymphocytes of workers exposed to trichloroethylene Mutation Research, 222(3,3), 279-282
Data Type:	TCE_exposed workers_SCE_lymphocytes-Other (please specify below)
HERO ID:	724723

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Not Rated	NA	NA	A statistical model was not 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‡		Unacceptable⋆⋆		2.5	
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.

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

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 28: **Boice et al. (2006): Evaluation of Cancer Outcomes**

Study Citation:	Boice, JD; Marano, DE; Cohen, SS; Mumma, MT; Blot, WJ; Brill, AB; Fryzek, JP; Henderson, BE; Mclaughlin, JK (2006). Mortality among Rocketdyne workers who tested rocket engines, 1948-1999 Journal of Occupational and Environmental Medicine, 48(10), 1070-1092
Data Type:	TCE_Workers_SMR_kidney cancer-Cancer
HERO ID:	729549

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	North American Aviation established Santa Susana Field Laboratory (SSFL) between Los Angeles and Ventura counties that tests rocket engines The cohort comprised of 41,123 Rocketdyne male workers employed in 1948 and on for at least 6 months. Exposure was assumed for those mechanics and technicians and less exposed workers were selected from nearby Rocketdyne facilities that did not test rocket engines - these workers also resided in the same communities and had similar socioeconomic characteristics and access to health care. Exclusion criteria is clear and well demonstrated in Figure 1
	Metric 2: Attrition	High	× 0.4	0.4	Of 54,384 unique workers - 6,601 worked less than 6 months, 289 had inadequate work history, 524 were not Rocketdyne employees, and 5,619 engaged in radiation work and were studied separately - leaving 41,351 eligible workers (8,372 SSFL workers and 32,979 workers at nearby facilities). Cause of death unavailable for 241 (0.5%) which were then excluded of the 9680 workers found to have died
	Metric 3: Comparison Group	High	× 0.2	0.2	4 comparison groups to allow for external and internal comparisons. External comparison was based on race-, age-, calendar-year, and gender-specific rates in the general population of CA and the US. The internal comparison was made to a group selected from nearby Rocketdyne facilities that did not test rocket engines. These workers also resided in the same communities and had similar socioeconomic characteristics and access to health care.
Domain 2: Exposure Characterization					

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Study Citation:	Boice, JD; Marano, DE; Cohen, SS; Mumma, MT; Blot, WJ; Brill, AB; Fryzek, JP; Henderson, BE; Mclaughlin, JK (2006). Mortality among Rocketdyne workers who tested rocket engines, 1948-1999 Journal of Occupational and Environmental Medicine, 48(10), 1070-1092
Data Type:	TCE_Workers_SMR_kidney cancer-Cancer
HERO ID:	729549

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Potential for exposure based on job title and years worked. 4 groups of workers; mechanics and technicians (heaviest chemical exposure - washed hands with TCE and had other direct contact), inspectors, engineers, instrumentation mechanics. Participants were invited in to discuss prior exposure and personal protective equipment worn.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	No approximation of intensity of exposure. Any TCE exposure O/E.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Approximately 8% of workers had <10years follow up.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Vital status as of 1999 was obtained; mortality sourced from California death tapes, the national death index, pension benefit information files, Social Security master file, health care financing administration employment works history cards, pension records and retirement records. Cause of death coded to international classification of disease in use at time of death from death certificates and coded by nosologist for underlying cause of death
	Metric 8:	Reporting Bias	High	× 0.333	0.33	SMRs and RR estimates are provided with 95% CIs
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Description of comparison group suggest that external analysis is adjusted for race-, age-, calendar-year, and gender-specific rates. RR estimates for internal analysis were adjusted for year of birth and year of hire (also some analyses were adjusted for gender and pay type).
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Covariate information was obtained from worker records.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Adjusted for hydrazine. Exposure to other chemicals (asbestos, beryllium, rocket fuels, oxidizers, exhaust gasses, and solvents) not considered likely.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cohort of workers who worked directly with TCE as part of rocket fuel production were selected and studied for adverse outcomes of cancer following employment with Rocketdyne

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Study Citation:	Boice, JD; Marano, DE; Cohen, SS; Mumma, MT; Blot, WJ; Brill, AB; Fryzek, JP; Henderson, BE; Mclaughlin, JK (2006). Mortality among Rocketdyne workers who tested rocket engines, 1948-1999 Journal of Occupational and Environmental Medicine, 48(10), 1070-1092
Data Type:	TCE_Workers_SMR_kidney cancer-Cancer
HERO ID:	729549

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Number of workers is adequate to detect an effect (n=41,123)
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	details provided on how analysis was conducted to determine RRs and SMRs
	Metric 15:	Statistical models	Medium	× 0.2	0.4	RR was approximated by Cox proportional hazard models for categories of years worked at nearby company and years worked as a test stand mechanic (directly with TCE). SMRs calculated excluding the first 10 years of follow up
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 29: **Nordstrom et al. 1998: Evaluation of Cancer Outcomes**

Study Citation:	Nordström, M; Hardell, L; Magnuson, A; Hagberg, H; Rask-Andersen, A (1998). Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study British Journal of Cancer, 77(11), 2048-2052
Data Type:	TCE_HairyCellLeukemia-Cancer
HERO ID:	729570

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Population-based study consisted of 121 male patients with hairy-cell leukemia reported to the Swedish Cancer Registry between 1987 and 1992. One case later turned out to have been diagnosed in 1993, but was still included in the analysis. Four controls for each case (484 in total) were drawn from the National Population Registry, matched for age and county. Subject characteristics besides exposure to various chemicals are not presented.
	Metric 2: Attrition	Medium	× 0.4	0.8	There was a minimal loss of subjects in the study. The study authors indicated that the questionnaire was answered by 91% of cases and 83% of controls. Ten cases and 84 controls refused to participate. For medical reasons, three cases and five controls were not capable of answering the questionnaire themselves. Proxy answers were used for these subjects.
	Metric 3: Comparison Group	Low	× 0.2	0.6	Controls (n = 400) were matched to cases by age and county (using information from the National Population Register). Only living cases and males were used to minimize recall bias. However, the matching was dissolved in the analysis to use all information obtained. By dissolving the matching bias may have been introduced by not controlling for county.
Domain 2: Exposure Characterization					

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Study Citation:	Nordström, M; Hardell, L; Magnuson, A; Hagberg, H; Rask-Andersen, A (1998). Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study British Journal of Cancer, 77(11), 2048-2052
Data Type:	TCE_HairyCellLeukemia-Cancer
HERO ID:	729570

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was assessed via a self-administered questionnaire (with telephone interview follow-up, when applicable). While the information obtained from the questionnaire included a complete work history (leisure activities, etc). the study does not indicate how job titles were used to assign TCE exposure. supplementary questions were made over the phone by a trained interviewer, using written instructions. The total numbers of days of exposure to various agents were estimated. A minimum exposure of 1 working day (8 h) and an induction period of at least 1 year were used in the coding of exposures to chemicals. Some exposures (e.g. organic solvents) that may occur both in leisure time activities and occupationally were calculated together in the coding process. All interviews and all coding were made blinded with respect to the persons case or control status
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reports two levels of TCE exposure only (exposed or unexposed).
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established, but it is unclear when exposure occurred relative to leukemia incidence. The study indicates that there was a minimum exposure of 1 working day and an induction period of 1 year.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cases were selected based on cancer registry information. The compulsory notification to the Swedish Cancer Registry makes it plausible that most cases of hairy cell leukemia were identified. A previous study concluded that only 6.7% of cases of lymphomas were not reported to this registry (Martinsson et al, 1992). It is, however, a possibility that patients with hairy cell leukemia might be misdiagnosed and treated under other diagnoses.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Data for hairy cell leukemia incidence are reported in a way that is amenable to data extraction (number of exposed cases and controls; OR with CIs).
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Nordström, M; Hardell, L; Magnuson, A; Hagberg, H; Rask-Andersen, A (1998). Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study British Journal of Cancer, 77(11), 2048-2052
Data Type:	TCE_HairyCellLeukemia-Cancer
HERO ID:	729570

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Other than the criteria used for matching (i.e., age and county), other potential confounders were not accounted for statistically. It appears that information for smoking was available. Unmatching also caused lack of accounting for county in some analyses.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Information on age and county was presumably obtained from registries (National Population Registry, Cancer Registry,). Limited information on other covariates (evaluated in the questionnaire) was reported.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Exposure to other substances was assessed in the study (herbicides, insecticides, organic solvents). There was no indication of an unbalanced provision of additional exposures across groups. Potential confounding between exposures of interest was evaluated using multivariate analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design (population based case control) was appropriate to address the research question. The case-control study used logistic regression to estimate the risk of illness associated with exposure.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were small numbers of exposed cases (n = 9) and controls (n = 26), limiting the statistical power of the analyses.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analyses used logistic regression, controlling for age. All of the calculations were performed using the EGRET program
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression, controlling for age was used to estimate odds ratios and confidence intervals
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:	Nordström, M; Hardell, L; Magnuson, A; Hagberg, H; Rask-Andersen, A (1998). Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study British Journal of Cancer, 77(11), 2048-2052
Data Type:	TCE_HairyCellLeukemia-Cancer
HERO ID:	729570

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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 30: **Persson and Fredrikson, 1999: Evaluation of Cancer Outcomes**

Study Citation:	Persson, B; Fredrikson, M (1999). Some risk factors for non-Hodgkin's lymphoma International Journal of Occupational Medicine and Environmental Health, 12(2), 135-142
Data Type:	Pooled case control study of NHL TCE-exposed workers-Cancer
HERO ID:	729578

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Data from two studies were pooled. Cases from the first study were diagnosed between 1964 and 1986 and obtained from the register at the Department of Oncology, Orebra Medical Centre Hospital. Cases from the second study were identified in the Regional Cancer Registry at the University Hospital in Linkopinf and were diagnosed between 1975 and 1984. This study applied some additional inclusion criteria, which were described. The response rates for the two studies were noted to be 96 and 90 percent, respectively. Controls were randomly drawn from the population registers.
	Metric 2: Attrition	High	× 0.4	0.4	Study participation was 90-96%. There does not appear to be any exclusion from the analysis as methods indicate 199 cases and 479 controls and the results table indicates 199 cases and 479 controls.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Controls were randomly selected and the same inclusion criteria were applied. Referents were selected from the same geographic area and results were stratified by age and gender.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Mailed questionnaire only (9 pages). For solvents, qualitative information was obtained from the questionnaires. Five categories of intensity were also assessed, but merged into two categories. It was noted that additional information could be found in Persson et al., 1989 (HERO ID 728757) and Persson et al., 1993 (HERO ID 729579), although neither study provided additional details.
	Metric 5: Exposure levels	Low	× 0.2	0.6	There were only two categories, no and any exposure.
	Metric 6: Temporality	Medium	× 0.4	0.8	Temporality was established, but unclear if the exposure falls within the relevant exposure windows for the outcome of interest as it considered minimum latency of 5 to 45 years without detailing when exposure occurred in relation to the diagnosis.
Domain 3: Outcome Assessment					

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Study Citation:	Persson, B; Fredrikson, M (1999). Some risk factors for non-Hodgkin's lymphoma International Journal of Occupational Medicine and Environmental Health, 12(2), 135-142
Data Type:	Pooled case control study of NHL TCE-exposed workers-Cancer
HERO ID:	729578

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	In the first study a physician at the Department of Oncology confirmed the diagnosis, but it was not stated that the confirmation was based on histopathology or what information confirmation was based. In the second study, two pathologists at the University Hospital in Linkoping re-examined the histopathological specimens. It was noted that only 5 of the histologically confirmed cases in the second study were considered to be misclassified.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Effect estimates are reported with confidence intervals and the number of exposed cases and controls.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	Only adjusted for age and sex, no other cofounders were considered or discussed including smoking or socioeconomic status.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Assessed by questionnaire; only age and sex were considered and are likely fairly accurate when self-reported.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Other exposures were described , but not adjusted for nor is there sufficient information to determine if there were specific co-exposures that could have biased the TCE results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control design is appropriate for studying if multiple different exposures are associated with a specific outcome.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	16 of 199 cases and 32 of 479 controls were exposed to TCE, which is likely sufficient to detect an effect, although was associated with large confidence intervals in this study.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Methods provide some details on the use of Mantel-Haenszel odds ratios and when logistic regression models were used.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Methods provide some details on the use of Mantel-Haenszel odds ratios and when logistic regression models were 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	

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Study Citation:	Persson, B; Fredrikson, M (1999). Some risk factors for non-Hodgkin's lymphoma International Journal of Occupational Medicine and Environmental Health, 12(2), 135-142
Data Type:	Pooled case control study of NHL TCE-exposed workers-Cancer
HERO ID:	729578

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		2.0	
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 31: **Charbotel et al. 2006: Evaluation of Cancer Outcomes**

Study Citation:	Charbotel, B; Fevotte, J; Hours, M; Martin, JL; Bergeret, A (2006). Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects Annals of Occupational Hygiene, 50(8), 777-787
Data Type:	Case-control study of renal cell cancer in occupational workers-Cancer
HERO ID:	729633

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Study described setting, participation rate,inclusion and exclusion criteria, and methods of case ascertainment. Participation was similar in cases and controls.
	Metric 2:	Attrition	Medium	× 0.4	0.8	8 cases and 10 controls were lost to follow up. Moderate attrition, but exposure and outcome data were largely complete.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Gender and age-matched controls; controls per case (if possible).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Job exposure matrix and occupational questionnaire (cumulative a peak exposures evaluated).. Described in 729415.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	5 exposure groups were described in 729415 (1-35 35-50, 50-75, 75-100, >100 ppm).
	Metric 6:	Temporality	High	× 0.4	0.4	Cases were selected retrospectively from 1993 to 2000. The exposure assessment describes exposure period by decades starting in the 1930s. The number of job periods involving TCE exposure reached a maximum in the 1970s.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Diagnosis by physican.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Odds ratio with confidence itervals, number of cases and controls reported for each exposure analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for smoking and BMI.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Based on data from questionnaires.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	OR was adjusted for other occupational exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design and conditional logistic regression analysis was appropriate to evaluate the risk of renal cell cancer associated with occupational TCE exposures.

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Study Citation:	Charbotel, B; Fevotte, J; Hours, M; Martin, JL; Bergeret, A (2006). Case-control study on renal cell cancer and occupational exposure to trichloroethylene. Part II: Epidemiological aspects Annals of Occupational Hygiene, 50(8), 777-787
Data Type:	Case-control study of renal cell cancer in occupational workers-Cancer
HERO ID:	729633

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Adequate to detect an effect in the primary analysis. The statistical power may not have been high enough when an adjustment was made for exposure to cutting fluids.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The conditional logistic regression analyses and the three exposure metrics were described sufficiently.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The conditional logistic regression analyses are transparent and authors discuss how covariates were tested for inclusion in multivariate models.
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 32: **Cocco et al. 2010: Evaluation of Cancer Outcomes**

Study Citation:	Cocco, P; T'Mannetje, A; Fadda, D; Melis, M; Becker, N; de Sanjosé, S; Foretova, L; Mareckova, J; Staines, A; Kleefeld, S; Maynadié, M; Nieters, A; Brennan, P; Boffetta, P (2010). Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study Occupational and Environmental Medicine, 67(5), 341-347
Data Type:	TCE_CaseControl_B-NHL_OR-Cancer
HERO ID:	729998

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	This study is part of the Epilymph study, a multicenter case-control study in the Czech Republic, France, Germany, Ireland, Italy and Spain focused on lymphoid neoplasms and environmental exposures conducted from 1998 to 2004. Controls selected from the population (Germany and Italy) or hospital patients without cancer, infectious diseases or immunodeficient diseases.
	Metric 2: Attrition	Medium	× 0.4	0.8	Participation rates of 88% (cases), 81% (hospital controls) and 52% (population controls). There was a low response rate from two centers from which controls were obtained.
	Metric 3: Comparison Group	High	× 0.2	0.2	Cases of lymphoma were matched to controls in the general population based on sex, age, and residence area, or matched to hospital controls (diagnoses other than cancer, infectious and immunodeficiency-related diseases). Other potential differences (i.e., age, gender, education, and center) were controlled for in the statistical analyses.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	In-person interviews were used to detail any jobs (based on self-reporting) held for more than 1 year were evaluated. job histories were coded using international standards, which were then used in a job-exposure matrix for 43 chemicals by industrial hygienists. Cumulative exposure scores calculated based on confidence (degree of certainty that exposure occurred), intensity (unexposed, low, medium, and high), and frequency (unexposed, 1-5% work time, >5-30% work time, >30% work time).
	Metric 5: Exposure levels	Medium	× 0.2	0.4	For analyses, cumulative exposure was classified as ever/never or low, medium, and high; only subjects with a high degree of confidence were included.
	Metric 6: Temporality	Low	× 0.4	1.2	Timing of TCE exposure relative to the diagnosis of lymphoma unknown.
Domain 3: Outcome Assessment					

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Study Citation:	Cocco, P; T'Mannetje, A; Fadda, D; Melis, M; Becker, N; de Sanjosé, S; Foretova, L; Mareckova, J; Staines, A; Kleefeld, S; Maynadié, M; Nieters, A; Brennan, P; Boffetta, P (2010). Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study Occupational and Environmental Medicine, 67(5), 341-347
Data Type:	TCE_CaseControl_B-NHL_OR-Cancer
HERO ID:	729998

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Lymphoma cases identified in patients in region centers classified according to the WHO Classification of Lymphoma; about 20% of cases from each center were also validated (by viewing slides) by a panel of pathologists. The incidence of lymphoma was classified by subtype (B-NHL,T-lymphoma, Hodgkin's lymphoma, diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, chronic lymphocytic lymphoma [CLL], and/or multiple myeloma).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Odds ratios (ORs) with 95% confidence intervals provided for ever/never and low, medium or high cumulative exposures. Some exposures provided in supplemental materials (not freely available), but ORs for TCE exposure provided by lymphoma subtype.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjustments were made for potential confounders in the statistical analyses (age, sex, education, and center). Other factors (smoking, alcohol consumption) were not factored into the statistical analyses because previous work showed no associations.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders were assessed in face-to-face interviews.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Exposure to 43 chemicals was assessed in the study. Solvents stated to be correlated, but details not provided.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control study evaluated links between lymphoma and 43 environmental pollutants as part of a multi-center study crossing 6 countries. Logistic regression analysis was used to calculate ORs for lymphoma subtypes and exposures.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 9-71 cases (across lymphoma subtypes) with TCE exposure, relative to 117 unexposed controls, which was sufficient for a significant trend in risk.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Adjustments and methods used to determine odds ratios are transparent, as are the number of cases/controls used for each effect estimate.

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Study Citation:	Cocco, P; T'Mannetje, A; Fadda, D; Melis, M; Becker, N; de Sanjosé, S; Foretova, L; Mareckova, J; Staines, A; Kleefeld, S; Maynadié, M; Nieters, A; Brennan, P; Boffetta, P (2010). Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study Occupational and Environmental Medicine, 67(5), 341-347
Data Type:	TCE_CaseControl_B-NHL_OR-Cancer
HERO ID:	729998

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratios (OR) determined with unconditional logistic regression. Adjustments clearly stated (age, sex, education, location). Although the multiple comparisons performed may have increased the chance for false positives, additional corrections were made (Bonferroni correction, trend tests) to minimize this effect.
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: **Barry et al. 2011: Evaluation of Cancer Outcomes**

Study Citation:	Barry, KH; Zhang, Y; Lan, Q; Zahm, SH; Holford, TR; Leaderer, B; Boyle, P; Hosgood, HD; Chanock, S; Yeager, M; Rothman, N; Zheng, T (2011). Genetic variation in metabolic genes, occupational solvent exposure, and risk of non-hodgkin lymphoma American Journal of Epidemiology, 173(4), 404-413
Data Type:	Barry_TCE_exposed workers_NHL-Cancer
HERO ID:	730513

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Participation rates provided as well as eligibility criteria.
	Metric 2:	Attrition	High	× 0.4	0.4	Study is a reanalysis of a case control study that included only participations with blood and or buccal cell samples (additional analyses evaluated genotypes). The subset of cases and controls with samples was similar (86 and 83%, respectively). No further attrition occurred.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were frequency-matched to cases, identified through random digit dialing and random selection from Centers for Medicare and Medicaid Services records. It is unclear if the controls were recruited from the same eligible population. No comparison between the groups are provided other than the application of frequency matching for age.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	A standardized structured questionnaire was used to collect information for the construction of a job-exposure matrix. Exposure was not directly measured and detailed employment records were not utilized.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was characterized as 'ever' or 'never' exposed' (2 levels of exposure)
	Metric 6:	Temporality	Medium	× 0.4	0.8	Little information is provided on the establishment of exposure prior to the ascertainment of the outcome.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcome assessed using well-established methods. Histologically confirmed incident NHL.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Effect estimate is reported with a confidence interval with the number of cases and controls that would allow with data extraction.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Barry, KH; Zhang, Y; Lan, Q; Zahm, SH; Holford, TR; Leaderer, B; Boyle, P; Hosgood, HD; Chanock, S; Yeager, M; Rothman, N; Zheng, T (2011). Genetic variation in metabolic genes, occupational solvent exposure, and risk of non-hodgkin lymphoma American Journal of Epidemiology, 173(4), 404-413
Data Type:	Barry_TCE_exposed workers_NHL-Cancer
HERO ID:	730513

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for age (continuous) and race (white/nonwhite). The addition of family history of hematopoietic disorders, alcohol consumption, tobacco smoking, education, annual family income, and medical history of immune-related disease did not appreciably alter effect estimates for solvent associations with NHL outcomes, and thus these covariates were not included in the final models
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	No method validation mentioned but no evidence that the method had poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Analyses not adjusted for co-exposure to other organic solvents evaluated by JEM
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 an appropriate statistical methods was used to address the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls were adequate to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis was sufficient to understand what was done.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The model for calculating the OR 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		1.6	
Extracted			Yes			

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Study Citation:	Barry, KH; Zhang, Y; Lan, Q; Zahm, SH; Holford, TR; Leaderer, B; Boyle, P; Hosgood, HD; Chanock, S; Yeager, M; Rothman, N; Zheng, T (2011). Genetic variation in metabolic genes, occupational solvent exposure, and risk of non-hodgkin lymphoma American Journal of Epidemiology, 173(4), 404-413
Data Type:	Barry_TCE_exposed workers_NHL-Cancer
HERO ID:	730513

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 34: **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_TCE_OR_Q3-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_TCE_OR_Q3-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_TCE_OR_Q3-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_TCE_OR_Q3-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.

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

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: **Billionnet et al. 2011: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_asthma-Hematological and Immune
HERO ID:	733119

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Main residences were randomly identified and chosen in a three-stage procedure. 4165 households were contacted with a response and participation rate of 19.5% and 13.6%, respectively. These households were sampled from numerous areas throughout France (74 municipalities). This study samples from a very inclusive population.. The study authors indicate that there was no difference between participants and non-participants except for median age (adjusted for in final model).
	Metric 2: Attrition	High	× 0.4	0.4	Low response rate from randomly selected households. Individuals residing in 77/567 dwellings did not complete health questionnaire and were excluded. The non-responding population did not differ from responding population regarding sex distribution, occupation, or educational level, but were significantly younger (median age of 36 vs. 44 years). Age was adjusted for in the final model.
	Metric 3: Comparison Group	High	× 0.2	0.2	Subjects were recruited from the same general population and potential confounders were assessed in the statistical analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Air monitoring was conducted for one week using passive samplers in the bedroom of the reference participant (radial diffuse sampling onto carbograph four adsorbents [Radiello, Fondazione Salvatore Maugeri (FSM)]). VOCs extracted through thermodesorption and analyzed by GC-MS. Questionnaires were also filled out to help interpret the activity of the household during the sampling period.
	Metric 5: Exposure levels	Low	× 0.2	0.6	Due to the amount of samples either below LOD or between the LOD and LOQ, subjects were divided into <Q3 and >Q3 (low vs. high exposed) for analysis. This represents only two levels of exposure.

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Study Citation:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_asthma-Hematological and Immune
HERO ID:	733119

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Low	× 0.4	1.2	Current exposures were used to evaluate incidence of rhinitis and asthma over the past month and past year. It is likely that the exposure levels are representative of exposures in the past year, but cannot be confirmed without longitudinal analysis. 97% of participants had lived in the home for the entire year preceding the study.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Outcome data were self-reported from a questionnaire derived from the International Study of Asthma and Allergies in Childhood. This represents self-reported information. Questions did not appear to be framed as asking about doctor diagnosis, but rather symptoms present. Results were not confirmed by physician or medical records.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All PECO-related outcomes outlined in the abstract, introduction, and methods were discussed in the results. Some results were only presented in a forest plot. Correlations between different pollutants was described qualitatively, but full results were not provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for gender, age, smoking habit, relative humidity ,time of survey, presence of pets, presence of mold, and the highest educational level among individuals of the dwelling and outdoor pollution
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Study authors state detailed surveys were administered within the home and other structured questionnaires were used to determine technical features of a dwelling that related to sample collection/measured VOC concentrations. Weekly logs were completed by the inhabitants to help inform the VOC measurements. A feasibility pilot study was conducted years prior (separate from current study population).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Models were not adjusted for other measured exposures. VOC score was analyzed as a separate outcome.
Domain 5: Analysis						

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Study Citation:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_asthma-Hematological and Immune
HERO ID:	733119

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study aimed to determine the effects of exposure to 20 VOCs in French households on adult rhinitis and asthma. This was a large cross-sectional study utilizing passive air samplers to determine exposure.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 490 dwellings and 1092 individuals included in the final analysis. There was enough statistical power to determine an effect. No issues.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of accounting for multiple exposure, participants of the same dwelling, and other potential confounders were adequately explained and could be reproduced given original data and information. The description of the analysis was transparent.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	GEE models were used to examine associations between health indicies individual VOC concentrations, and VOC score. GEE models were also used to account for participants from the same dwelling. A sensitivity analysis was also done to examine the effect of unrelated participants of the same dwelling. Due to the number of samples below the LOQ, the analysis of TCE was looked at as a dichotomous exposure--at or below 3rd quartile vs above 3rd quartile.
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:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_asthma-Hematological and Immune
HERO ID:	733119

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 36: **Billionnet et al. 2011: Evaluation of Respiratory Outcomes**

Study Citation:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_rhinitis-Respiratory
HERO ID:	733119

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Main residences were randomly identified and chosen in a three-stage procedure. 4165 households were contacted with a response and participation rate of 19.5% and 13.6%, respectively. These households were sampled from numerous areas throughout France (74 municipalities). This study samples from a very inclusive population.. The study authors indicate that there was no difference between participants and non-participants except for median age (adjusted for in final model).
	Metric 2:	Attrition	High	× 0.4	0.4	Individuals residing in 77/567 dwellings did not complete health questionnaire and were excluded. The non-responding population did not differ from responding population regarding sex distribution, occupation, or educational level, but were significantly younger (median age of 36 vs. 44 years). Age was adjusted for in the final model.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Subjects were recruited from the same general population and potential confounders were assessed in the statistical analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Air monitoring was conducted for one week using passive samplers in the bedroom of the reference participant (radial diffuse sampling onto carbograph four adsorbents [Radiello, Fondazione Salvatore Maugeri (FSM)]). VOCs extracted through thermodesorption and analyzed by GC-MS. Questionnaires were also filled out to help interpret the activity of the household during the sampling period.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Due to the amount of samples either below LOD or between the LOD and LOQ, subjects were divided into <Q3 and >Q3 (low vs. high exposed) for analysis. This represents only two levels of exposure.

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Study Citation:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_rhinitis-Respiratory
HERO ID:	733119

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Low	× 0.4	1.2	Current exposures were used to evaluate incidence of rhinitis and asthma over the past month and past year. It is likely that the exposure levels are representative of exposures in the past year, but cannot be confirmed without longitudinal analysis. 97% of participants had lived in the home for the entire year preceding the study.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Outcome data were self-reported from a questionnaire derived from the European Community Respiratory Health Survey. This represents self-reported information. Questions did not appear to be framed as asking about doctor diagnosis, but rather symptoms present. Results were not confirmed by physician or medical records.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All PECO-related outcomes outlined in the abstract, introduction, and methods were discussed in the results. Some results were only presented in a forest plot. Correlations between different pollutants was described qualitatively, but full results were not provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for gender, age, smoking habit, relative humidity, time of survey, presence of pets, presence of mold, and the highest educational level among individuals of the dwelling and outdoor pollution. Age, sex, and smoking were included a priori, others were selected if they affected 20% or more of coefficient estimates. Utilized consistent confounder inclusion across chemicals.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Study authors state detailed surveys were administered within the home and other structured questionnaires were used to determine technical features of a dwelling that related to sample collection/measured VOC concentrations. Weekly logs were completed by the inhabitants to help inform the VOC measurements. A feasibility pilot study was conducted years prior (separate from current study population).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Models were not adjusted for other measured exposures. VOC score was analyzed as a separate outcome.

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Study Citation:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_rhinitis-Respiratory
HERO ID:	733119

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study aimed to determine the effects of exposure to 20 VOCs in French households on adult rhinitis and asthma. This was a large cross-sectional study utilizing passive air samplers to determine exposure.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 490 dwellings and 1092 individuals included in the final analysis. There was enough statistical power to determine an effect. No issues.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Description of accounting for multiple exposure, participants of the same dwelling, and other potential confounders were adequately explained and could be reproduced given original data and information. The description of the analysis was transparent.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	GEE models were used to examine associations between health indicies individual VOC concentrations, and VOC score. GEE models were also used to account for participants from the same dwelling. A sensitivity analysis was also done to examine the effect of unrelated participants of the same dwelling. Due to the number of samples below the LOQ, the analysis of TCE was looked at as a dichotomous exposure--at or below 3rd quartile vs above 3rd quartile.
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:	Billionnet, C., Gay, E., Kirchner, S., Leynaert, B., Annesi-Maesano, I (2011). Quantitative assessments of indoor air pollution and respiratory health in a population-based sample of French dwellings Environmental Research, 111(3), 425-434
Data Type:	Billionnet_TCE_residential_rhinitis-Respiratory
HERO ID:	733119

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 37: **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:	TCE_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 period 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:	TCE_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 meteorologic 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:	TCE_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:	TCE_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 38: **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 TCE through soil vapor intrusion-all 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 period (NY State). QC[BG] 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	QC[BG] 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	QC[BG] 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	QC[BG] 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	Exposed vs. unexposed
	Metric 6:	Temporality	Medium	× 0.4	0.8	Birth records from 1978-2002. Exposures through soil vapor intrusion may date back the 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	QC[BG] 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 TCE through soil vapor intrusion-all cardiac defects-Cardiovascular
HERO ID:	827030

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	QC[BG] 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 from birth records. [BG] These data are generally valid in birth certificates.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	QC[BG] 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. QC[BG] 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 TCE through soil vapor intrusion-all 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 39: **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 (TCE, 1-4 year 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 of these 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 similar to 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 (TCE, 1-4 year 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 58% of the 5543 TCE 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 (TCE, 1-4 year 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 TCE exposed workers, 71%, 42%, 52% and 1.4% were also exposed to chromate, PCE, 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 (TCE, 1-4 year 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 40: **Zhang et al. 2013: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Zhang, L., Bassig, B. A., Mora, J. L., Vermeulen, R., Ge, Y., Curry, J. D., Hu, W., Shen, M., Qiu, C., Ji, Z., Reiss, B., McHale, C. M., Liu, S., Guo, W., Purdue, M. P., Yue, F., Li, L., Smith, M. T., Huang, H., Tang, X., Rothman, N., Lan, Q. (#year#). Alterations in serum immunoglobulin levels in workers occupationally exposed to trichloroethylene Carcinogenesis,
Data Type:	Zhang_TCE_exposedworkers_IgM_control-Hematological and Immune
HERO ID:	1480812

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Exposed subjects from six factories that use TCE in Guangdong, China; control subjects age- and sex-matched from four factories that did not use TCE in the same geographic region. Complete details were noted to be found in Lan 2010 (HERO ID 736090). There they described the selection for the six factories. Factories were included if they used TCE in manufacturing processes, had no detectable benzene. styrene, ethylene oxide, formaldehyde or epichlorohydrin, and low to negligible levels of other solvents.
	Metric 2:	Attrition	High	× 0.4	0.4	Workers with a history of cancer, chemotherapy, radiotherapy or a previous occupation with notable exposure to benzene, butadiene, styrene and/or ionizing radiation were excluded from the study. There is no evidence of any other attrition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Exposed subjects from six factories that use TCE in Guangdong, China; control subjects age- and sex-matched from four factories that did not use TCE in the same geographic region. A table of characteristics was provided.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Full-shift personal air exposure measurements using 3M organic vapor monitoring badges were made before blood sampling. Samples were analyzed for TCE, but methods were not provided, however, the methods were likely standard for 3M organic vapor monitoring badges.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Exposed group split into high (>median) and low (<median)
	Metric 6:	Temporality	Low	× 0.4	1.2	cross-sectional design. Full-shift air monitoring on the day of blood draw (at end of shift). Unclear if prior exposures impact findings.
Domain 3: Outcome Assessment						

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Study Citation:	Zhang, L., Bassig, B. A., Mora, J. L., Vermeulen, R., Ge, Y., Curry, J. D., Hu, W., Shen, M., Qiu, C., Ji, Z., Reiss, B., McHale, C. M., Liu, S., Guo, W., Purdue, M. P., Yue, F., Li, L., Smith, M. T., Huang, H., Tang, X., Rothman, N., Lan, Q. (#year#). Alterations in serum immunoglobulin levels in workers occupationally exposed to trichloroethylene Carcinogenesis,
Data Type:	Zhang_TCE_exposedworkers_IgM_control-Hematological and Immune
HERO ID:	1480812

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Immunoglobulin levels measured, no assessment of immune function. Unclear if changes in levels observed are biologically relevant for immune function.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All description of measured outcomes is reported in the methods, abstract, and/or introduction. Means with interquartile ranges were provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	All models adjusted for age and sex. Other covariates were evaluated (current smoking, alcohol consumption, BMI, and recent infection), but only included in the final analysis if the regression coefficient was altered by >=10%. Based on analysis, IgE was also adjusted for alcohol and recent infection
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	All subjects were interviewed using a questionnaire that assessed demographic and lifestyle characteristics.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Subjects with prior occupational exposure to benzene, butadiene, styrene, and/or ionizing radiation were excluded. Although it was noted that air samples collected also measured benzene, methylene chloride, perchloroethylene, and epichlorohydrin, no information was provided to indicate that there was not a differential exposure in the TCE or control groups.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants (80 exposed and 45 controls) are adequate to detect an effect in the exposed population even with exposure broken into two groups of 39 and 41 subjects.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand what was done and be conceptually reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Risk estimates were not calculated, but the statistical methods used were transparent and appropriate.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	Biomarkers of exposure were not used; personal air monitoring

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Study Citation:	Zhang, L., Bassig, B. A., Mora, J. L., Vermeulen, R., Ge, Y., Curry, J. D., Hu, W., Shen, M., Qiu, C., Ji, Z., Reiss, B., McHale, C. M., Liu, S., Guo, W., Purdue, M. P., Yue, F., Li, L., Smith, M. T., Huang, H., Tang, X., Rothman, N., Lan, Q. (#year#). Alterations in serum immunoglobulin levels in workers occupationally exposed to trichloroethylene Carcinogenesis,
Data Type:	Zhang_TCE_exposedworkers_IgM_control-Hematological and Immune
HERO ID:	1480812

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	Biomarkers of effect are related to immune function, but the mechanism of action is not fully understood.
	Metric 18:	Method Sensitivity	Low	× 0.2	0.6	LOD are not stated
	Metric 19:	Biomarker stability	High	NA	NA	Stability is not a concern. Blood samples were delivered to the processing lab within 6 hours and were analyzed the same day.
	Metric 20:	Sample contamination	High	× 0.2	0.2	no discussion of sample contamination, but unlikely for the biomarker of effect. Intra- and interassay variation was tested with good results.
	Metric 21:	Method requirements	High	× 0.2	0.2	ELISA assays were used with complete description of the methods including blinding of the technician to exposure status and randomization of the sample to the plates. Intra and interassay variation was also measured and was <10% for each assay.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	No matrix adj conducted or necessary.
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.

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

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 41: **Charbotel et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Charbotel, B., Massardier-Pilonchery, A., Fort, E., Dananché, B., Févotte, J., Confavreux-Romestaing, C., Bergeret, A. (2013). Occupational trichloroethylene exposure and cervical pathology: A case-control study Annals of Occupational Hygiene, 57(3), 407-416
Data Type:	Charbotel_TCE_exposed workers_cervical cancer-Cancer
HERO ID:	1514222

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.25	0.5	Women were recruited form the same eligible population with the same inclusion criteria from the same hospital. Some key elements of the study design were not reported.
	Metric 2: Attrition	High	× 0.4	0.4	Of original 75 cases, four refused to take part or could not be contacted and two were excluded due to lack of appropriate matched control. So initial number was 69 cases and 69 controls. Two withdrew before answering questionnaire, so final number was 67 cases and 67 controls.
	Metric 3: Comparison Group	Unacceptable	× 0.2	0.04	All cases were positive for HPV infection, which study authors state is a necessary factor in the development of cervical cancer. Only 5.8% of controls were positive for HPV infection. HPV infection was not accounted for in statistical analysis. A proper control group would also had 100% HPV infection without cervical cancer - then the potential role of TCE exposure could have been adequately examined.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Task exposure metric, allowing for calculation of cumulative exposures for entire work history. JEM was based on self-reported employment information from participants and exposure was adjusted by industrial hygienist .
	Metric 5: Exposure levels	Medium	× 0.2	0.4	TCE exposure separated into low, medium, and high. This represents three levels of exposure.
	Metric 6: Temporality	Medium	× 0.4	0.8	included subjects with as little as 1 year work history. This represents partial coverage of an appropriate exposure window for the development of cancer, but likely does not include the entire relevant exposure window.
Domain 3: Outcome Assessment					

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Study Citation:	Charbotel, B., Massardier-Pilonchery, A., Fort, E., Dananché, B., Févotte, J., Confavreux-Romestaing, C., Bergeret, A. (2013). Occupational trichloroethylene exposure and cervical pathology: A case-control study Annals of Occupational Hygiene, 57(3), 407-416
Data Type:	Charbotel_TCE_exposed workers_cervical cancer-Cancer
HERO ID:	1514222

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	All diagnoses confirmed by conization samples or other biopsies. Controls confirmed to have healthy cervical cells from cervicovaginal smear. Appears to be done at the same hospital, but it is not stated whether this was abstracted from medical records or done in a blinded fashion.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All PECO-relevant outcomes listed in the abstract, introduction, and methods were provided in the results. Detailed tables of occupational risk factors included.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Unacceptable	× 0.5	0.25	No adjustment for HPV diagnosis (all cases, 5.8% controls). HPV key in the development of cervical cancer.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed through self-reported questionnaire. This represents self-reported information and may subject to recall bias, however, there is no evidence to suggest that this is an invalid method.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	No control for other potential exposures or jobs evaluated, but similar distribution in cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This was a case-control study aimed at investigating occupational risk factors and the effects of TCE exposure on the development of cancer. This is an appropriate design for the development of cervical cancer.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study authors explicitly state the power calculation. There is enough power to detect an effect of a 2.7 times increased risk of developing cervical cancer.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	There is sufficient information about the handling of confounders and other information to reproduce the analysis given original data. The determination of occupational exposure was detailed in the methods.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	This was a case-control study using logistic regression. This is an appropriate statistical model for determining the effect of TCE on developing cervical cancer.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	Charbotel, B., Massardier-Pilonchery, A., Fort, E., Dananché, B., Févotte, J., Confavreux-Romestaing, C., Bergeret, A. (2013). Occupational trichloroethylene exposure and cervical pathology: A case-control study Annals of Occupational Hygiene, 57(3), 407-416
Data Type:	Charbotel_TCE_exposed workers_cervical cancer-Cancer
HERO ID:	1514222

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‡			Unacceptable⋆⋆		2.0	
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 42: **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_TCE_case-control_Autism endpoint_males and females-Neurological/Behavior
HERO ID:	1790951

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

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Study Citation:	Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Koenen, K.C., Ascherio, A., Weisskopf, M.G. (2013). Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants Environmental Health Perspectives, 121(8), 978-984
Data Type:	Nurses' Health Study II_TCE_case-control_Autism endpoint_males and females-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_TCE_case-control_Autism endpoint_males and females-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 43: **Bahr et al. 2011: Evaluation of Cancer Outcomes**

Study Citation:	Bahr, D.E., Aldrich, T.E., Seidu, D., Brion, G.M., Tollerud, D.J., Paducah Gaseous Diffusion Plant Project Team, Muldoon, S., Reinhart, N., Youseefagha, A., McKinney, P., Hughes, T., Chan, C., Rice, C., Brewer, D.E., Freyberg, R.W., Mohlenkamp, A.M., Hahn, K., Hornung, R., Ho, M., Dastidar, A., Freitas, S., Saman, D., Ravdal, H., Scutchfield, D., Eger, K.J., Minor, S. (2011). Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant International Journal of Occupational Medicine and Environmental Health, 24(1), 67-77
Data Type:	TCE occupational cohort mortality study-Cancer
HERO ID:	2127848

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	Setting, number of workers, time period and number of deaths were given; however, the paper does not describe participation rate, inclusion/exclusion criteria or participant selection.
	Metric 2:	Attrition	Low	× 0.4	1.2	Attrition is not specifically described. The study describes the total number of workers, workers with usable data, and the number of deaths.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	U.S. population; indirect evidence that groups are similar.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Job exposure matrix was developed based on discussions with current and past employees - NOT based on direct measurements of TCE.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Reported 5 levels of qualitative exposure - UNCLEAR if there was sufficient range as there was not exposure-response reported.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposure 1953 to 2003. Unclear whether latency to cancer is adequate for some members of the cohort. Early cancer deaths not likely due to TCE exposures. Failure to excluded follow-up person-time during cancer latency period would dilute rate ratios with immortal person-time.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Death certificates were used to ascertain outcomes - BUT there was no description of how the death certificates were obtained or how many were missing ICD codes. While death certificates properly obtained and documented could meet the 'gold standard', the methodology in the paper did not meet that standard.

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Study Citation:	Bahr, D.E., Aldrich, T.E., Seidu, D., Brion, G.M., Tollerud, D.J., Paducah Gaseous Diffusion Plant Project Team, Muldoon, S., Reinhart, N., Youseefagha, A., McKinney, P., Hughes, T., Chan, C., Rice, C., Brewer, D.E., Freyberg, R.W., Mohlenkamp, A.M., Hahn, K., Hornung, R., Ho, M., Dastidar, A., Freitas, S., Saman, D., Ravdal, H., Scutchfield, D., Eger, K.J., Minor, S. (2011). Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant International Journal of Occupational Medicine and Environmental Health, 24(1), 67-77
Data Type:	TCE occupational cohort mortality study-Cancer
HERO ID:	2127848

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	SMRs were reported with confidence intervals, but not all endpoints were reported in the same level of detail.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	SMRs and SRRs provided for white males only. Age was controlled for in the standardization methodology.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	No description of how covariates were measured - but basic demographic data are less likely to be mischaracterized.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposures were not discussed. There was no direct evidence of imbalance because there was no mention of co-exposure - even radiation at a uranium enrichment plant went unmentioned. Could be unacceptable for cancer strongly related to radiation.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Occupational cohort used to assess association between TCE exposure and mortality
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Of the 6766 with sufficient data, 1638 had a defined mortality. Sample size was sufficient for analysis.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Documentation of analyses is poor.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Authors appear unaware that the LTAS methodology cannot be used for deaths prior to 1960 as there were no comparison rates for that time period. However, relatively few deaths <1960 were included.
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:	Bahr, D.E., Aldrich, T.E., Seidu, D., Brion, G.M., Tollerud, D.J., Paducah Gaseous Diffusion Plant Project Team, Muldoon, S., Reinhart, N., Youseefagha, A., McKinney, P., Hughes, T., Chan, C., Rice, C., Brewer, D.E., Freyberg, R.W., Mohlenkamp, A.M., Hahn, K., Hornung, R., Ho, M., Dastidar, A., Freitas, S., Saman, D., Ravdal, H., Scutchfield, D., Eger, K.J., Minor, S. (2011). Occupational exposure to trichloroethylene and cancer risk for workers at the Paducah Gaseous Diffusion Plant International Journal of Occupational Medicine and Environmental Health, 24(1), 67-77
Data Type:	TCE occupational cohort mortality study-Cancer
HERO ID:	2127848

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Overall Quality Determination‡		~~Low~~ ⟶ Unacceptable§		~~2.4~~	
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

§ Evaluator's explanation for rating change: "Repeated examples of poor quality of study design and execution and ignorance of potential biases that went unmentioned even is the discussion indicate inexperience and poor quality control."

Table 44: **Bassig et al. 2013: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Bassig, B.A., Zhang, L., Tang, X., Vermeulen, R., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Reiss, B., Hosgood, H.D. III., Liu, S., Bagni, R., Guo, W., Purdue, M., Hu, W., Yue, F., Li, L., Huang, H., Rothman, R., Lan, Q. (2013). Occupational exposure to trichloroethylene and serum concentrations of IL-6, IL-10, and TNF-alpha Environmental and Molecular Mutagenesis, 54(6), 450-454
Data Type:	Bassig_TCE_exposed workers_IL10_high exposure-Hematological and Immune
HERO ID:	2127856

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Exposed participants were drawn from six selected factories in Guangdong, China. The same exclusion criteria applied to both exposed and unexposed participants. Unexposed participants were drawn from factories in the same area during the same time period. Exposed factories were chosen based on exposure sampling for TCE and other chemicals. Unexposed factories (those not using TCE) were chosen using the same method. Some key details on participant selection and participation were not presented in this reference or in a parent reference (Lan et al. 2010; HERO ID 736090), but there is no evidence to suggest that this would appreciably bias the results.
	Metric 2: Attrition	High	× 0.4	0.4	There was minimal attrition from the analysis sample. Participants were excluded if they presented signs of a respiratory infection during their baseline interview.
	Metric 3: Comparison Group	High	× 0.2	0.2	Unexposed participants were drawn from the same area, age and sex matched to those drawn from the exposed factories. The factories were were located in the same region and were appropriately similar. Both exposed and unexposed were similar. Important potential confounders were considered in the analysis.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Exposure measurements were detailed in Lan et al. 2010 (HERO ID 736090). In the three weeks prior to drawing blood, two to three measurements were taken per exposed participant. Exposure was measured using 3M Organic Vapor Monitoring Badges. This directly measures exposure in proximity to the participant's breathing zone. There was no discussion (in this reference or HERO ID 736090) on the analysis of the 3M badges which may introduce some uncertainty in the exposure assessment methods.

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Study Citation:	Bassig, B.A., Zhang, L., Tang, X., Vermeulen, R., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Reiss, B., Hosgood, H.D. III., Liu, S., Bagni, R., Guo, W., Purdue, M., Hu, W., Yue, F., Li, L., Huang, H., Rothman, R., Lan, Q. (2013). Occupational exposure to trichloroethylene and serum concentrations of IL-6, IL-10, and TNF-alpha Environmental and Molecular Mutagenesis, 54(6), 450-454
Data Type:	Bassig_TCE_exposed workers_IL10_high exposure-Hematological and Immune
HERO ID:	2127856

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	There were three exposure groups: unexposed, low exposed, and high exposed. This represents three levels exposure.
	Metric 6:	Temporality	Medium	× 0.4	0.8	This was a cross-sectional study. Participants were excluded if they had a history of cancer or cancer treatment. Measurements were taken in the three weeks preceding blood sampling. This establishes exposure before outcome measurement, but it is unclear whether this is the appropriate sampling window. This may lead to some insensitivity.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cytokine levels measured, no assessment of immune function. Unclear if changes in levels observed are biologically relevant for immune function. IL-6, IL-10, and TNF-alpha were all measured in serum with a multiplex high sensitivity human cytokine Milliplex assay (Billerica) for the BioPlex200 platform (BioRad). Multiplex assays have been validated against ELISA (Selvarajah et al. 2014).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All outcomes outlined in the abstract, introduction, and methods were provided in the results. Some information was presented graphically only, which would cause difficulties with inclusion in meta-analyses.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	All models adjusted for age, sex, and total lymphocytes. Other covariates were evaluated (current smoking, alcohol consumption, BMI, and recent infection), but were not included in the final published analysis. These other potential covariates were included only if the regression coefficient was altered by >=10%.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariate information was collected by questionnaire. There is was not validated and may be subject to some information bias, however, there is no evidence to suggest that this was an invalid method.

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Study Citation:	Bassig, B.A., Zhang, L., Tang, X., Vermeulen, R., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Reiss, B., Hosgood, H.D. III., Liu, S., Bagni, R., Guo, W., Purdue, M., Hu, W., Yue, F., Li, L., Huang, H., Rothman, R., Lan, Q. (2013). Occupational exposure to trichloroethylene and serum concentrations of IL-6, IL-10, and TNF-alpha Environmental and Molecular Mutagenesis, 54(6), 450-454
Data Type:	Bassig_TCE_exposed workers_IL10_high exposure-Hematological and Immune
HERO ID:	2127856

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Exposed group had low to negligible levels of other chlorinated solvents and no detectable exposure to benzene, styrene, ethylene oxide, formaldehyde, or epichlorohydrin. Subjects with prior occupational exposure to benzene, butadiene, styrene, and/or ionizing radiation were excluded. A subsample of participants from unexposed factories were measured for the same chemicals.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was cross-sectional. Exposure was assessed before blood sampling. This was sufficient to investigate short-term effects of TCE on circulating cytokine levels in healthy individuals.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 78 unexposed and 71 exposed participants. The number of participants was sufficient to see an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis is described sufficiently to reproduce given original data. Details on covariate analysis, the handling of cytokine measurements below the LOD, and other details were provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Exposure and outcome measurements were appropriately log-transformed. Covariate information and reasoning was included in the statistical analysis.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	Biomarkers of exposure were not used; personal air monitoring.
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	IL-6, IL-10, and TNF-alpha have all been demonstrated to be critical to lymphoid development and immune response, but it is not necessarily clear what implication individual cytokine levels may have on overall immune function.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	The range of individual cytokine levels below the LOD were between 6 and 17%. Those below the LOD were assigned a value of LOD/sqrt(2).
	Metric 19:	Biomarker stability	Medium	× 0.2	0.4	It was stated that samples were tested within 6 hours of being drawn (Lan et al. 2010; HERO ID 736090).
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	There was no discussion of sample contamination in either the current reference or Lan et al. 2010 (HERO ID 736090).

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Study Citation:	Bassig, B.A., Zhang, L., Tang, X., Vermeulen, R., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Reiss, B., Hosgood, H.D. III., Liu, S., Bagni, R., Guo, W., Purdue, M., Hu, W., Yue, F., Li, L., Huang, H., Rothman, R., Lan, Q. (2013). Occupational exposure to trichloroethylene and serum concentrations of IL-6, IL-10, and TNF-alpha Environmental and Molecular Mutagenesis, 54(6), 450-454
Data Type:	Bassig_TCE_exposed workers_IL10_high exposure-Hematological and Immune
HERO ID:	2127856

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 21:	Method requirements	Medium	× 0.2	0.4	Multiplex high sensitivity human cytokine Milliplex assay (Billerica) was used with BioPlex200 platform (BioRad). It is unclear if this is a well-established method.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment is not necessary for this outcome measurement.
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 45: **Siemiatycki 1991: Evaluation of Cancer Outcomes**

Study Citation:	Siemiatycki, J (1991). Risk factors for cancer in the workplace
Data Type:	TCE_substantially 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, the provincial election of 1981, were noncancer patients hospitalized in the same institutions as those with cancer - a subgroup of control cancer cases unrelated to occupational exposure or with cancer at another site deemed not occupationally relevant was also interviewed.
	Metric 2:	Attrition	High	× 0.4	0.4	81.5% of eligible cases completed interviews. 72% of controls. Nonresponses due to refusal, death, no next of kin found, patient discharged, no valid address, psychiatric cases, no translator, or physician refusal
	Metric 3:	Comparison Group	High	× 0.2	0.2	Baseline characteristics were collected from participants and adjusted for; cases and controls were similar in that they were selected from Montreal, Canada, between 35-70 years old, male and recruited from 1979-1985.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure determined by questionnaire, no occupational records. Chemist-hygienists interview consultants to better grasp the workings of particular industries, occupations were selected and coded as low medium or high concentrations of exposure to a host of chemicals based on job title
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Any or substantial exposure was assigned to each job title and patients were assigned to one of the two categories for analysis. Assignments made by a chemist-hygienist
	Metric 6:	Temporality	Low	× 0.4	1.2	Cases aged 35-70, time since first exposure not estimated; study was initiated in 1979 with exposures occurring before or between 1945-1975.
Domain 3: Outcome Assessment						

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

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

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Study Citation:	Siemiatycki, J (1991). Risk factors for cancer in the workplace
Data Type:	TCE_substantially 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 46: **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; TCE melanoma-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	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 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	TCE exposure characterized as "any" or "substantial exposure" (the latter assessed based on confidence, frequency, and relative concentration of predicted exposure). Referent group + 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						
	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.

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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; TCE melanoma-Cancer
HERO ID:	2127914

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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
	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	
Extracted			Yes			

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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; TCE melanoma-Cancer
HERO ID:	2127914

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 47: **Cordier et al. 2012: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Cordier, S., Garlantézec, R., Labat, L., Rouget, F., Monfort, C., Bonvallot, N., Roig, B., Pulkkinen, J., Chevrier, C., Multigner, L. (2012). Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations Epidemiology, 23(6), 806-812
Data Type:	Brittany mothers TCOH limb defects OR adj for metabolites-Growth (early life) and Development
HERO ID:	2127919

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 (i.e., inclusion/exclusion criteria) but available information indicates a low risk of selection bias. The setting and participation rate (80%) were all described in detail. Results from the demographic survey were presented clearly in Table 1 there was no indication of selection bias. Women were recruited prior to 19 weeks gestation through practitioners which represented about 30% of available practitioners in the area.
	Metric 2:	Attrition	Medium	× 0.4	0.8	Estimated participation rate (returned the inclusion questionnaire) of 80%.
	Metric 3:	Comparison Group	High	× 0.2	0.2	This study was a nested case-control; controls were taken from the same eligible population as the cases. Table 1 includes demographics of the entire cohort, the cases, and the selected controls. There were slight, non-significant differences in the two groups. For example, controls were more likely to have had folic acid supplementation. Maternal age, tobacco/alcohol use, folic acid, and education were all considered covariates, a priori.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Two metabolites of Perc and TCE (TCAA and TCOH) were analyzed in urine of mothers completing the exposure and demographic surveys. Urine was collected for all these women before 19 weeks of gestation and measured by GC-MS. This is a well-established method for detecting Perc and TCE metabolites. However, TCAA and TCOH are metabolites of both Perc and TCE, therefore it is not possible to identify a chemical-specific effect on congenital malformations. JEM and self-report exposure assessment methods were not solvent-specific.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	For TCAA and TCOH, only two levels of exposure are used. Those with concentrations less than 0.01 mg/L and those with greater than or equal to 0.01 mg/L.

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Study Citation:	Cordier, S., Garlantézec, R., Labat, L., Rouget, F., Monfort, C., Bonvallot, N., Roig, B., Pulkkinen, J., Chevrier, C., Multigner, L. (2012). Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations Epidemiology, 23(6), 806-812
Data Type:	Brittany mothers TCOH limb defects OR adj for metabolites-Growth (early life) and Development
HERO ID:	2127919

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	For all malformation outcomes, the critical period of embryonic development ranges from 4 weeks to around 13 weeks (longer in the case of male genitalia malformations). The results indicate the majority of women were included at or prior to gestational week 13 which would fall in this critical window. There is slight concern of urine collected and exposures assessed beyond these 13 weeks, but is likely to have minimal and/or nondifferential impact on the results.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Congenital malformations were assessed by staff pediatricians at maternity wards where women gave birth. Pediatricians were given specific questions about oral clefts and genital abnormalities. In the case of fetal death, malformations were determined by pathology. Reported male genital malformations confirmed with follow-up surgery reports. All malformations were identified according to European Registration of Congenital Anomalies guidelines. This would constitute a well-established method.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes listed in the abstract, introduction, and methods were presented in full. Urinary metabolite outcomes were presented in a table, easily extracted. Self-report and JEM determined outcomes were presented in-text, but clearly. There was a separate set of analyses regarding urine sample storage practices that was not reported in an easily extractable manner, but is not of major relevance to this exposure-outcome relationship.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjustments were made for the following covariates: maternal age at inclusion, tobacco use, alcohol use, folic acid supplementation, educational level, district of residence, and year of inclusion. Sampling condition covariates and other risk factors (such as preterm birth, parity, and sex) were considered in each model. This level of adjustment sufficiently considers important potential confounders.

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Study Citation: Cordier, S., Garlantézec, R., Labat, L., Rouget, F., Monfort, C., Bonvallot, N., Roig, B., Pulkkinen, J., Chevrier, C., Multigner, L. (2012). Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations Epidemiology, 23(6), 806-812
Data Type: Brittany mothers TCOH limb defects OR adj for metabolites-Growth (early life) and Development
HERO ID: 2127919

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 questionnaire used to gather demographic characteristics was validated.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	This study simultaneously investigates exposures to chlorinated solvents (i.e., TCE, Perc) and glycol ethers. Metabolites of chlorinated solvents and glycol ethers are measured in urine and results are presented for single metabolite and multi-metabolite (EEAA, TCOH, and TCAA) models. Although it is possible to distinguish between the effects of glycol ethers and chlorinated solvents, respectively, since TCAA and TCOH are metabolites of both Perc and TCE it is not possible to identify a chemical-specific effect on congenital malformations. 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						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This was a nested case-control study using logistic regression to investigate associations between solvent exposure during pregnancy (primarily through occupational exposure; measured in appropriate development window) and congenital malformations. There are no issues with this study design.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	For urinalysis-based analyses, there were 51 cases of major malformations and 459 controls. For self-report/JEM-based analyses, there were 73 major malformations and 580 controls. This represents a sufficient number of participants to detect an effect in the exposed population in both analyses.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses were sufficient to be reproduced given original data. No apparent issues.
	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	Medium	× 0.167	0.33	The measured metabolites have an accurate and clear relationship with the external exposure to Perc and/or TCE, however, they are not derived from one parent chemical.

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Study Citation:	Cordier, S., Garlantézec, R., Labat, L., Rouget, F., Monfort, C., Bonvallot, N., Roig, B., Pulkkinen, J., Chevrier, C., Multigner, L. (2012). Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations Epidemiology, 23(6), 806-812
Data Type:	Brittany mothers TCOH limb defects OR adj for metabolites-Growth (early life) and Development
HERO ID:	2127919

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker	Not Rated	NA	NA	
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	The limit of detection for both TCAA and TCOH was 0.01 mg/L. Among controls, TCAA and TCOH were detected in 7% and 6% of samples, respectively. This represents a small fraction of controls and may be too low to adequately address the research question.
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	Authors note some urine samples were stored with HCL as their stabilizer which prohibited them from taking TCAA/TCOH measurements from 21% of controls and 28% of cases.
	Metric 20:	Sample contamination	Low	× 0.167	0.5	There is no discussion on samples being contamination free. Samples were sent in by the participants, suggesting that samples were collected at home or at another non-clinical location. In addition, there is no discussion on the use of blanks in the present study or in cited studies (Dehon et al. 2000, HERO ID 701723; Ferrario et al. 1988, HERO ID 737545).
	Metric 21:	Method requirements	High	× 0.167	0.17	Urine samples were analyzed by GC-MS, which provides unambiguous identification and quantitation of the biomarker at the required sensitivity.
	Metric 22:	Matrix adjustment	Medium	× 0.167	0.33	TCOH and TCAA were measured only as unadjusted matrix measurements (mg/L).
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 48: **Gilboa et al. 2012: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Gilboa, S.M., Desrosiers, T.A., Lawson, C.,Lupo, P.J., Riehle-Colarusso, T.J., Stewart, P.A., van Wijngaarden, E., Waters, M. A., Correa, A., National Birth Defects Prevention Study (2012). Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997-2002 Occupational and Environmental Medicine, 69(9), 628-635
Data Type:	Developmental toxicity- congenital heart defects-Growth (early life) and Development
HERO ID:	2127986

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	The key elements of the study design are reported; the reported information does not suggest that there was bias with respect to selection in or out of the study. Participation rates were similar for cases (69%) and controls (67%) who were approached for recruitment into the study.
	Metric 2: Attrition	High	× 0.4	0.4	There was minimal exclusion from analyses; exposure and outcome data were largely complete.
	Metric 3: Comparison Group	High	× 0.2	0.2	Key study details were reported. Cases and controls were recruited from the same eligible population (i.e., the National Birth Defects Prevention Study; NBDPS). Numbers of cases and controls were reported (2047 case-mothers and 2951 control-mothers). Mothers were recruited in the same time frame (1997-2002) and were matched geographically.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Occupational exposure was determined by industrial hygienist review using a literature-based approach (only this approach evaluated agent-specific exposures). Job-exposure matrices were developed and used in combination with an expert industrial hygiene review of the self-reported job information. However, exposure was analyzed based on exposure to any chlorinated solvent. There was the potential for exposure misclassification. Potential for recall bias as job histories were determined by questionnaire administered after the estimated date of delivery.
	Metric 5: Exposure levels	Low	× 0.2	0.6	The study dichotomized exposure (i.e., exposed vs. non-exposed).
	Metric 6: Temporality	High	× 0.4	0.4	There is appropriate temporality between outcome (birth defects) and exposure (early pregnancy). The study evaluated exposure from 1 month before conception through the end of the first trimester, a relevant window for cardiac development.

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Study Citation:	Gilboa, S.M., Desrosiers, T.A., Lawson, C.,Lupo, P.J., Riehle-Colarusso, T.J., Stewart, P.A., van Wijngaarden, E., Waters, M. A., Correa, A., National Birth Defects Prevention Study (2012). Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997-2002 Occupational and Environmental Medicine, 69(9), 628-635
Data Type:	Developmental toxicity- congenital heart defects-Growth (early life) and Development
HERO ID:	2127986

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed in cases using well-established methods (cases were from a National Birth Defects Registry); diagnostic information was reviewed by a team of clinicians with expertise in the field of pediatric cardiology. It was noted that methodology for ascertainment of cases does not account for congenital heart defects (CHDs) that manifest in later childhood or adulthood (i.e., these data are not included in the NBDPS); however, > 90% of CHDs are diagnosed before 1 year of age (no evidence for misclassification across groups).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The measured outcomes described in the methods are reported, complete with effect estimates (ORs) and confidence intervals. The numbers of cases and controls included in analyses are specified. Note: Although the outcomes outlined in the methods are reported in the paper, no TCE-specific effect estimates (ORs) were promised/presented (other than prevalance data).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate adjustments were made for potential confounders. Multivariable logistic regression models were adjusted for maternal age, race/ethnicity, education, periconceptional smoking, and periconceptional folic acid intake.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Potential confounders were assessed using appropriate methodology (based on data from interviewers). There was the potential for recall bias because of: 1) a delay in the time from delivery to interview, and 2) mothers of cases might be more concerned about potentially hazardous occupational exposures than mothers of controls. However, the study indicated that there was little to no evidence that these factors affected recall of occupational history.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence that co-exposures occurred; the overlap in exposures to various agents (e.g., chlorinated solvents) is why associations with individual solvents were not evaluated.
Domain 5: Analysis						

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Study Citation:	Gilboa, S.M., Desrosiers, T.A., Lawson, C.,Lupo, P.J., Riehle-Colarusso, T.J., Stewart, P.A., van Wijngaarden, E., Waters, M. A., Correa, A., National Birth Defects Prevention Study (2012). Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997-2002 Occupational and Environmental Medicine, 69(9), 628-635
Data Type:	Developmental toxicity- congenital heart defects-Growth (early life) and Development
HERO ID:	2127986

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen is appropriate to evalute effects between exposure and outcome (i.e., case-control study); appropriate statistical analyses were performed.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The numbers of cases and controls are adequate to detect effects in exposed populations. The large number of congenital heart defects (CHD) cases is a strength of the study.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Details regarding analyses were sufficiently descriptive (i.e., reproducible).
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The methods for calculating ORs were 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 49: **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 TCE Parkinson's dichotomous pairwise OR-Neurological/Behavior
HERO ID:	2127988

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

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

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

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

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

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

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

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 50: **Hansen et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Hansen, J., Sallmen, M., Selden, A.I., Anttila, A., Pukkala, E., Andersson, K., Bryngelsson, I.L., Raaschou-Nielsen, O., Olsen, J.H., McLaughlin, J.K. (2013). Risk of cancer among workers exposed to trichloroethylene: Analysis of three Nordic cohort studies Journal of the National Cancer Institute, 105(12), 869-877
Data Type:	Pooled analysis of TCE worker cohorts and incidence of cancer-Cancer
HERO ID:	2128005

Domain	Metric		Rating†	MWF*	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	A brief summary of each cohort is provided in Supplementary materials.
	Metric 2:	Attrition	Low	× 0.4	1.2	Although moderate losses occurred reasons for loss to follow up were not apparent.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Key elements of the study design are reported and indicates that individuals in the cohorts were similar. The three cohorts evaluated are based on workers who have been exposed to TCE at specific workplaces with similar sampling strategies and a prospective design. The subcohorts were, compared with studies from other countries, derived from populations with relatively homogeneous ethnicity and socioeconomic conditions, which likely limits confounding by these factors.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Urinary TCA was used as a biomarker of exposure.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Urinary TCA concentrations of <5, 5-24, 25-49 and >=50 mg/L allow for the evaluation of an exposure-response estimate.
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure precedes the disease. Latency was considered by lag time analyses (see Table 3).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcome was assessed using national cancer registry data.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Data presented for all cancer sites; pooled analysis and cohorts presented separately. Effect estimates are reported with a Confidence Interval
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.667	0.67	Adjusted for sex, country and 5-year calendar time periods.

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Study Citation:	Hansen, J., Sallmen, M., Selden, A.I., Anttila, A., Pukkala, E., Andersson, K., Bryngelsson, I.L., Raaschou-Nielsen, O., Olsen, J.H., McLaughlin, J.K. (2013). Risk of cancer among workers exposed to trichloroethylene: Analysis of three Nordic cohort studies Journal of the National Cancer Institute, 105(12), 869-877
Data Type:	Pooled analysis of TCE worker cohorts and incidence of cancer-Cancer
HERO ID:	2128005

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Low	× 0.333	1	Lack of information on potential confounders is a limitation of this study. Cancer incidence rates were based on sex, age, and calendar year. Country was also considered. No data on smoking or alcohol consumption were available. Indirect analysis by evaluating SIRs for cancers that are thought to be causally associated with these specific confounders. An increase in the cancers considered related to smoking or alcohol consumption would be considered to suggest confounding of smoking and drinking. This is not considered an acceptable method for addressing the issue of confounding as TCE could also be associated with these cancers and there is no evidence that the smoking or drinking rates in the exposed workers would be different from those of the reference population.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	No reference to co-exposures in the pooled analysis reference.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question. The study uses an appropriate statistical method for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study authors indicated that the study had limited statistical power to detect associations of cancers of modest magnitude like kidney cancer.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient to understand precisely what has been done for the analyses and to conceptually reproduce the results.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for calculating risk estimates is transparent.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.167	0.33	The biomarker of exposure used in this study has a quantitative relationship with exposure; it is also a biomarker of disinfection byproducts.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarker of effect was measured.
	Metric 18:	Method Sensitivity	Medium	× 0.167	0.33	LOD low enough to detect TCE in a sufficient percentage of the samples.

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Study Citation:	Hansen, J., Sallmen, M., Selden, A.I., Anttila, A., Pukkala, E., Andersson, K., Bryngelsson, I.L., Raaschou-Nielsen, O., Olsen, J.H., McLaughlin, J.K. (2013). Risk of cancer among workers exposed to trichloroethylene: Analysis of three Nordic cohort studies Journal of the National Cancer Institute, 105(12), 869-877
Data Type:	Pooled analysis of TCE worker cohorts and incidence of cancer-Cancer
HERO ID:	2128005

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Biomarker stability	Low	× 0.167	0.5	Urinary TCA was measured as a biomarker for TCE exposure. No stability information was provided nor was information provided on how long the samples from the different cohorts were stored.
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	No known contamination issues for TCA. It was not indicated that any steps were taken to reduce contamination or to determine if there was contamination by TCE or TCA. However, it is unlikely to be a substantial issue.
	Metric 21:	Method requirements	Medium	× 0.167	0.33	Method for measuring biomarkers described briefly as being measured by the alkali-pyridine two phase method based on the Fujiwara reaction; supplemental information available.
	Metric 22:	Matrix adjustment	Low	× 0.167	0.5	There does not appear to be any metric adjustement considered as TCA in the urine was reported as mg/L. There is no indication that urine dilution was considered. However, these measurements were generally used to determine exposure and make some comparison between the different populations and was not used in the analysis.
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 51: **Jia et al., 2012: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Jia, Q., Zang, D., Yi, J., Dong, H., Niu, Y., Zhai, Q., Teng, Y., Bin, P., Zhou, W., Huang, X., Li, H., Zheng, Y., Dai, Y. (2012). Cytokine expression in trichloroethylene-induced hypersensitivity dermatitis: An in vivo and in vitro study Toxicology Letters, 215(1), 31-39
Data Type:	TCE_exposed workers_cytokine_control-Hematological and Immune
HERO ID:	2128052

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	22 exposed workers from 20 factories using TCE and 22 non-exposed controls from the same residential areas; also 28 patients with TCE-induced hypersensitivity from the same factories, participants recruited between 2008-2010. No indication was given to how TCE induced hypersensitivity dermatitis was diagnosed or how patients were recruited. Exposed controls were defined as workers with the same job title and longer occupational exposure (>90d) with no skin abnormalities. 22 non-exposed workers were selected from same residential area as patients but never exposed to TCE or other occupational hazard factors (undefined). All subjects with prior history of immune-related diseases or drug allergies were excluded data collected by trained interviewer whole blood was collected at the time of the interview.
	Metric 2:	Attrition	High	× 0.4	0.4	No mention of participant withdrawal from study; All patients had detectable levels of biomarkers in their serum and therefore were accounted for in the analysis.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	For exposed and controls - well matched by age and gender. TCE-exposure time differed per group; patients had a median of 30 days exposure while exposed control workers had a median of 365 days and unexposed controls were presumed to have none. TCE-induced dermatitis group was primarily evaluated in terms of mechanisms, and is not the primary group evaluated here. An additional control group (dermatitis patients without TCE exposure) would have allowed for better analysis and interpretation.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Classified as exposed or not exposed based on employment in factory (no JEM, no exposure level measurement or estimate)
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposed vs unexposed. No description is provided on the levels or range of exposure

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Study Citation:	Jia, Q., Zang, D., Yi, J., Dong, H., Niu, Y., Zhai, Q., Teng, Y., Bin, P., Zhou, W., Huang, X., Li, H., Zheng, Y., Dai, Y. (2012). Cytokine expression in trichloroethylene-induced hypersensitivity dermatitis: An in vivo and in vitro study Toxicology Letters, 215(1), 31-39
Data Type:	TCE_exposed workers_cytokine_control-Hematological and Immune
HERO ID:	2128052

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Those with TCE induced hypersensitivity dermatitis had worked a median of 30 days while TCE-exposed employees with the same job title and longer occupational exposure (>90d) and no skin abnormalities had been employed and median of 265 days.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cytokines were measured via Bio-Plex Pro magnetic color-based multiplex assay - fluorescence intensity from immunoassay was acquired and analyzed.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Only graphical representation, no confidence or standard deviation provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	No discussion of adjustments. Groups were matched for age and sex. Participant exclusion of those with prior history of immune-related diseases or drug allergies. No adjustment made for race.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Trained interviewers collected information from participants to fill out a questionnaire.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Participants exposed to TCE were selected based on employment at electronic-element or metal-plating production factories therefore there is a high likely hood they were exposed to other chemicals. Because the 28 exposed-patients and 22 exposed-control participants were each employed at one of 20 factories it is likely that they each have different levels of co-exposure.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This is a case-control study where TCE induced hypersensitivity dermatitis patients were compared to TCE exposed workers and non-exposed controls to assess inflammatory cytokine markers (IL-8, IL-6, IL-1b, TNF-a).
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Low subject numbers n=28, 22, 22 for TCE-exposed patients, TCE-exposed controls, and unexposed controls, respectively), but effects were observed
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Baseline demographic characteristics compared using one-way analysis of variance test or Pearson chi-squared test.

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Study Citation:	Jia, Q., Zang, D., Yi, J., Dong, H., Niu, Y., Zhai, Q., Teng, Y., Bin, P., Zhou, W., Huang, X., Li, H., Zheng, Y., Dai, Y. (2012). Cytokine expression in trichloroethylene-induced hypersensitivity dermatitis: An in vivo and in vitro study Toxicology Letters, 215(1), 31-39
Data Type:	TCE_exposed workers_cytokine_control-Hematological and Immune
HERO ID:	2128052

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Cytokines among patients and workers compared by nonparametric Mann-Whitney U-test - two -tailed nonparametric Spearman method used to assess correlations ($p<0.05$)
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	Biomarker of exposure not used, classified as exposed or not exposed based on employment in factory
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	cytokines levels, unclear if observed changes are biologically relevant
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	Cytokines detected from all participants, those below LOD were considered as 1/2 detectable value
	Metric 19:	Biomarker stability	Medium	× 0.2	0.4	No discussion of stability, however whole blood samples were processed to serum within 4 hours of collection from participant and frozen at -80C until detection assay run. Cytokine assays of blood samples are typically reliable under such storage conditions
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	no discussion of contamination
	Metric 21:	Method requirements	Medium	× 0.2	0.4	Serum cytokine measure using Bio-Plex Pro magnetic color bead-based multiplex assay (fluorescence immunoassay)
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	no matrix adj conducted or necessary
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 52: **Murata et al. 2010: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Murata, K., Inoue, O., Akutsu, M., Iwata, T. (2010). Neuromotor effects of short-term and long-term exposures to trichloroethylene in workers American Journal of Industrial Medicine, 53(9), 915-921
Data Type:	TCE_exposed workers_postural sway-Neurological/Behavior
HERO ID:	2128228

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	57 workers recruited from 5 factories using TCE in Akita, Japan, and 60 control volunteers residing in Akita, Japan without history of exposure to neurotoxic compounds. Both males and females included; participants excluded if they exhibited obvious neurological disorders.
Metric 2:	Attrition	High	× 0.4	0.4	3 exposed subjects excluded due to diagnosis of obvious neurological disorder by medical doctor.
Metric 3:	Comparison Group	High	× 0.2	0.2	Unexposed controls (no TCOH or TCAA detected in urine) from same geographic region, no significant difference in basal characteristics
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Current exposure measured using well-established biomarkers urinary metabolite concentration of trichloroethanol (TCOH) and trichloroacetic acid (TCAA) analyzed by electron capture detector-equipped gas-chromatograph (ECD-GC) connected to a chromato-processor. Cumulative exposure index (CEI) was also estimated based on current exposure and years of employment (no further details). Confidence in CEI is lower due to unknown previous exposure levels and unclear methods (was a JEM used, or just years working at current plant)? Extract data only from current exposure level analysis. Confidence rating is for acute measures of TCE metabolites measured directly from the urine - not for CEI.
Metric 5:	Exposure levels	Low	× 0.2	0.6	Reliable data is from cross-sectional analysis of exposed vs. unexposed and regression data for postural sway and TCE biomarkers in exposed group. Due to uncertainties in CEI calculations (see metric 4), the low, medium, high CEI groups are not considered reliable. Confidence score therefore only reflects exposed vs unexposed groups

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Study Citation:	Murata, K., Inoue, O., Akutsu, M., Iwata, T. (2010). Neuromotor effects of short-term and long-term exposures to trichloroethylene in workers American Journal of Industrial Medicine, 53(9), 915-921
Data Type:	TCE_exposed workers_postural sway-Neurological/Behavior
HERO ID:	2128228

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Cross-sectional design, but study authors make CEI estimates to evaluate potential temporality. However, details on CEI estimates are lacking and assume that the current exposure levels are the same as in previous years (employment duration of 0.1-37 years).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	hand tremor and postural sway are established tests, but no measure of task neuromotor function during tasks or motor nerve conduction (gold standard)
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	For regression analysis, only effect and p-value were reported (no confidence intervals)
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	adjusted for age, sex, height, smoking status, and alcohol consumption. Level of education was not used as a covariate because there is no evidence on any association between education status and either postural sway or hand tremor (Era, 1988; as cited by study authors)
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariate information was collected from subjects by means of a questionnaire; no indication that the survey was validated
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Study authors indicate that exposed group worked in plants that had never used neurotoxic metals - no mention of other solvents. Control group had no history of occupational exposure to neurotoxic chemicals such as lead, mercury, or solvents.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Subjects were recruited from 5 factories in Japan and urine samples were collected to determine TCE metabolite concentrations at the same time sway test and hand tremor assay were run by a physician.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Differences were detected; there were 57 subjects employed 0.1-37 years at a TCE manufacturer and 60 subjects with no known occupational history of working with a neurotoxicant
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The cumulative exposure index (CEI) is calculated by multiplying work duration years by the total sum of TCOH and TCAA

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Study Citation:	Murata, K., Inoue, O., Akutsu, M., Iwata, T. (2010). Neuromotor effects of short-term and long-term exposures to trichloroethylene in workers American Journal of Industrial Medicine, 53(9), 915-921
Data Type:	TCE_exposed workers_postural sway-Neurological/Behavior
HERO ID:	2128228

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The significance of differences in basal characteristics such as age and height between the exposed workers and control subjects was analyzed by the Student's t-test for continuous variables and by Fisher exact probability test for dichotomous variables. No assumptions stated.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.167	0.17	well established urinary biomarkers: Urinary metabolite concentration of trichloroethanol (TCOH) and trichloroacetic acid (TCAA) were measured
	Metric 17:	Effect biomarker	Not Rated	NA	NA	
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	LOD/LOQ not reported
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	no discussion of stability, but standard biomarker for TCE so unlikely to have high instability
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	no discussion of contamination, but standard biomarker for TCE so unlikely to have known contamination issues
	Metric 21:	Method requirements	Medium	× 0.167	0.33	analyzed by electron capture detector-equipped gas-chromatograph (ECD-GC) connected to a chromato-processor.
	Metric 22:	Matrix adjustment	Medium	× 0.167	0.33	adjusted for creatinine: only provides adjusted concentrations. Creatinine in urine was analyzed by creatinine amidohydrolase method
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 =≥ 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 53: **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:	TCE_male_subjects_probableexp_Glioma-Cancer
HERO ID:	2128240

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

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

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

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 54: **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_TCE_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	Study population consisted of 1175 controls and 798 cases. 97& of the controls (1141/1175) were interviewed and all cases had interviews with 360 being proxy interviews. Some analysis was restricted to cases that were directly interviewed.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls were randomly selected and age and sex stratified. There were some differences in the level of education, but this was adjusted for in the analysis. Details comparing cases and controls as well as ineligible and non-participants are detailed in companion publication (Ruder et al. 2006).
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Complete occupational history was obtained using a questionnaire modified from the one developed by the National Cancer Institute. Jobs of at least one years duration between the age of 16 and the end of 1992 were included. The questionnaire also asked about specific exposures including solvent and on which jobs and for how many hours a week these exposures occurred. There is potential for cases to have better recall. The probability, intensity, and frequency of exposure in non-farm related jobs was estimated based on occupation, industry, and decade using an annotated appendix of sources of exposure data as well as bibliographic databases of published exposure levels. Complete descriptions of the methods were provided. JEM with complete job history, but based on recalled jobs and some judgement on exposure (although used several cited references).

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

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

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 55: **Vermeulen et al. 2012: Evaluation of Renal Outcomes**

Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	80 healthy workers exposed to TCE were recruited from 6 factories that use TCE in manufacturing processes (4 metal, 1 optical lens and 1 circuit board factory) in Guangdong, China in June-July 2006. Factories were selected as recruitment locations after an initial screen of 40 potential factories was conducted over a 1 year period, and factories were included if they 1) used TCE in manufacturing, 2) had no detectable benzene, styrene, ethylene oxide, formaldehyde or epichlorohydrin levels, and 3) had low to negligible levels of DCM, chloroform or Perc. 45 unexposed subjects were recruited from 2 separate factories without TCE in manufacturing processes (1 clothing manufacturing and 1 food production factory) in the same geographic region. Unexposed participants were frequency matched by age to exposed workers. Exclusion criteria for all participants included history of cancer, chemotherapy and radiotherapy, and previous occupations with notable exposure to benzene, butadiene, styrene and/or ionizing radiation. Note that participants were not excluded for other health conditions potentially related to kidney toxicity. The exclusion of subjects with cancer history is potential source of bias.
	Metric 2: Attrition	High	× 0.4	0.4	Of the original 80 exposed workers and 45 unexposed subjects, all participants had complete exposure and outcome data, and were included in the final analysis.

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Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 3: Comparison Group	Medium	× 0.2	0.4	45 unexposed subjects were recruited from 2 separate factories without TCE in manufacturing processes (1 clothing manufacturing and 1 food production factory) in the same geographic region. Unexposed participants were frequency matched by age to exposed workers. Although authors suggested these factories were similar since located in same geographic region, no further evidence on similarity. Exposed and unexposed individuals were compared on age, BMI, sex, current smoking, and current alcohol use. These differences were considered as potential confounders in linear regression models, although more potential covariates could have been measured and reported. Exposed workers worked for an average of 2 years in TCE factories, while unexposed workers for 2.3 years at other factories. Reasonable concern regarding the selection of cases/controls from different factories.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	For TCE exposed workers, 2-3 full-shift personal air exposure measurements were taken in a 2 week time period using 3M OVM badges. Exposure measurement procedures differed for unexposed workers, whereby only a single OVM badge was collected and it was not reported how long monitored. All OVM badges were analyzed for TCE using GC-MS (LOD 0.12 ppm). Additional information was collected via an interview questionnaire including: demographic and lifestyle characteristics and occupational history. Peripheral blood, buccal cell mouth rinse, urine samples, brief physical exam, blood pressure, height, weight, and temperature collected. Medium selected because exposure measurement method differed between exposed and unexposed, and exposure was only estimated for 2 weeks out of the 2-3 years of working in that factory without mention of historical records. High quality analysis and interlab reliability.

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Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Linear regression models included TCE exposure levels as a continuous variable. Study included two exposure indicators: 1) current TCE air levels (ppm) based on mean of an average of 2-3 measurements per subject, and 2) cumulative exposure (ppm years) calculated by multiplying individual mean TCE levels with duration of employment at current job. Current TCE levels were reported as <0.03 ppm (unexposed) and 22.2 +/- 35.9 ppm (exposed). Cumulative TCE levels were reported as <0.1 ppm years (unexposed) and 35.8 +/- 68.2 ppm years (exposed).
	Metric 6:	Temporality	Low	× 0.4	1.2	In this cross-sectional study, exposure and outcome data was measured at the same time point, and the temporality of exposure and outcome is therefore uncertain and it is unclear whether the interval has an appropriate consideration of relevant exposure windows. Personal air exposure measurements were taken over a small time period of 2 weeks for exposed individuals and assumed to be representative of typical exposure in the workplace.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Assessment of kidney toxicity was based on a panel of nephrotoxicity markers measured in urine, including traditional and new markers: Creatinine, VEGF, Alpha-GST, Pi-GST, KIM-1, NAG. Alpha-GST, Pi-GST and KIM-1 noted by authors as new sensitive markers. Levels were measured using established methods: ELISA kit (VEGF, Alpha-GST, Pi-GST), luminex-based XMAP technology (KIM-1), enzyme substrate-based colorimetric assay (NAG), and automated Jaffe reaction (creatinine). Little or no evidence methods had poor validity.

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Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	For both exposed and unexposed groups, authors reported arithmetic mean, geometric mean and geometric standard deviation for all measured nephrotoxicity markers. Linear regression analysis for current and cumulative TCE exposure included estimates, 95% Cis and p values for each nephrotoxicity marker measured. Authors stated they repeated analyses without creatinine correction and per millimole creatinine and stated the same results were found but did not report them.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Four potential confounders were considered for adjustment: sex, current smoking, current alcohol consumption, and BMI. Ln(creatinine), sex, current alcohol use and BMI were included in the final model (confounders included if altered regression coefficient by +/-15%). Study did not consider a large number of covariates, most notably not considering SES, but it is unclear whether these would appreciably alter the results.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	All covariates were measured via a questionnaire administered by interviewers. BMI was measured during a physical exam. Only current smoking and alcohol use was measured, not including potential previous behavior.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Factories were excluded as potential sampling locations if they had detectable benzene, styrene, ethylene oxide, formaldehyde or epichlorohydrin levels; however, factories could be included if they had low to negligible levels of DCM, chloroform or Perc. To evaluate the influence of exposure to other chlorinated solvents at low levels in factories, factories were excluded one at a time from the analyses and results were found to remain unchanged. Participants were also excluded if they had previous occupations with notable exposure to benzene, butadiene, styrene and/or ionizing radiation.
Domain 5: Analysis						

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Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A cross-sectional study was used to determine TCE exposure and acute kidney toxicity in exposed and unexposed factory workers. Student t-test used to test for difference in natural log of each endpoint between exposed and unexposed workers. Exposure response analyses were performed by linear regression using current and cumulative TCE exposure for all nephrotoxicity markers.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	80 TCE exposed participants and 45 unexposed participants were sufficient to detect an effect for TCE and nephrotoxicity. Statistical power not reported, but p values show some statistically significant relationships.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	All analyses were described clearly and precisely, and would be reproducible given access to analytic data. All confounders included in linear regression models clearly defined, and process for model selection detailed.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Exposure response analyses were performed by linear regression using current and cumulative TCE exposure for all nephrotoxicity markers. Confounders included if altered regression coefficient by +/- 15%. Linear regression models included natural log-transformed exposure variables with frequency-matching factor age (continuous variable) and corrected for ln(creatinine) as continuous variable. Student t test used to test for difference in natural log of each endpoint between exposed and unexposed workers. Model assumptions were met and the variables included were clearly stated and appropriate.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	No biomarker of exposure measured.
	Metric 17:	Effect biomarker	Medium	× 0.167	0.33	Assessment of kidney toxicity was based on a panel of nephrotoxicity markers measured in urine, including traditional and new markers: Creatinine, VEGF, Alpha-GST, Pi-GST, KIM-1, NAG. Alpha-GST, Pi-GST and KIM-1 noted by authors as new sensitive markers, but the authors include citations for research supporting the role of these markers in kidney damage and their use as biomarkers.

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Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	LOD/LOQ not reported for any of the nephrotoxicity markers measured. However, well established assays were used (see below) and assay coefficients of variability were reported (see below). Biomarkers detected in most samples (missing for 3 individuals for VEGF).
	Metric 19:	Biomarker stability	Medium	× 0.167	0.33	Urine samples were reported to be stored at 4 degrees C until processing within 10 hours of collection. Samples were centrifuged and 1.4 mL of urine supernatant was mixed with 0.3 mL freezing buffer. Samples were then stored at -80 degrees C. Stability details not provided.
	Metric 20:	Sample contamination	Medium	× 0.167	0.33	The study does not explicitly say that the samples were contaminant free, although they do not mention there were any contamination issues and it does walk through the process for sample collection and storage in detail (see above).
	Metric 21:	Method requirements	Low	× 0.167	0.5	Levels were measured using established methods: ELISA kit (VEGF, Alpha-GST, Pi-GST), luminex-based XMAP technology (KIM-1), enzyme substrate-based colorimetric assay (NAG), and automated Jaffe reaction (creatinine). Assay CV levels reported: 5% Pi-GST, 10% NAG, 15% Alpha-GS and KIM-1, 20% VEG-F. LOD/LOQ not reported. Unclear if these method have the required level of specificity.
	Metric 22:	Matrix adjustment	Medium	× 0.167	0.33	Arithmetic mean, geometric mean, geometric standard deviation of all unadjusted nephrotoxicity markers reported in Table II for exposed and unexposed groups. For all statistical analyses, urinary markers were adjusted for creatinine. Study only reports creatinine adjusted exposure-response models, but states that unadjusted models obtained essentially the same results.
Overall Quality Determination‡			Medium		2.0	
Extracted			Yes			

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Study Citation:	Vermeulen, R., Zhang, L., Spierenburg, A., Tang, X., Bonventre, J.V., Reiss, B., Shen, M., Smith, M.T., Qiu, C., Ge, Y., Ji, Z., Xiong, J., He, J., Hao, Z., Liu, S., Xie, Y., Yue, F., Guo, W., Purdue, M., Beane Freeman, L.E., Sabbisetti, V., Li,L., Huang, H., Rothman, N., Lan, Q. (2012). Elevated urinary levels of kidney injury molecule-1 among Chinese factory workers exposed to trichloroethylene Carcinogenesis, 33(8), 1538-1541
Data Type:	Cross-Sectional_Occupational_TCE_Renal_KIM-1_beta_continuousTCE-Renal
HERO ID:	2128431

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 56: **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_TCE_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, which reported a hospital diagnosis of astrocytic brain tumor, was used.
	Metric 2: Attrition	Medium	× 0.4	0.8	Among 483 cases with completed interviews (74% of traced next-to-kin) a hospital diagnosis was reported for 300 individuals. 229 cases had been pathologically confirmed. Of the matched controls 66 were excluded due to a possible association between their cause of death and occupational exposure to CAHs. In logistic regression analysis, omitted 30 subjects with electronics-related jobs.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Controls were frequency matched to cases by age, year of death, cause of death other than brain tumor/ cerebrovascular disease/ homicide/ suicide, and study area. 320 total controls.
Domain 2: Exposure Characterization					

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_TCE_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 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_TCE_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	Characterized within methods, study population section. Confounders not assessed by method or instrument- used previous analyses to assess. Cases and controls matched by confounding factors (age, study area). Controlled for employment in electronics-related occupations or industries (which was associated with an excess risk of astrocytic brain tumors in a previous analysis).
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposure to electromagnetic fields was not assessed or considered in the analysis.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Used appropriate statistical analyses and study design. Retrospective case-control included matrices on likelihood of a certain chemical to have been used in each industry and occupation by decade and provided probability and intensity of exposure level. Cumulative exposure indices were calculated for subjects.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	300 cases and 320 controls were used in the analysis.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	It would be difficult to reproduce this analysis because of the lack of direct information on exposure to various solvents. Information acquired from next-of-kin was likely less accurate then information from the subjects themselves or from industries that could have provided it.

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_TCE_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 57: **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 (TCE 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 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 (TCE 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 in sufficient details. A description of measured outcomes is reported in the methods, abstract, and/or introduction. Effect estimates are reported with a confidence interval and the number of cases/controls are reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Results were adjusted by age, smoking habit, educational attainment, SES, and ethnicity.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Information was obtained from a questionnaire of unknown reliability and validity. The authors note that "Although it is very difficult to establish the validity of retrospective exposure assessments, we have demonstrated satisfactory levels of reliability and validity in the job histories and in the expert exposure assessments.'
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	It was noted that results were adjusted for exposure to eight known carcinogens. Although there are potential co-exposures for any given job, it is unlikely that they were differential across jobs and within the specific chemicals of interest. Supplemental Table S2 indicated 5 different jobs with exposure to TCE 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 (TCE 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 58: **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:	TCE_intensity x prevalence_Kidney Cancer_BG QC-Cancer
HERO ID:	2128436

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	High rating: key elements of study design were reported. 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 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 to 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	High rating: 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:	TCE_intensity x prevalence_Kidney Cancer_BG QC-Cancer
HERO ID:	2128436

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Low rating: 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; 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 perchloroethylene 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	Medium rating: range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported
	Metric 6:	Temporality	High	× 0.4	0.4	High rating: temporality is established and the interval between 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. NHL is a heterogenous cancer category, which could result in bias toward the null if TCE or perchloroethylene exposure is not associated with all the subtypes.

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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:	TCE_intensity x prevalence_Kidney Cancer_BG QC-Cancer
HERO ID:	2128436

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed cases reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Medium rating: cases matched to controls for age (±1 year), country and sex. No adjustment for potential confounding factors (excluding co-exposures) in statistical models; no adjustment for tobacco smoking, alcohol consumption, and the hepatitis B and C virus in this study. However, the authors consider these factors are not to appreciably bias the results
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Medium rating: 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	Medium rating: moderate correlations reported between PER 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	Medium rating: appropriate design (i.e., nested case-control for assessment of rare diseases in relation to perchloroethylene 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	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: 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	

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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:	TCE_intensity x prevalence_Kidney Cancer_BG QC-Cancer
HERO ID:	2128436

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‡		~~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 59: **Zungun et al., 2013: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Zungun, C; Yilmaz, FM; Tutkun, E; Yilmaz, H; Uysal, S (2013). Assessment of serum S100B and neuron specific enolase levels to evaluate the neurotoxic effects of organic solvent exposure Clinical Toxicology, 51(8), 748-751
Data Type:	TCE_S100B_exposed workers-Neurological/Behavior
HERO ID:	2128542

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	Exposed group (n=25) recruited from Ankara Occupational Disease Hospital during annual periodical exam with TCE levels >10 mg/L. From different section so various companies that used TCE-painters, welders, truck company. Exposure at least 3 years. Control group (n=25) were selected due to no history of solvent exposure and with similar demographics to exposed individuals. Study authors did not identify how control workers were recruited. All participants were male.
Metric 2:	Attrition	High	× 0.4	0.4	no attrition
Metric 3:	Comparison Group	Medium	× 0.2	0.4	Age- and sex-matched.. Study authors did not identify how control workers were recruited. No report on other baseline similarities or differences (like alcohol consumption).
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Measured trichloroacetic acid levels in urine. Also confirmed TCE exposure levels in workplace air based on measurements based on annual workplace monitoring (48.7 ppm TCE mean measurement). Doesn't appear that urinary trichloroacetic acid was measured in controls. Blood and urine samples collected after shift; not clear what time frame these samples were collected
Metric 5:	Exposure levels	Low	× 0.2	0.6	Median trichloroacetic acid was 12.30 mg/L in exposed (not reported/measured in control). Based on annual air monitoring, mean TCE exposure was 48.7 ppm. Study authors state that unexposed controls had no history of solvent exposure, but later indicate that workers in control group had "several short-term air monitoring results were below 50 ppm)".
Metric 6:	Temporality	High	× 0.4	0.4	Cross-sectional study
Domain 3: Outcome Assessment					

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Study Citation: Zungun, C; Yilmaz, FM; Tutkun, E; Yilmaz, H; Uysal, S (2013). Assessment of serum S100B and neuron specific enolase levels to evaluate the neurotoxic effects of organic solvent exposure Clinical Toxicology, 51(8), 748-751
Data Type: TCE_S100B_exposed workers-Neurological/Behavior
HERO ID: 2128542

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Astrocyte damage was assessed using the biomarker serum S100B (a calcium binding protein in glial cells); mechanism of S100B secretion is unknown. Neuron damage was assessed using biomarker serum neuron specific enolase (NSE), which increases in serum following destruction in neurons. EMG and subjective signs were measured, but not statistically analyzed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Measures of serum biomarkers of hepatotoxicity and neurotoxicity were measured and reported on. Measures of urine Trichloroacetic acid levels were also reported on (for exposed individuals)
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	No adjustment for covariates
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	covariates not assessed
	Metric 11:	Co-exposure Confounding	Low	× 0.333	1	In the annual workplace air monitoring of these sections, ethanol (mean 136.6; range 55 – 250 ppm), xylene (mean 18; range 15 – 25 ppm), toluene (mean 50; range 25 – 80 ppm), benzene (mean 0.042; range 0.01 – 0.09 ppm) and methylene chloride (mean 11.4; range 5 – 21 ppm) has been found within normal range.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design for this cross-sectional study to assess neurotoxic and hepatotoxic endpoints to TCE occupational exposure were acceptable.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	only 25 subjects per group; no effects detected but unclear is sample size is large enough; however, the resulting data may be useful in a WOE approach
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The methods are adequate to reproduce analysis calculation data normality and statistical significance were adequate and described, reported levels of alanine aminotransferase and aspartate aminotransferase for the exposed and control group
	Metric 15:	Statistical models	Medium	× 0.2	0.4	To compare the differences between solvent-exposed group and healthy control group, Mann – Whitney ' s U test was performed because our data set was not normally distributed
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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Study Citation:	Zungun, C; Yilmaz, FM; Tutkun, E; Yilmaz, H; Uysal, S (2013). Assessment of serum S100B and neuron specific enolase levels to evaluate the neurotoxic effects of organic solvent exposure Clinical Toxicology, 51(8), 748-751
Data Type:	TCE_S100B_exposed workers-Neurological/Behavior
HERO ID:	2128542

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 16:	Use of Biomarker of Exposure	High	× 0.143	0.14	urinary trichloroacetic acid levels were measured by headspace GC technique, after methyl esterification by methanol
	Metric 17:	Effect biomarker	Low	× 0.143	0.43	Unclear how robust the biomarkers of S100B and NSE are. No apparent differences in reported symptoms or EMG (not statistically analyzed by study authors).
	Metric 18:	Method Sensitivity	Low	× 0.143	0.43	LOQ/LOD not reported
	Metric 19:	Biomarker stability	Medium	× 0.143	0.29	stability not discussed; trichloroacetic acid urine levels were refrigerated prior to analysis and measured within 3 days; likely to be standard and relatively stable for this assay
	Metric 20:	Sample contamination	Low	× 0.143	0.43	Contamination not discussed
	Metric 21:	Method requirements	Medium	× 0.143	0.29	For exposure: headspace GC technique
	Metric 22:	Matrix adjustment	Low	× 0.143	0.43	While measured, levels were not creatinine adjusted: however creatinine was found to be relatively similar between exposed and control groups
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 60: **Zungun et al., 2013: Evaluation of Hepatic Outcomes**

Study Citation:	Zungun, C; Yilmaz, FM; Tutkun, E; Yilmaz, H; Uysal, S (2013). Assessment of serum S100B and neuron specific enolase levels to evaluate the neurotoxic effects of organic solvent exposure Clinical Toxicology, 51(8), 748-751
Data Type:	TCE_ALT_exposed workers-Hepatic
HERO ID:	2128542

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Exposed group (n=25) recruited from Ankara Occupational Disease Hospital during annual periodical exam with TCE levels >10 mg/L. From different section so various companies that used TCE-painters, welders, truck company. Exposure at least 3 years. Control group (n=25) were selected due to no history of solvent exposure and with similar demographics to exposed individuals. Study authors did not identify how control workers were recruited. All participants were male.
	Metric 2:	Attrition	High	× 0.4	0.4	no attrition
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Age- and sex-matched.. Study authors did not identify how control workers were recruited. No report on other baseline similarities or differences (like alcohol consumption).
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Measured trichloroacetic acid levels in urine. Also confirmed TCE exposure levels in workplace air based on measurements based on annual workplace monitoring (48.7 ppm TCE mean measurement). Doesn't appear that urinary trichloroacetic acid was measured in controls. Blood and urine samples collected after shift; not clear what time frame these samples were collected
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Median trichloroacetic acid was 12.30 mg/L in exposed (not reported/measured in control). Based on annual air monitoring, mean TCE exposure was 48.7 ppm. Study authors state that unexposed controls had no history of solvent exposure, but later indicate that workers in control group had "several short-term air monitoring results were below 50 ppm)".
	Metric 6:	Temporality	High	× 0.4	0.4	Cross-sectional study
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Standard serum measures of hepatic toxicity

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Study Citation: Zungun, C; Yilmaz, FM; Tutkun, E; Yilmaz, H; Uysal, S (2013). Assessment of serum S100B and neuron specific enolase levels to evaluate the neurotoxic effects of organic solvent exposure Clinical Toxicology, 51(8), 748-751
Data Type: TCE_ALT_exposed workers-Hepatic
HERO ID: 2128542

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Measures of serum biomarkers of hepatotoxicity and neurotoxicity were measured and reported on. Measures of urine Trichloroacetic acid levels were also reported on (for exposed individuals)
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	No adjustment for covariates
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	covariates not assessed
	Metric 11:	Co-exposure Confounding	Low	× 0.333	1	In the annual workplace air monitoring of these sections, ethanol (mean 136.6; range 55 – 250 ppm), xylene (mean 18; range 15 – 25 ppm), toluene (mean 50; range 25 – 80 ppm), benzene (mean 0.042; range 0.01 – 0.09 ppm) and methylene chloride (mean 11.4; range 5 – 21 ppm) has been found within normal range.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design for this cross-sectional study to assess neurotoxic and hepatotoxic endpoints to TCE occupational exposure were acceptable.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	only 25 subjects per group; no effects detected but unclear is sample size is large enough; however, the resulting data may be useful in a WOE approach
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The methods are adequate to reproduce analysis calculation data normality and statistical significance were adequate and described, reported levels of alanine aminotransferase and aspartate aminotransferase for the exposed and control group
	Metric 15:	Statistical models	Medium	× 0.2	0.4	To compare the differences between solvent-exposed group and healthy control group, Mann – Whitney ' s U test was performed because our data set was not normally distributed
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	High	× 0.143	0.14	urinary trichloroacetic acid levels were measured by headspace GC technique, after methyl esterification by methanol
	Metric 17:	Effect biomarker	High	× 0.143	0.14	Acceptable biomarkers of hepatic toxicity were measured (alanine and aspartate aminotransferase)
	Metric 18:	Method Sensitivity	Low	× 0.143	0.43	LOQ/LOD not reported

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Study Citation:	Zungun, C; Yilmaz, FM; Tutkun, E; Yilmaz, H; Uysal, S (2013). Assessment of serum S100B and neuron specific enolase levels to evaluate the neurotoxic effects of organic solvent exposure Clinical Toxicology, 51(8), 748-751
Data Type:	TCE_ALT_exposed workers-Hepatic
HERO ID:	2128542

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Biomarker stability	Medium	× 0.143	0.29	stability not discussed; trichloroacetic acid urine levels were refrigerated prior to analysis and measured within 3 days; likely to be standard and relatively stable for this assay
	Metric 20:	Sample contamination	Low	× 0.143	0.43	Contamination not discussed
	Metric 21:	Method requirements	Medium	× 0.143	0.29	For exposure: headspace GC technique
	Metric 22:	Matrix adjustment	Low	× 0.143	0.43	While measured, levels were not creatinine adjusted: however creatinine was found to be relatively similar between exposed and control groups.
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: **Hosgood et al. 2012: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Hosgood, H. D.,Zhang, L.,Tang, X.,Vermeulen, R.,Qiu, C.,Shen, M.,Smith, M. T.,Ge, Y.,Ji, Z.,Xiong, J.,He, J.,Reiss, B.,Liu, S.,Xie, Y.,Guo, W.,Galvan, N.,Li, L.,Hao, Z.,Rothman, N.,Huang, H.,Lan, Q. (2011). Decreased numbers of CD4(+) naive and effector memory T cells, and CD8(+) naïve T cells, are associated with trichloroethylene exposure Frontiers in Oncology, 1 53
Data Type:	Hosgood_TCE_exposed workers_CD8naive_high-Hematological and Immune
HERO ID:	2129170

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Exposed subjects from six factories that use TCE in Guangdong, China; control subjects age- and sex-matched from four workplaces that did not use TCE in the same geographic region; enrolled in June and July of 2006. Selection criteria detailed in cited study (Lan et al. 2010), which states that over 40 factories were subjected to initial screening and "Factories were included if they used TCE in manufacturing processes, had no detectable benzene, styrene, ethylene oxide, formaldehyde or epichlorohydrin levels, and low to negligible levels of other chlorinated solvents." Also, "Exclusion criteria for both TCE-exposed and control workers were history of cancer, chemotherapy and radiotherapy, as well as previous occupations with notable exposure to benzene, butadiene, styrene and/or ionizing radiation." However, it is not clear how many participants (exposed and controls) were eligible and what was the criteria that lead to a final selection of 80 exposed and 96 control subjects.
	Metric 2:	Attrition	Low	× 0.4	1.2	Workers with a history of cancer, chemotherapy, radiotherapy or a previous occupation with notable exposure to benzene, butadiene, styrene and/or ionizing radiation were excluded from the study. Initial included count was 80 exposed and 96 controls; T-cell counts only available for 70 exposed and 86 controls. Reason for difference in group number not reported.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Exposed subjects from six factories that use TCE in Guangdong, China; control subjects age- and sex-matched from four workplaces that did not use TCE in the same geographic region; enrolled in June and July of 2006. Reported demographic characteristics (Table 1) are similar between TCE-exposed and control subjects.
Domain 2: Exposure Characterization						

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Study Citation:	Hosgood, H. D.,Zhang, L.,Tang, X.,Vermeulen, R.,Qiu, C.,Shen, M.,Smith, M. T.,Ge, Y.,Ji, Z.,Xiong, J.,He, J.,Reiss, B.,Liu, S.,Xie, Y.,Guo, W.,Galvan, N.,Li, L.,Hao, Z.,Rothman, N.,Huang, H.,Lan, Q. (2011). Decreased numbers of CD4(+) naive and effector memory T cells, and CD8(+) naïve T cells, are associated with trichloroethylene exposure Frontiers in Oncology, 1 53
Data Type:	Hosgood_TCE_exposed workers_CD8naive_high-Hematological and Immune
HERO ID:	2129170

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure assessment was based on personal air monitoring (using 3 M organic vapor monitoring badges) of TCE-exposed workers and a subgroup of control workers in the food and clothes production factories. According to the cited study (Lan et al. 2010), two to three full-shift measurements per subject were taken in a three-week time-period before blood collection. However, methods for measurement of the chemicals detected in the badges are not detailed (e.g. accuracy, temperature correction factors, recovery coefficients, etc.)
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Median TCE concentration of exposed subjects = 12 ppm. Study reports 3 levels of exposure: exposed, split into low (<median) and high (>=median), and controls, with mean (SD), ppm: Controls: <0.03 (n =96) Low exposed = 5.19 (3.47) (n = 39) High Exposed = 38.36(44.61) (n = 41)
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposure was assessed during the month prior to blood draw (effect biomarker measurement). It is unclear if prior exposures might impact the findings.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Total lymphocytes and lymphocyte subsets were measured, but there was no assessment of immune function. It is unclear if changes in levels observed are biologically relevant for immune function.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Unadjusted means and standard deviations of T cell subset counts were reported for each exposure group, as well as the p-value for linear regressions used for testing for differences between groups and to evaluate for dose-response across exposure groups (adjusted models) .
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Besides age and sex, which were included in all models, the following potential confounders were considered: current cigarette smoking status, current alcohol consumption status, recent infections, body mass index. For each subset of endpoints, when the inclusion of a covariate changed the regression coefficient +/- 15%, it was included in the model.

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Study Citation:	Hosgood, H. D.,Zhang, L.,Tang, X.,Vermeulen, R.,Qiu, C.,Shen, M.,Smith, M. T.,Ge, Y.,Ji, Z.,Xiong, J.,He, J.,Reiss, B.,Liu, S.,Xie, Y.,Guo, W.,Galvan, N.,Li, L.,Hao, Z.,Rothman, N.,Huang, H.,Lan, Q. (2011). Decreased numbers of CD4(+) naive and effector memory T cells, and CD8(+) naïve T cells, are associated with trichloroethylene exposure Frontiers in Oncology, 1 53
Data Type:	Hosgood_TCE_exposed workers_CD8naive_high-Hematological and Immune
HERO ID:	2129170

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	With the exception of current alcohol consumption, covariates are characterized in Table 1. Only considering current cigarette smoking and alcohol consumption status may limit the assessment of the effect of these potential confounders. Covariates characterization was based on participants' responses to a questionnaire, but questionnaire validation is not reported.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Subjects with prior occupational exposure to benzene, butadiene, styrene, and/or ionizing radiation were excluded. According to cited study (Lan et al. 2010), "a subset (48 from TCE-exposed workers) was analyzed for a panel of organic hydrocarbons including benzene, methylene chloride, perchloroethylene and epichlorohydrin." Results from this analysis or evaluation of additional potential exposures at TCE-exposed and control facilities were not reported.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cross-sectional study design is appropriate to assess the association between exposure to TCE and the levels of effect biomarkers at a point in time, and linear regression is an appropriate statistical method for testing for differences in means between groups.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants, although low, was sufficient to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description provided is sufficient to understand the steps followed in the analyses.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The use of linear regression models to test for differences in means between exposure groups is described, including covariates considered in the final models and criterion for their inclusion.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	biomarker of exposure not used; personal air monitoring
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	The effect biomarkers considered in this study (T cell subset counts) are related to immune function but the mechanism of action is not well understood, as acknowledged by the authors in the Discussion section.

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Study Citation:	Hosgood, H. D.,Zhang, L.,Tang, X.,Vermeulen, R.,Qiu, C.,Shen, M.,Smith, M. T.,Ge, Y.,Ji, Z.,Xiong, J.,He, J.,Reiss, B.,Liu, S.,Xie, Y.,Guo, W.,Galvan, N.,Li, L.,Hao, Z.,Rothman, N.,Huang, H.,Lan, Q. (2011). Decreased numbers of CD4(+) naive and effector memory T cells, and CD8(+) naïve T cells, are associated with trichloroethylene exposure Frontiers in Oncology, 1 53
Data Type:	Hosgood_TCE_exposed workers_CD8naive_high-Hematological and Immune
HERO ID:	2129170

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	The study reports that "measurements from blinded quality control replicates interspersed among the samples did not identify outlier batches"; no additional information is provided on method sensitivity.
	Metric 19:	Biomarker stability	Medium	× 0.2	0.4	The study reports that lymphocyte subsets were analyzed on the day blood samples were collected but storage history is not detailed.
	Metric 20:	Sample contamination	Medium	× 0.2	0.4	Contamination of blood samples was not discussed in the study, but contamination is not anticipated.
	Metric 21:	Method requirements	High	× 0.2	0.2	According to the authors, T cell subset count measurements were obtained using the Anti-Human Foxp3 Staining Set kit according to the manufacturer's instructions, followed by flow cytometry by fluorescence-activated cell sorting.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	Matrix adjustment was not used nor is it necessary.
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 =≥ 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 62: **Cocco et al. 2013: Evaluation of Cancer Outcomes**

Study Citation:	Cocco, P; Vermeulen, R; Flore, V; Nonne, T; Campagna, M; Purdue, M; Blair, A; Monnereau, A; Orsi, L; Clavel, J; Becker, N; de Sanjosé, S; Foretova, L; Staines, A; Maynadié, M; Nieters, A; Miligi, L; 'T Mannetje, A; Kricker, A; Brennan, P; Boffetta, P; Lan, Q; Rothman, N (2013). Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: A pooled linterLlymph analysis Occupational and Environmental Medicine, 70(11), 795-802
Data Type:	Pooled analysis of 4 case-control studies; risk of non-Hodgkins Lymphoma and occupational exposure to TCE-NHL >150 ppm-Cancer
HERO ID:	2129584

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	The key elements of study design and info. about the study population were reported in the references for each of the primary studies that contributed to the pooled analysis (primary studies were referenced). Selection bias with respect to exposure status not likely.
	Metric 2: Attrition	High	× 0.4	0.4	Work histories and histological information was complete for all individuals who participated and responded.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls for the 4 primary studies were combined for the pooled analysis. In all of the studies, controls were frequency matched to cases with age and gender strata, individually matched, or selected to represent the age and gender distribution in the source population. Each study presented information comparing cases and controls by demographic and other characteristics.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Each primary study utilized expert industrial hygienists who scored exposure by intensity level, frequency, duration and probability of exposure, based on occupational data and job-exposure-matrices. Based on complete work history for all participants. Methods for harmonizing these scores were described in the pooled analysis
	Metric 5: Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure was adequate. Intensity of exposure was based on a 4 point scale, frequency of exposure was based on 4 points that ranged from no exposure to >30% of work time, and probability of exposure was based on a three point scale (low, medium, and high used in the analysis).
	Metric 6: Temporality	High	× 0.4	0.4	All cases were incident cases and exposures occurred prior to the diagnosis of NHL
Domain 3: Outcome Assessment					

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Study Citation:	Cocco, P; Vermeulen, R; Flore, V; Nonne, T; Campagna, M; Purdue, M; Blair, A; Monnereau, A; Orsi, L; Clavel, J; Becker, N; de Sanjosé, S; Foretova, L; Staines, A; Maynadié, M; Nieters, A; Miligi, L; 'T Mannetje, A; Kricker, A; Brennan, P; Boffetta, P; Lan, Q; Rothman, N (2013). Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: A pooled linterLlymph analysis Occupational and Environmental Medicine, 70(11), 795-802
Data Type:	Pooled analysis of 4 case-control studies; risk of non-Hodgkins Lymphoma and occupational exposure to TCE-NHL >150 ppm-Cancer
HERO ID:	2129584

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histological information was available for each case in each primary study.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the measured outcomes outlined in the abstract, introduction, and methods were reported. The number of cases and controls along with the estimate and 95% CI were provided for all outcomes and exposure levels.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Regression models were adjusted by age, gender and study. While other potential confounders were not controlled for in the analysis, appreciable bias is not expected. Smoking, BMI, and education are not known to be strongly associated with NHL. The prevalence of family history and occupational exposure to pesticides was low in the study groups, therefore not expected to be confounders.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Methods to assess analyzed covariates were adequate. Specifics for each case-control study were provided in the original publications and are likely via questionnaire. These studies contributed to the International Lymphoma Epidemiology Consortium formed under the US National Cancer Institute.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Benzene exposure was assessed and not found to be a confounder. Other chlorinated solvents were not adjusted for, but since the pooled analysis included four different studies during different time frames, located in different regions and populations in different industries, it is unlikely that the same pattern of coexposures would have been experienced by cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study pooled the results from three separate studies on non-Hodgkin lymphoma in order to increase the sample size. Studies were selected because they contained the same criteria. Case-controls studies are useful when evaluating cancer outcomes in order to obtain a large enough cancer incidence.

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Study Citation:	Cocco, P; Vermeulen, R; Flore, V; Nonne, T; Campagna, M; Purdue, M; Blair, A; Monnereau, A; Orsi, L; Clavel, J; Becker, N; de Sanjosé, S; Foretova, L; Staines, A; Maynadié, M; Nieters, A; Miligi, L; 'T Mannetje, A; Kricker, A; Brennan, P; Boffetta, P; Lan, Q; Rothman, N (2013). Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: A pooled linterLlymph analysis Occupational and Environmental Medicine, 70(11), 795-802
Data Type:	Pooled analysis of 4 case-control studies; risk of non-Hodgkins Lymphoma and occupational exposure to TCE-NHL >150 ppm-Cancer
HERO ID:	2129584

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	While the sample sized is considered adequate, only 9% of participants were ever exposed to TCE and the probability of exposure was only 1%, reducing the sensitivity of the study to detect associations.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the unconditional logistic regression analysis used for estimates of odds ratios along with the Wald statistics used for calculating the 95% confidence intervals and the confounders included 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	The method for calculating the risk estimates (i.e. odds ratios and 95% CI) 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‡			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 =≥ 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 63: **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_TCE_MycosisFungoides_OR_aboveMedian_All-Cancer
HERO ID:	2129849

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

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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_TCE_MycosisFungoides_OR_aboveMedian_All-Cancer
HERO ID:	2129849

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Multiple levels of exposure. Classified by probability of exposure, exposure frequency, and exposure intensity. Results reported according to unexposed, above median and below median. Details of exposure intensity by chemical not reported. 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 reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Confounders considered in adjusted analysis: age, sex, country, current smoking habit (cigarettes/day), alcohol intake, BMI, and education level.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Primary confounders were assessed using a less-established method with no reporting of validation against well-established methods. Specifically, covariates were determined from interviews. Next of kin completed interviews for 4 cases and 95 controls.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were not accounted for in this analysis, but no direct evidence that co-exposures differ across cases and controls.
Domain 5: Analysis						

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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_TCE_MycosisFungoides_OR_aboveMedian_All-Cancer
HERO ID:	2129849

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control design was appropriate for investigating chlorinated solvents and a rare disease such as MF, and appropriate statistical methods (logistic regression) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	100 cases and 2846 controls. Exposed cases relatively low (27 trichloroethylene, 6 perchloroethylene, 9 methylene chloride), but sufficient to detect an effect.
	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 64: **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:	TCE (>2 ppb) _oral cleft 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	High rating: 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	Medium rating: 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	High rating: 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	Low rating: 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	Medium rating: range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported
	Metric 6: Temporality	High	× 0.4	0.4	High rating: temporality is established and the interval between 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:	TCE (>2 ppb) _oral cleft 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	High rating: 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	High rating: 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	High rating: 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	Medium rating: 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	Medium rating: 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	Medium rating: 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:	TCE (>2 ppb) _oral cleft 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	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: 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 65: **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 (<=2 ppb) TCE_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	High rating: 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	Medium rating: 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	High rating: 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	Low rating: 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	Medium rating: range and distribution of exposure was sufficient to develop an exposure-response estimate; 3 or more levels of exposure were reported
	Metric 6:	Temporality	High	× 0.4	0.4	High rating: temporality is established and the interval between 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:	Low (<=2 ppb) TCE_childhood cancers-Cancer
HERO ID:	2214077

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	High rating: 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	High rating: 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	High rating: 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	Medium rating: 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	Medium rating: 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	Medium rating: 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:	Low (<=2 ppb) TCE_childhood cancers-Cancer
HERO ID:	2214077

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: 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 66: **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_TCE_Neuroblastoma_OR_IQR_5km-Cancer
HERO ID:	2225094

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

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Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_TCE_Neuroblastoma_OR_IQR_5km-Cancer
HERO ID:	2225094

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

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Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_TCE_Neuroblastoma_OR_IQR_5km-Cancer
HERO ID:	2225094

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

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Study Citation:	Heck, JE; Park, AS; Qiu, J; Cockburn, M; Ritz, B (2013). An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring Environmental Research, 127 1-6
Data Type:	Case-Control_Children_TCE_Neuroblastoma_OR_IQR_5km-Cancer
HERO ID:	2225094

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 67: **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:	>4.4, <=35 ppm*yrs TCE_HL-Cancer
HERO ID:	194429

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

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Study Citation:	Seidler, A; Möhner, M; Berger, J; Mester, B; Deeg, E; Elsner, G; Nieters, A; Becker, N (2007). Solvent exposure and malignant lymphoma: A population-based case-control study in Germany Journal of Occupational Medicine and Toxicology, 2 2
Data Type:	>4.4, <=35 ppm*yrs TCE_HL-Cancer
HERO ID:	194429

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

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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:	>4.4, <=35 ppm*yrs TCE_HL-Cancer
HERO ID:	194429

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

⋆ MWF = Metric Weighting Factor

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

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

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

where High $=\geq 1$ 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: **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_TCE_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 born 1995-2006 to mothers residing within 5 km of air-toxics monitoring stations in Los Angeles County. Birth records 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: 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), and 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 selected from some 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. Potential that these factors may have increased diagnosis, which were 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 estimated from air-toxics monitoring stations within 3-5 km of maternal address. 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_TCE_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 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. Possibility that some controls are cases, if 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 reported with confidence interval; number of cases 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 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	Low	× 0.25	0.75	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 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_TCE_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		1.5	
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 69: **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 TCE and Hodgkin lymphoma 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	High rating: key elements of study design were reported, and the reported information indicates selection in or out of the study and participation is not likely to be biased. 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	High rating: 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 include din 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	High rating: 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	Low rating: 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	Medium rating: 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 TCE and Hodgkin lymphoma retrospective cohort study-Cancer
HERO ID:	2799547

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	High rating: 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	High rating: The outcome was assessed using well-established methods. Personal identifier information from thr Defense Manpower Data Center was matched to the Social Security Administratoon 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	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	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	Medium rating: 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; 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	Medium rating: 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 TCE and Hodgkin lymphoma retrospective cohort study-Cancer
HERO ID:	2799547

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Medium rating: appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to TCE exposure, and appropriate statistical methods (i.e., Cox regression model) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Medium rating: the number of participants were adequate to detect an effect in the exposed population
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data. Specific details were provided of the Life Table Analysis System used to compute cause-specific, standardized mortality ratios and 95% confidence intervals and the Cox extended regression models to calculate hazard ratios.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: 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 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 TCE 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	High rating: key elements of study design were reported, and the reported information indicates selection in or out of the study and participation is not likely to be biased. 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	High rating: 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 include din 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	High rating: 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	Low rating: 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	Medium rating: 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 TCE and ALS retrospective cohort study-Neurological/Behavior
HERO ID:	2799547

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	High rating: 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	High rating: The outcome was assessed using well-established methods. Personal identifier information from thr Defense Manpower Data Center was matched to the Social Security Administratoon 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	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	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	Medium rating: 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; 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	Medium rating: 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 TCE 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	Medium rating: appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to TCE exposure, and appropriate statistical methods (i.e., Cox regression model) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Medium rating: the number of participants were adequate to detect an effect in the exposed population
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data. Specific details were provided of the Life Table Analysis System used to compute cause-specific, standardized mortality ratios and 95% confidence intervals and the Cox extended regression models to calculate hazard ratios.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: 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: **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:	TCE_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	Nested case-control study included cases and controls identified from the Nordic Occupational Cancer Study (NOCCA) cohort. 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden and Iceland from 1961-2005 and 76,660 controls 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 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 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. No evidence 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:	TCE_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 which covers 300 occupations and 29 exposure agents for periods: 1945-59, 1960-74, 1975-84, 1985-94. Estimates take into account proportion of exposed, mean level of exposure in exposed in specific time period and occupation. Cumulative exposure estimated based on entire working career. 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 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, we assumed that an individual held his/her occupation until the mid-year between two censuses.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	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. 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:	TCE_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 estimated based on entire working career, capturing all relevant exposure information. 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 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 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:	TCE_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 co-exposures measured. Model 1 included benzene and toluene but not ARHC; and Model 2 included ARCH but neither benzene nor toluene. All other solvents were included in both models, and they 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 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 appropriated for the nested case-control design.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Study has large number of participants adequate to detect an effect in the exposure 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 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:	TCE_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 72: **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 (TCE men CEI 4)-Cancer
HERO ID:	2799644

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

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Study Citation:	Mattei, F; Guida, F; Matrat, M; Cenée, S; Cyr, D; Sanchez, M; Radoi, L; Menvielle, G; Jellouli, F; Carton, M; Bara, S; Marrer, E; Luce, D; Stücker, I (2014). Exposure to chlorinated solvents and lung cancer: Results of the ICARE study Occupational and Environmental Medicine, 71(10), 681-689
Data Type:	ICARE cohort (TCE men CEI 4)-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 (TCE men CEI 4)-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 73: **Brender et al. 2014: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Brender, JD; Shinde, MU; Zhan, FB; Gong, X; Langlois, PH (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: a case-control study Environmental Health: A Global Access Science Source, 13 96
Data Type:	Developmental toxicity- septal heart defects (exposure = 0.01-56.69)-Growth (early life) and Development
HERO ID:	2799700

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	The key elements of the study design are reported (including methods of case ascertainment); the information seems to indicate that selection for the study was not biased.
	Metric 2: Attrition	High	× 0.4	0.4	Exclusion from the analysis sample was largely limited to elective terminations; however it was documented why they were excluded (lack of linkage to a vital record).
	Metric 3: Comparison Group	High	× 0.2	0.2	Cases and controls were recruited from the same population (in Texas), during the same time period (1996–2008) and within the same public health service region (11regions). The eligibility criteria for cases (diagnosis of one of the selected birth defects) was defined. Differences in baseline characteristics (e.g., race/ethnicity, education) were controlled for in statistical analyses.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure was not directly assessed using a well-established method. Exposure risk was estimated based on proximity of maternal residence to TCE emissions and the amounts of that chemical released (Emission Weighted Proximity Model; EWPM). EWPM values were positively associated with air measurements. There is no evidence that exposure misclassification was different among cases and controls.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	The study reports 4 levels of exposure risk (3 + referent) to further evaluate septal heart defects (a weakly significant finding with respect to TCE). The range and distribution of exposure is sufficient to develop an exposure-response measurement.
	Metric 6: Temporality	Medium	× 0.4	0.8	Maternal residential address at the time of delivery was used to evaluate the proximity to exposure. This corresponds to the location of exposure during the first trimester (relevant to morphogenesis) most of the time, but not always. In evaluating the outcomes of interest there is some uncertainty that exposure as indicated occurred during the first trimester.

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Study Citation:	Brender, JD; Shinde, MU; Zhan, FB; Gong, X; Langlois, PH (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: a case-control study Environmental Health: A Global Access Science Source, 13 96
Data Type:	Developmental toxicity- septal heart defects (exposure = 0.01-56.69)-Growth (early life) and Development
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcomes of interest (birth defects) were evaluated in cases based by examination of medical records by trained staff for the Texas Birth Defects Registry (TBDR).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The outcomes of interest are specified in the study report. Effects estimates (ORs) are reported with 95% confidence intervals; the numbers of cases and controls evaluated in each analysis are clearly denoted.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	There is evidence that potential confounders were not accounted for (e.g., the recurrence of birth defects in subsequent pregnancies for case-women; a known risk factor). All risk estimates were adjusted for year of delivery, maternal age, education, race/ethnicity, and public health region of residence.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on potential confounders were obtained from birth and/or fetal death records. Certain characteristics (e.g., smoking) appeared to be underreported based on these records.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures to pollutants (other chlorinated solvents) were estimated using EWPM and were adjusted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen is appropriate to evalute effects between exposure and outcome (i.e., case-control study); appropriate statistical analyses were performed.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of cases and controls was sufficient to detect effects. The offspring of 60,613 case-mothers and 244,927 control-mothers were evaluated (large sample size).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of estimation procedures and categorization of exposure risk for TCE were described sufficiently to understand and conceptually reproduce the results.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Methods for calculating risk estimates (ORs) are transparent.
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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Study Citation:	Brender, JD; Shinde, MU; Zhan, FB; Gong, X; Langlois, PH (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: a case-control study Environmental Health: A Global Access Science Source, 13 96
Data Type:	Developmental toxicity- septal heart defects (exposure = 0.01-56.69)-Growth (early life) and Development
HERO ID:	2799700

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 74: **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 TCE small for GA Q3 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 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 lends 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 TCE small for GA Q3 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 , 3 categorizations were evaluated: (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 TCE small for GA Q3 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; 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. No apparent issues. 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 TCE small for GA Q3 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. 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 75: **Singthong et al. 2015: Evaluation of Respiratory Outcomes**

Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-respiratory symptoms-Respiratory
HERO ID:	2799736

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	The factory was described. but there was no mention of participant recruitment or participation rate, resulting in minor deficiencies. Floor workers were chosen as a source of exposed participants with office workers serving as unexposed participants. There is no evidence to suggest this sample does not represent the exposure distribution in the population.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of eligible participants recruited in the study and number completing the study were not provided at any point. It is not possible to determine attrition with the given information.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Control workers were drawn from office workers of the same plant. The study authors state the populations were similar. The study authors do not address any issues comparing factory floor workers and office/managerial employees. It appears some of the information collected for floor workers was not collected for office workers. There is, however, no attempt to control for SES or other indicators of economic status. This may bias the results towards seeing an effect.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure was determined by job type. It is unclear how this was exactly determined, but exposure groups included those working in offices (control) and those occupationally exposed. Urinalysis and environmental monitoring confirmed that, by group, the controls were significantly less exposed than those on the floor. Determining solely based on job type may still introduce some exposure misclassification.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There were two levels of exposure, those unexposed office controls and the exposed workers on the floor.
	Metric 6:	Temporality	Low	× 0.4	1.2	Exposure and outcome measured at the same time. The temporality relationship between exposure and outcome, in this case TCE and genotoxicity, is uncertain.
Domain 3: Outcome Assessment						

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Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-respiratory symptoms-Respiratory
HERO ID:	2799736

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Well-established method for measuring genotoxicity in humans.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods were provided in the results. Means and standard errors were provided. There were some instances of variance being reported without stating SD or SEM.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, smoking, and alcohol consumptions were evaluated as potential confounders. There is very little detail on the covariate analysis and which covariates were included in the final model.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed by interview with self-reported answers. This is based on self-reported information, but there is no evidence to suggest this is an insensitive method.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were not described. It was stated that TCE was used for cleaning metal parts, but no other chemical exposures were described.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was sufficient to investigate the effects of TCE on respiratory symptoms. There were some issues with exposure categorization and outcome assessment.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study authors outline their power calculation at the beginning of the methods. The number of participants is sufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Some portions of the analysis were described, but there was no discussion on covariate analysis or logistic regression.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Logistic regression analysis was not fully 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	

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Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-respiratory symptoms-Respiratory
HERO ID:	2799736

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	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 76: **Singthong et al. 2015: Evaluation of Genotoxicity-Micronucleus Frequency Outcomes**

Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-micronucleus frequency-Other (please specify below)
HERO ID:	2799736

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	The factory was described. but there was no mention of participant recruitment or participation rate, resulting in minor deficiencies. Floor workers were chosen as a source of exposed participants with office workers serving as unexposed participants. There is no evidence to suggest this sample does not represent the exposure distribution in the population.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of eligible participants recruited in the study and number completing the study were not provided at any point. It is not possible to determine attrition with the given information.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Control workers were drawn from office workers of the same plant. The study authors state the populations were similar. The study authors do not address any issues comparing factory floor workers and office/managerial employees. It appears some of the information collected for floor workers was not collected for office workers. There is, however, no attempt to control for SES or other indicators of economic status. This may bias the results towards seeing an effect.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Urinary TCA was determined by GC-ECD using a modified HS technique. Details on this technique can be found in Christensen et al. 1988 (HERO ID 701518). This method is a well-established method for determining urinary metabolites of TCE.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Multiple linear regression using continuous urinary TCA was used for this portion of the analysis. This represents a wide range of exposures.
	Metric 6:	Temporality	Low	× 0.4	1.2	Exposure and outcome measured at the same time. The temporality relationship between exposure and outcome, in this case TCE and genotoxicity, is uncertain.
Domain 3: Outcome Assessment						

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Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-micronucleus frequency-Other (please specify below)
HERO ID:	2799736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Blood samples taken during a work shift and were measured for genotoxicity using the Cytokinesis Block Micronucleus (CBMN) assay. Details on the method can be found in the current reference and Fenech et al. 2003 (HERO ID 2443662). This is a well-established method of assessing genotoxicity.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods were provided in the results. Means and standard errors were provided. There were some instances of variance being reported without stating SD or SEM.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, duration of work in years, smoking, and alcohol consumptions were evaluated as potential confounders. The details on covariate inclusion were not reported. It is assumed these are the appropriate covariates from Table 6.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed by interview with self-reported answers. This is based on self-reported information, but there is no evidence to suggest this is an insensitive method.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were not described. It was stated that TCE was used for cleaning metal parts, but no other chemical exposures were described.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design for this study was sufficient to investigate genotoxic effects of exposure to TCE among an occupational cohort of factory floor workers and office workers. For the linear regression-genotoxicity portion of this study, there were only minor issues.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study authors outline their power calculation at the beginning of the methods. The number of participants is sufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Some portions of the analysis were described, but there was no discussion on covariate analysis. It was unclear if data were transformed or which covariates were included in the final model.

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Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-micronucleus frequency-Other (please specify below)
HERO ID:	2799736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Low	× 0.2	0.6	There were few details on the linear regression portion of the analysis. From the description, it is not able to be determined whether endpoints were skewed (and transformed) or whether model assumptions were met.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Medium	× 0.143	0.29	The only reported exposure in this study was TCE, but TCA can be derived from multiple parent chemicals. As a result, some specificity is lost.
	Metric 17:	Effect biomarker	Medium	× 0.143	0.29	Micronucleus frequency in peripheral blood lymphocytes was the measured outcome. This was measured by cytokinesis block micronucleus (CBMN) assay. This has been shown to be implicated in genotoxicity, but appears to have some uncertainty.
	Metric 18:	Method Sensitivity	Medium	× 0.143	0.29	For urinalysis, the LOD is stated, but there was no discussion of the number or proportion of participants at or below the LOD.
	Metric 19:	Biomarker stability	Medium	× 0.143	0.29	Urine samples were stored at -20C an analyzed within a month. No other information was provided.
	Metric 20:	Sample contamination	Medium	× 0.143	0.29	No discussion of possible sample contamination was provided. There is no evidence to suggest there was contamination in the sample.
	Metric 21:	Method requirements	Medium	× 0.143	0.29	TCA was determined using GC-ECD with modified HS technique. See Christensen et al. 1988 (HERO ID 701518).
	Metric 22:	Matrix adjustment	Low	× 0.143	0.43	No established method for matrix adjustment was conducted.
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 77: **Singthong et al. 2015: Evaluation of Skin And Connective Tissue Outcomes**

Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-skin symptoms-Skin and Connective Tissue
HERO ID:	2799736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	The factory was described. but there was no mention of participant recruitment or participation rate, resulting in minor deficiencies. Floor workers were chosen as a source of exposed participants with office workers serving as unexposed participants. There is no evidence to suggest this sample does not represent the exposure distribution in the population.
	Metric 2:	Attrition	Low	× 0.4	1.2	Numbers of eligible participants recruited in the study and number completing the study were not provided at any point. It is not possible to determine attrition with the given information.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Control workers were drawn from office workers of the same plant. The study authors state the populations were similar. The study authors do not address any issues comparing factory floor workers and office/managerial employees. It appears some of the information collected for floor workers was not collected for office workers. There is, however, no attempt to control for SES or other indicators of economic status. This may bias the results towards seeing an effect.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure was determined by job type. It is unclear how this was exactly determined, but exposure groups included those working in offices (control) and those occupationally exposed. Urinalysis and environmental monitoring confirmed that, by group, the controls were significantly less exposed than those on the floor. Determining solely based on job type may still introduce some exposure misclassification.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There were two levels of exposure, those unexposed office controls and the exposed workers on the floor.
	Metric 6:	Temporality	Low	× 0.4	1.2	Exposure and outcome measured at the same time. The temporality relationship between exposure and outcome, in this case TCE and genotoxicity, is uncertain.
Domain 3: Outcome Assessment						

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Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-skin symptoms-Skin and Connective Tissue
HERO ID:	2799736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	Symptoms were asked by self-reported questionnaire. This represents self-reported information and is subject to recall bias and is an insensitive instrument.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes outlined in the abstract, introduction, and methods were provided in the results. Means and standard errors were provided. There were some instances of variance being reported without stating SD or SEM.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, smoking, and alcohol consumptions were evaluated as potential confounders. There is very little detail on the covariate analysis and which covariates were included in the final model.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were assessed by interview with self-reported answers. This is based on self-reported information, but there is no evidence to suggest this is an insensitive method.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were not described. It was stated that TCE was used for cleaning metal parts, but no other chemical exposures were described.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was sufficient to investigate the effects of TCE on dermal symptoms. There were some issues with exposure categorization and outcome assessment.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study authors outline their power calculation at the beginning of the methods. The number of participants is sufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Some portions of the analysis were described, but there was no discussion on covariate analysis or logistic regression.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Logistic regression analysis was not fully 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	

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Study Citation:	Singthong, S; Pakkong, P; Choosang, K; Wongsanit, S (2015). Occupational health risks among trichloroethylene-exposed workers in a clock manufacturing factory Global Journal of Health Science, 7(1), 38234
Data Type:	Cross-sectional study of TCE exposed workers-skin symptoms-Skin and Connective Tissue
HERO ID:	2799736

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 78: **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 TCE-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 TCE-Cancer
HERO ID:	194813

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

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Study Citation:	Dosemeci, M; Cocco, P; Chow, WH (1999). Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons American Journal of Industrial Medicine, 36(1), 54-59
Data Type:	renal cancer and occupational TCE-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 79: **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_TCE_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 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 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 presented in previous publication (Fleming 3013 - HERO 2128566). Chemical use and exposure 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 from ATSDR study of community air quality (1969-1980). Work histories from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and 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_TCE_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 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 when COD not provided by NDI. ICD codes for cause of death 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						
	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.

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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_TCE_RenalDisease_HazardRatio-Renal
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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: **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_TCE_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 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 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 presented in previous publication (Fleming 3013 - HERO 2128566). Chemical use and exposure 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 from ATSDR study of community air quality (1969-1980). Work histories from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and 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 2003 - HERO 212856), and the prevalence of TCE was low (e.g., 13.9% with likely TCE 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_TCE_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 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 when COD not provided by NDI. ICD codes for cause of death 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						
	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.

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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_TCE_NervousSystemDisease_HazardRatio-Neurological/Behavior
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 81: **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_TCE_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 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 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 presented in previous publication (Fleming 3013 - HERO 2128566). Chemical use and exposure 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 from ATSDR study of community air quality (1969-1980). Work histories from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and 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 2003 - HERO 212856), and the prevalence of TCE was low (e.g., 13.9% with likely TCE 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_TCE_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 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 when COD not provided by NDI. ICD codes for cause of death 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						
	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.

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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_TCE_BladderUrinaryCancer_HazardRatio-Cancer
HERO ID:	2799800

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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.

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

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 82: **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_TCE_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 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 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 presented in previous publication (Fleming 3013 - HERO 2128566). Chemical use and exposure 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 from ATSDR study of community air quality (1969-1980). Work histories from 2 company electronic personnel databases. Cumulative exposure scores were derived based on department/year exposure matrix modified to incorporate intensity information and 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_TCE_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 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_TCE_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 83: **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:	TCE_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	High rating: key elements of study design were reported, and the reported information indicates selection in or out of the study and participation is not likely to be biased.
	Metric 2:	Attrition	High	× 0.4	0.4	High rating: 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	High rating: 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	Low rating: 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	Medium rating: 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	High rating: 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:	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:	TCE_Parkinson's Disease_BG QC-Neurological/Behavior
HERO ID:	2800329

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	High rating: The outcome was assessed using well-established methods.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Medium rating: 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	Medium rating: 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	Medium rating: 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	Medium rating: 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. However, results using both log 10 transformed and untransformed exposures were reported with no analyses provided to support selection of one over the other.

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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:	TCE_Parkinson's Disease_BG QC-Neurological/Behavior
HERO ID:	2800329

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Unacceptable	× 0.2	0.04	Unacceptable rating: the number of participants and cases were not adequate to evaluate dose-response in the exposed population. For example, there were 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	Medium rating: description of the analyses is sufficient to understand what has been done and to be reproducible with access to the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Medium rating: 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.

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

where High =≥ 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 84: **Swartz et al. 2015: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Swartz, MD; Cai, Y; Chan, W; Symanski, E; Mitchell, LE; Danysh, HE; Langlois, PH; Lupo, PJ (2015). Air toxics and birth defects: A Bayesian hierarchical approach to evaluate multiple pollutants and spina bifida Environmental Health: A Global Access Science Source, 14(1), 16
Data Type:	Swartz_TCE_genpop_spinabifida_low vs high-Growth (early life) and Development
HERO ID:	2857703

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 identified through active surveillance system in state of Texas, including pregnancy terminations. Cases with associated chromosomal abnormality or other syndrome, those with a closed defect, and those with anencephaly were excluded. Cases and controls with missing geocoded maternal addresses were excluded. 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	Attrition was minimal. Cases (n=61, 11.4%) and controls (n=437, 10.5%) with missing geocoded maternal addresses were excluded.
	Metric 3:	Comparison Group	High	× 0.2	0.2	4 matched controls per case; matched by year of birth. Similar in most characteristics, but mothers of cases were more likely to be Hispanic and live in census tracts with higher poverty levels than controls. These covariates were controlled for in analysis.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Non-direct measure of exposure was used: ASPEN model predictions for exposure in 1999. Some potential for exposure misclassification by using geocoded model predictions from only 1 year for the entire study period. Some potential for exposure misclassification by using maternal residence at birth, not at conception or during entire pregnancy, to estimate exposure.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Reports 3 levels: low, medium, high
	Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established, but it is unclear whether exposures fall within relevant exposure windows for birth defects. Used ASPEN model predictions for exposure in 1999 as surrogate for entire study period of 1999-2004 . Exposure estimated based on maternal residence at birth, not at conception or during entire pregnancy.

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Study Citation:	Swartz, MD; Cai, Y; Chan, W; Symanski, E; Mitchell, LE; Danysh, HE; Langlois, PH; Lupo, PJ (2015). Air toxics and birth defects: A Bayesian hierarchical approach to evaluate multiple pollutants and spina bifida Environmental Health: A Global Access Science Source, 14(1), 16
Data Type:	Swartz_TCE_genpop_spinabifida_low vs high-Growth (early life) and Development
HERO ID:	2857703

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases obtained from Texas Birth Defects Registry, a well-established method. The registry is a population-based, active surveillance system that has monitored births, fetal deaths, and terminations throughout the state since 1999.
	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 and controls reported for each analysis.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Multi-pollutant models adjusted for year of birth, maternal education, maternal race/ethnicity, maternal smoking, and census tract poverty status
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Medium rating: Primary confounders (excluding co-exposures) were assessed. However, it is unclear whether some of the covariates (e.g., education, maternal smoking) were assessed using validated methods.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Multi-pollutant models were employed to directly adjust for co-pollutant effects.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Medium rating: appropriate design (i.e., case control for assessment of a rare disease - birth defects - in relation to TCE exposure, and appropriate statistical methods (i.e., Bayesian hierarchical logistic regression) were employed to analyze data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Medium rating: the number of participants (3,695 controls, 533 cases) 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	Bayesian hierarchical 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	

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Study Citation:	Swartz, MD; Cai, Y; Chan, W; Symanski, E; Mitchell, LE; Danysh, HE; Langlois, PH; Lupo, PJ (2015). Air toxics and birth defects: A Bayesian hierarchical approach to evaluate multiple pollutants and spina bifida Environmental Health: A Global Access Science Source, 14(1), 16
Data Type:	Swartz_TCE_genpop_spinabifida_low vs high-Growth (early life) and Development
HERO ID:	2857703

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‡			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 85: **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 TCE 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 TCE 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 is small (e.g. 14 cases and 13 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 TCE 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 86: **Alanee et al. 2015: Evaluation of Cancer Outcomes**

Study Citation:	Alanee, S; Clemons, J; Zahnd, W; Sadowski, D; Dynda, D (2015). Trichloroethylene is associated with kidney cancer mortality: A population-based analysis Anticancer Research, 35(7), 4009-4013
Data Type:	Mortality from kidney cancer-Cancer
HERO ID:	2965860

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, including data sources for TCE releases, kidney cancer incidence/mortality for 2005-2010, county attributes, and behavioral information. There are no individual data for participants, as the study is an ecological analysis at the county level. Inclusion and exclusion data are clearly defined (i.e. counties with both TCE release and cancer incidence/mortality data).
	Metric 2:	Attrition	High	× 0.4	0.4	Incidence rate and mortality rate for kidney cancer determined for counties with TCE exposure. No indication of exclusion bias.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The methods of selection for the reference population is indicated (i.e., categorical cutoffs determined so that the number of counties per group [low, intermediate, high] were equal). County attributes across TCE release categories were comparable, except that the number of primary care providers was higher in the highest TCE category.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	Exposure was classified by environmental TCE releases, and was not validated using other methods. County-level data do not provide information on individual TCE exposures. TCE release information could be a surrogate for other exposures, environmental or occupational, not measured in this study. Exposure may be underestimated (across all groups) because TRI data (the source of information on TCE releases) only includes data for facilities that have a certain number of employees/release a certain amount of the chemical annually.
	Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	TCE releases, but not TCE exposures among individuals were estimated. These data are not adequate to determine an exposure-response relationship.
	Metric 6:	Temporality	High	× 0.4	0.4	Incidence/mortality from kidney cancer were assessed for 2005-2010; TCE release data are for the period form 1988-1997; therefore, the study accounted for a latency period of up to 22 years.

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Study Citation:	Alanee, S; Clemons, J; Zahnd, W; Sadowski, D; Dynda, D (2015). Trichloroethylene is associated with kidney cancer mortality: A population-based analysis Anticancer Research, 35(7), 4009-4013
Data Type:	Mortality from kidney cancer-Cancer
HERO ID:	2965860

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	The outcomes (kidney cancer incidence and mortality) were obtained from a national registry (Surveillance, Epidemiology, and End Results [SEER] Cancer Registry).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Data for the outcomes of interest (kidney cancer incidence and mortality) were reported with p-values (but without a measure of variance).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	There is indirect evidence that some of the adjustments were made (e.g. age); various adjustments (smoking, obesity, hypertension, etc) were made for multivariate linear regression analyses.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariate data were obtained from SEER Stat software (county attributes; in 2000) and Behavioral Risk Factor Surveillance System (smoking obesity, and hypertension rates; 2003 to 2006); exposure and outcome assessments were conducted from 1988 to 1997 and 2005 to 2010 (respectively). Covariate data could not adjusted for individual occupational exposure, smoking, obesity or hypertension; changes in these risk factors over time could not be tracked. However, these factors are not considered likely to bias the assessment.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposures to pollutants were not measured and were not adjusted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Unacceptable	× 0.4	0.16	The ecological study design and analyses are not adequate to address the research question assessing the association of TCE releases with kidney cancer incidence or mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The statistical power is high enough o detect an effect in the exposure population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to be reproducible (with access to the appropriate data).
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for calculating the effect estimates is 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	

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Study Citation:	Alanee, S; Clemons, J; Zahnd, W; Sadowski, D; Dynda, D (2015). Trichloroethylene is associated with kidney cancer mortality: A population-based analysis Anticancer Research, 35(7), 4009-4013
Data Type:	Mortality from kidney cancer-Cancer
HERO ID:	2965860

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‡			Unacceptable⋆⋆		2.1	
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 87: **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_TCE_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_TCE_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_TCE_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_TCE_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 88: **Bassig et al. 2016: Evaluation of Hematological And Immune Outcomes**

Study Citation:	Bassig, BA; Zhang, L; Vermeulen, R; Tang, X; Li, G; Hu, Wei; Guo, W; Purdue, MP; Yin, S; Rappaport, SM; Shen, Min; Ji, Z; Qiu, C; Ge, Y; Hosgood, HD; Reiss, B; Wu, B; Xie, Y; Li, L; Yue, Fei; Freeman, LEB; Blair, A; Hayes, RB; Huang, H; Smith, MT; Rothman, N; Lan, Q (2016). Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde and trichloroethylene Carcinogenesis, 37(7), 692-700
Data Type:	Cross-sectional study of TCE exposed workers (analysis of blood)->=12 ppm group-Hematological and Immune
HERO ID:	3420801

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	Details for the three cross-sectional studies were noted to be described elsewhere (citing 4 other publications, but the one that appears to be relevant to TCE exposure is HERO ID 736090, Lan et al, 2010). 736090 indicates that factories were selected based in an initial screening of >40 potential factories to measure TCE exposure. Specific details on selection of the 80 workers and 96 unexposed controls were not reported nor were participation rates reported. However, there is no indication of selection bias based on the details provided.
	Metric 2:	Attrition	High	× 0.4	0.4	No attrition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Sex and age-matched controls.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	2-3 personal exposure air exposure measures taken during a 3 week period before blood sampling.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	control, <12 ppm, >12 ppm (median conc.)
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure was measured prior to blood sampling.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Sensitive markers of hematological and immune function.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Means and standard errors reported in figures for all outcomes outlined in the methods. Sample size was not provided in the figures, but can be determined from the information provided.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Linear regression analyses were adjusted for age, sex, cigarette smoking alcohol consumption, BMI and recent respiratory infection.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Questionnaire was used to assess potential confounders.

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Study Citation:	Bassig, BA; Zhang, L; Vermeulen, R; Tang, X; Li, G; Hu, Wei; Guo, W; Purdue, MP; Yin, S; Rappaport, SM; Shen, Min; Ji, Z; Qiu, C; Ge, Y; Hosgood, HD; Reiss, B; Wu, B; Xie, Y; Li, L; Yue, Fei; Freeman, LEB; Blair, A; Hayes, RB; Huang, H; Smith, MT; Rothman, N; Lan, Q (2016). Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde and trichloroethylene Carcinogenesis, 37(7), 692-700
Data Type:	Cross-sectional study of TCE exposed workers (analysis of blood)->=12 ppm group-Hematological and Immune
HERO ID:	3420801

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Factories were selected only if they had no other co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The cross-sectional study design is acceptable for the study purpose. Although exposure and outcome were assessed at the same time, TCE exposure was assessed over a three-week period (not clear when this started and finished in terms of the blood collection) and subjects were likely exposed for longer durations. Because of the hematological effects evaluated, exposure closer to the outcome may be more relevant.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 96 controls and 80 exposed subjects evaluated. Even after breaking the exposed into two groups based on the median exposure, this should have been a sufficient sample size to detect an effect of exposure and there was a significant effect on lymphocytes noted.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The main purpose of the study was comparison on the results from three studies evaluating different exposures. However, in order to do that, trend tests were conducted on the results. Description of the linear trend test used for TCE exposure and the confounders adjusted for were described.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Only trend test results (no pair-wise testing). The study only presented results for the trend tests, however, the original publication (HERO ID 736090) indicated the linear regression was used to determine trend as well as differences between exposed and control workers and also presented the significant differences in that report.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	No biomarkers of exposure
	Metric 17:	Effect biomarker	Medium	× 0.2	0.4	The mechanism of action is not completely understood.
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	These are standard outcome bioassays with no sensitivity issues. Although LODs are not provided, it would not be expected that samples would be below detection for these methods.

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Study Citation:	Bassig, BA; Zhang, L; Vermeulen, R; Tang, X; Li, G; Hu, Wei; Guo, W; Purdue, MP; Yin, S; Rappaport, SM; Shen, Min; Ji, Z; Qiu, C; Ge, Y; Hosgood, HD; Reiss, B; Wu, B; Xie, Y; Li, L; Yue, Fei; Freeman, LEB; Blair, A; Hayes, RB; Huang, H; Smith, MT; Rothman, N; Lan, Q (2016). Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde and trichloroethylene Carcinogenesis, 37(7), 692-700
Data Type:	Cross-sectional study of TCE exposed workers (analysis of blood)->=12 ppm group-Hematological and Immune
HERO ID:	3420801

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 19:	Biomarker stability	High	NA	NA	Storage issues are not a concern in this study as samples were processed within 6 hours of obtaining the blood samples. There should be minimal loss during this time and it is generally accepted that samples should be run within a day.
	Metric 20:	Sample contamination	High	× 0.2	0.2	Contaminant free, with QC
	Metric 21:	Method requirements	High	× 0.2	0.2	Cell counts
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	These are standard assays and no metric adjustment is applied with results being presented as cell counts per microliter of blood.
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 =≥ 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 89: **Bove et al. 1995: Evaluation of Growth (Early Life) And Development Outcomes**

Study Citation:	Bove, FJ; Fulcomer, MC; Klotz, JB; Esmart, J; Dufficy, EM; Savrin, JE (1995). Public drinking water contamination and birth outcomes American Journal of Epidemiology, 141(9), 850-862
Data Type:	Developmental- CNS defects at > 1 to 5 ppb-Growth (early life) and Development
HERO ID:	194932

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	The key elements of the study design were reported, including exclusion criteria, participant selection, and outcome ascertainment. The outcomes of interest for live births and live births and fetal deaths were clearly defined. Participation is not likely to be biased; the study authors noted that towns were selected and exposure data were collected without knowledge of the prevalence of birth outcomes.
	Metric 2:	Attrition	Medium	× 0.4	0.8	There was moderate exclusion from the study, but outcome data were largely complete. Exclusion from analyses was adequately addressed (e.g., low/very low birth weights, small for gestational age, preterm birth, and birth weight among 'term' births were only evaluated for live births [not fetal deaths]; preterm birth, small for gestational age, term low birth weight, and birth weight among term births were also not evaluated in a large number of births [n = 5158] for which information on gestational age was not available).
	Metric 3:	Comparison Group	High	× 0.2	0.2	The study design suggests that subjects were recruited from the same eligible population, using the same method of ascertainment, within the same time frame, and using the same inclusion/exclusion criteria.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	There is evidence that there was exposure misclassification due to the number of assumptions that were required to estimate exposures. Measurements in drinking water sources were conducted biannually (sometimes more frequently); TCE is volatile. The study authors suggested that non-monotonic trends observed in the study may be due to exposure misclassification.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The study reports 4 exposure levels (referent group +3); the range/distribution is adequate to evaluate exposure-response relationships.

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Study Citation:	Bove, FJ; Fulcomer, MC; Klotz, JB; Esmart, J; Dufficy, EM; Savrin, JE (1995). Public drinking water contamination and birth outcomes American Journal of Epidemiology, 141(9), 850-862
Data Type:	Developmental- CNS defects at $>$ 1 to 5 ppb-Growth (early life) and Development
HERO ID:	194932

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	The study presents appropriate temporality; exposure (throughout pregnancy) precedes the outcome (developmental effects). The interval between exposure and outcome assessments appears to be appropriate.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcomes were assessed using well-established methods (birth and/or fetal death certificates, and data from the New Jersey Birth Defects Registry).
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	The study's measured outcomes are reported, but not in a way that would allow for detailed extraction. For some endpoints, results were discussed in the text, but not all data were shown.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	There is indirect evidence (discussion) that cofounders that may have affected the analysis were not accounted for in the analysis. Data for maternal alcohol consumption, folic acid, and smoking were not reported; paternal factors were not considered.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	The confounders assessed (maternal age, race, and education; previous stillbirth and miscarriage, sex of birth, prenatal care) were obtained from birth/fetal death certificates and/or using statistical algorithms (for prenatal care). Considerable data were missing.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Co-exposures were measured and adjusted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate to evaluate the relationship between exposure and developmental effects; statistical analyses were appropriately applied.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants was adequate to detect an effect in the exposed population. The number of cases of developmental effects was small.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analyses is sufficient so that the results would be reproducible with access to the appropriate data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method for calculating odds ratios is transparent. 99% confidence interval (CI), 90% CI, and 50% CI were reported instead of the more traditional 95% CI and p-value.
Domain 6: Other Considerations for Biomarker Selection and Measurement						

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Study Citation:	Bove, FJ; Fulcomer, MC; Klotz, JB; Esmart, J; Dufficy, EM; Savrin, JE (1995). Public drinking water contamination and birth outcomes American Journal of Epidemiology, 141(9), 850-862
Data Type:	Developmental- CNS defects at > 1 to 5 ppb-Growth (early life) and Development
HERO ID:	194932

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 =≥ 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 90: **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 (TCE-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 (TCE-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 (TCE-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.

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

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 91: **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_TCE_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_TCE_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, perc, 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_TCE_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 92: **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 - TCE_high intensity T2 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 TCE exposures
	Metric 2:	Attrition	Medium	× 0.4	0.8	77% participation in cases; 54% participation in controls; rationale was provided.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Age-, gender- and race-matched controls.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Job exposure matrix
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Indicators of probability, frequency and intensity; tertiles for cumulative hours exposed.
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure lagged to account for cancer latency.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases identifies by cancer surveillance system and many histologically confirmed.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Odds ratios reported with 95% confidence intervals for kidney cancer and exposure to TCE, CCL4, DCM and Perc
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for age, sex, race, study centre, education level, smoking status, BMI and history of hypertension.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Some covariate information was self-reported (smoking, hypertension, race)
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	TCE exposure did not confound Perc results - therefore, Perc would not confound TCE results.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control study used to evaluate occupational TCE, Perc, DCM, and CCl4 exposure and kidney cancer.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Between Medium and Unacceptable, Medium is the better characterization. An elevated risk of TCE was detected - it just wasn't stat sig.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Odds ratios calculated with unconditional logistic regression.

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Study Citation:	Purdue, MP; Stewart, PA; Friesen, MC; Colt, JS; Locke, SJ; Hein, MJ; Waters, MA; Graubard, BI; Davis, F; Ruterbusch, J; Schwartz, K; Chow, WH; Rothman, N; Hofmann, JN (2016). Occupational exposure to chlorinated solvents and kidney cancer: A case-control study Occupational and Environmental Medicine, 74(4), 268-274
Data Type:	Case-control study of kidney cancer in workers exposed to chlorinated solvents - TCE_high intensity T2 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 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_TCE_BreastCancer_aOR_HighMonthlyAverageExposure-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 selected from incident cancer cases not associated with solvents (skin, mesothelioma, and bone) randomly selected within skin to obtain 5 controls/case. Control characteristics similar to cases and considered as variables (race, Vietnam service). Controls diagnosed earlier than cases.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Constructed residential cumulative exposure to PCE and TCE through drinking water. 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 based on 1980-1985 measurements at 3 contaminated water treatment plants. Estimate exposure based on likely residence and duration of tour.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	Sufficient exposure to determine an effect. Exposures 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_TCE_BreastCancer_aOR_HighMonthlyAverageExposure-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 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 provided and extractable. Odds ratios reported with confidence interval and number of cases and controls 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 missing for 7% cases and 13% controls. Vietnam service, rank, Military Occupational Specialty (MOS) codes from NPRC.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Service related co-exposure to solvents and electromagnetic fields determined from MOS codes. Neither Perc or TCE were isolated exposures in the drinking water, however, exposures outside of Camp Lejeune not anticipated to be significantly different between cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Logistic regression 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 used to determine odds ratios. Sufficient detail 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_TCE_BreastCancer_aOR_HighMonthlyAverageExposure-Cancer
HERO ID:	3489298

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Logistic regression used to calculated OR, adjusted OR and 95% confidence intervals for breast cancer. Similar models 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: **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 (TCE-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 >129.50 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 (TCE-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 (TCE-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 95: **Buhagen et al. 2016: Evaluation of Cancer Outcomes**

Study Citation:	Buhagen, M; Grønskag, A; Ragde, SF; Hilt, B (2016). Association between kidney cancer and occupational exposure to trichloroethylene Journal of Occupational and Environmental Medicine, 58(9), 957-959
Data Type:	Retrospective cohort study of kidney cancer in train repair workers-Cancer
HERO ID:	3502047

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All male workers at a specific train repair and maintenance facility in Norway employed after 1954 were eligible. Persons excluded had worked <1 yr or had missing or incorrect employment information
	Metric 2:	Attrition	High	× 0.4	0.4	997 of 1077 eligible workers were included; persons excluded had worked <1 yr or had missing or incorrect employment information. Follow up of the 997 was complete.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Compared to national (Norway) cancer rates for men stratified by age and calendar period (5 yr grps)
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure for all employees was inferred from employment at the facility. TCE exposure was confirmed only for kidney cancer cases.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Only exposed v. unexposed evaluated.
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality confirmed by detailed analysis of work history and year of diagnosis for the 17 subjects with kidney cancer
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cancer cases identified by social security number linkage to national cancer registry
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Focus of study was on kidney cancer, but SIRs for other cancers were also reported, with CIs.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age, sex, and race were all controlled for.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Age, sex, and race are all well characterized.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Workers were employed in a train repair and maintenance facility with exposure to welding fumes, paints, cleaning fluids, diesel exhaust, and organic solvents, but TCE was used "extensively". Study authors did not consider potential confounding by co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	SIR analysis.

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Study Citation:	Buhagen, M; Grønskag, A; Ragde, SF; Hilt, B (2016). Association between kidney cancer and occupational exposure to trichloroethylene Journal of Occupational and Environmental Medicine, 58(9), 957-959
Data Type:	Retrospective cohort study of kidney cancer in train repair workers-Cancer
HERO ID:	3502047

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Incidence ratios provided for cancers with more than 3 cases. Total of 215 cases.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Standardized incidence ratios (SIR) and 95% confidence intervals for TCE and cancer were determined using the STATA program. Incidence provided and calculations reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Method for calculating SIRs is 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~~ ⟶ Low§		~~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

§ Evaluator's explanation for rating change: "Exposure was inferred from employment in the facility. Coexposures were likely but no information was presented. Demographic characteristics of the cohort were not reported and covariates were not considered."

Table 96: **Montani et al. 2015: Evaluation of Respiratory Outcomes**

Study Citation:	Montani, D; Lau, EM; Descatha, A; Jaïs, X; Savale, L; Andujar, P; Bensefa-Colas, L; Girerd, B; Zendah, I; Le Pavec, J; Seferian, A; Perros, F; Dorfmüller, P; Fadel, E; Soubrier, F; Sitbon, O; Simonneau, G; Humbert, M (2015). Occupational exposure to organic solvents: A risk factor for pulmonary veno-occlusive disease European Respiratory Journal, 46(6), 1721-1731
Data Type:	TCE_case-control_occupational_pulmonary hypertension-Respiratory
HERO ID:	3503369

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	100 consecutive subjects were recruited from the National Reference Center for Severe Pulmonary Hypertension in Le Kremlin Bicêtre, France, between Sept 2008 and Feb 2010. Only patients over 18 years of age were included. Cases were defined as patients diagnosed with pulmonary veno-occlusive disease (n = 34 cases), and controls were patients with idiopathic, anorexigen-induced or heritable pulmonary arterial hypertension (n = 66 controls). Potential for selection bias was minimized by selecting cases and controls from consecutive consenting patients with diagnosis who presented to the outpatient clinic for routine follow-up assessment.
	Metric 2: Attrition	High	× 0.4	0.4	During the course of the study two patients with an initial case classification and control classification had alternative final diagnoses (systemic sclerosis, n=1 and portal hypertension, n=1, respectively), resulting in a total of 33 cases and 65 controls included in the final analysis. Note that 8 case patients died before DNA collection was possible for EIF2AK4 testing.
	Metric 3: Comparison Group	Low	× 0.2	0.6	Controls (patients with idiopathic, anorexigen-induced or heritable pulmonary arterial hypertension) were selected from the same outpatient clinic as the cases. Cases and controls were subject to the same exclusion criteria: history of connective tissue disease, portal hypertension, HIV infection, congenital heart disease and thromboembolic disease. Study presented comparison of covariates for controls and cases. Controls were younger and had a higher proportion of females, which may bias towards a reduced probability of relevant occupational exposures. However, PVOD remained significantly associated with TCE after adjustment for age, sex, and smoking history. Authors note that inclusion of a population level control group may strengthen the findings.
Domain 2: Exposure Characterization					

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Study Citation:	Montani, D; Lau, EM; Descatha, A; Jaïs, X; Savale, L; Andujar, P; Bensefa-Colas, L; Girerd, B; Zendah, I; Le Pavec, J; Seferian, A; Perros, F; Dorfmüller, P; Fadel, E; Soubrier, F; Sitbon, O; Simonneau, G; Humbert, M (2015). Occupational exposure to organic solvents: A risk factor for pulmonary veno-occlusive disease European Respiratory Journal, 46(6), 1721-1731
Data Type:	TCE_case-control_occupational_pulmonary hypertension-Respiratory
HERO ID:	3503369

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Two methods for exposure assessment were used based on self-reported work history: 1) expert consensus assessment (from three blinded independent occupational medicine physicians) and 2) job exposure matrix assessment. Job exposure matrix was used to estimate cumulative exposure with or without a 10-year lag. Use of two methods helped increase robustness of exposure assessment (two methods found moderate to good agreement).
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Two exposure groups: Exposed vs. unexposed. No levels or range of exposures estimated (cumulative exposure index score > 10 = positive exposure, but average or range of cumulative exposure index were not reported in cases or controls). 14/33 cases reported TCE as a main occupational exposure. The number of controls reporting TCE as a main occupational exposure was not reported.
	Metric 6:	Temporality	High	× 0.4	0.4	Study accounted for appropriate latency period and adequately presented appropriate temporality between exposure and disease. Recent exposures (<10 years from date of diagnosis) were considered separately, considering plausible latency between exposure and disease development.
Domain 3: Outcome Assessment						

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Study Citation:	Montani, D; Lau, EM; Descatha, A; Jaïs, X; Savale, L; Andujar, P; Bensefa-Colas, L; Girerd, B; Zendah, I; Le Pavec, J; Seferian, A; Perros, F; Dorfmüller, P; Fadel, E; Soubrier, F; Sitbon, O; Simonneau, G; Humbert, M (2015). Occupational exposure to organic solvents: A risk factor for pulmonary veno-occlusive disease European Respiratory Journal, 46(6), 1721-1731
Data Type:	TCE_case-control_occupational_pulmonary hypertension-Respiratory
HERO ID:	3503369

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Diagnosis of pulmonary veno-occlusive disease and pulmonary arterial hypertension were both made according to current guidelines. Patients were considered to have confirmed PVOD if a histological specimen (from either lung biopsy, explanted lung or post mortem examination) was consistent with PVOD or they were carriers of bi-allelic mutations in the EFI2AK4 gene. Patients were also deemed to have confirmed PVOD if they presented with highly probable PVOD and developed pulmonary oedema following the initiation of specific PAH therapy. Highly probable PVOD was considered to be present if patients fulfilled at least two of the following three criteria: 1) two or more characteristic radiological signs of PVOD (septal lines, centrilobular ground glass opacities, enlarged mediastinal lymph nodes) on high-resolution computed tomography (HRCT) of the chest, 2) diffusing capacity of the lung for carbon monoxide to alveolar volume ratio (DLCO/VA) <55% or resting arterial oxygen tension (PaO2) on room air <65 mmHg or 3) presence of alveolar haemorrhage on bronchoalveolar lavage (Golde score >80 or haemosiderin-laden macrophages >30%). Only confirmed or highly probable PVOD patients were recruited.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	Cumulative exposure index scores were calculated but not reported. Individual solvent exposures were not reported for control group. Odds Ratios and 95% CI were reported for adjusted and crude models. Number of cases and controls for all effect estimates included.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Models were adjusted for age, sex, and smoking history (pack years). Models were not adjusted for EIF2Ak4 mutations.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Covariates adjusted for included age, sex and smoking history, which was demographic and clinical information all determined from a valid data source: the Registry of the French Public Health Network.

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Study Citation:	Montani, D; Lau, EM; Descatha, A; Jaïs, X; Savale, L; Andujar, P; Bensefa-Colas, L; Girerd, B; Zendah, I; Le Pavec, J; Seferian, A; Perros, F; Dorfmüller, P; Fadel, E; Soubrier, F; Sitbon, O; Simonneau, G; Humbert, M (2015). Occupational exposure to organic solvents: A risk factor for pulmonary veno-occlusive disease European Respiratory Journal, 46(6), 1721-1731
Data Type:	TCE_case-control_occupational_pulmonary hypertension-Respiratory
HERO ID:	3503369

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There was no adjustment for potential co-exposures which could have impacted the exposure-outcome relationship. However, there is minimal indication that potential co-exposures differed across cases and controls.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case-control study design was used to estimate an odds ratio for the relationship between TCE exposure and pulmonary veno-occlusive disease. Case-control study design was appropriate to address a rare disease.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	While the study sample was relatively small (33 cases and 65 controls), PVOD is a rare outcome and observed associations demonstrate that sample size was sufficient to detect an effect. Study authors acknowledge the wide confidence intervals that resulted from the small sample sizes. 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 analyses is provided and are sufficient to reproduce the analysis. The confounders used to adjust the OR models are clear and provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Continuous variables were compared with independent sample t-test or Mann-Whitney U-test. Proportions were compared using Chi-squared and Fisher's Exact Tests. Unconditional logistic regression analysis was performed to assess the association between exposures and outcome, and multivariate analysis was done to adjust for presence of confounding factors. 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	

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Study Citation:	Montani, D; Lau, EM; Descatha, A; Jaïs, X; Savale, L; Andujar, P; Bensefa-Colas, L; Girerd, B; Zendah, I; Le Pavec, J; Seferian, A; Perros, F; Dorfmüller, P; Fadel, E; Soubrier, F; Sitbon, O; Simonneau, G; Humbert, M (2015). Occupational exposure to organic solvents: A risk factor for pulmonary veno-occlusive disease European Respiratory Journal, 46(6), 1721-1731
Data Type:	TCE_case-control_occupational_pulmonary hypertension-Respiratory
HERO ID:	3503369

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 97: **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_TCE_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 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_TCE_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_TCE_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	Reports 2 levels of exposure: exposed vs. unexposed
	Metric 6:	Temporality	Low	× 0.4	1.2	The temporality of exposure and outcome is uncertain. Only 1 study that evaluated TCE and perc exposure (Goldman 1996) reported on 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.
Domain 4: Potential Counfounding/Variable Control						

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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_TCE_exposed workers_metaanalysis_SSc-Hematological and Immune
HERO ID:	3503809

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 provided on covariate characterization in the studies included in meta-analysis.
	Metric 11:	Co-exposure Confounding	Not Rated	NA	NA	No description 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	Medium rating: 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_TCE_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 98: **Wright et al. 2017: Evaluation of Cardiovascular Outcomes**

Study Citation:	J. M. Wright, A. Evans, J. A. Kaufman, Z. Rivera-Núñez, M. G. Narotsky (2017). Disinfection by-product exposures and the risk of specific cardiac birth defects Environmental Health Perspectives, 125(2,2), 269-277
Data Type:	Case-control_TCE_CVD_trichloraceticacid_low-Cardiovascular
HERO ID:	3671764

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Cases were selected from 68 towns in Massachusetts with populations >500 trihalomethane and haloacetic acid exposure data from 1999 to 2004. All births in these towns from 2000-2004 with non-chromosomal cardiac birth defects were included (904). Controls were selected from the entire state. Limited to singleton live births, 22-44 weeks gestation, and 350+ grams.
	Metric 2: Attrition	High	× 0.4	0.4	All eligible cases were included. No attrition or exclusion is discussed. The number of subject is provided for each step.
	Metric 3: Comparison Group	High	× 0.2	0.2	Controls from live births the general state population were matched based on birth week, with 10 controls included for each case. Covariates analysis showed that mothers in the control group were more healthy overall, but showed no major differences across cases and controls.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Study evaluated disinfection by-products in drinking water, including 3 metabolites of trichloroethylene (TCE): monochloroacetic acid, dichloroacetic acid and trichloroacetic acid. These metabolites were not directly correlated to a known TCE exposure. Quarterly drinking water data was obtained from the Massachusetts Department of Environmental Protection and individual public water utilities. Maternal exposure in first trimester was estimated based on the average for all samples within the public drinking water system associated with the zip-code from birth records.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	Although trichloroethylene (TCE) was not directly assessed, exposure data was provided for 3 metabolites: monochloroacetic acid, dichloroacetic acid and trichloroacetic acid. Three levels of exposure were assessed for dichloroacetic acid and trichloroacetic acid. A single exposure was assessed for monochloroacetic acid due to low exposure occurrence.

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Study Citation:	J. M. Wright, A. Evans, J. A. Kaufman, Z. Rivera-Núñez, M. G. Narotsky (2017). Disinfection by-product exposures and the risk of specific cardiac birth defects Environmental Health Perspectives, 125(2,2), 269-277
Data Type:	Case-control_TCE_CVD_trichloraceticacid_low-Cardiovascular
HERO ID:	3671764

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Exposure was estimated for the first trimester of pregnancy for cardiovascular birth defects, which covers the appropriate window of susceptibility.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Birth records were obtained from the Massachusetts Department of Public Health and Massachusetts Birth Defects Monitoring Program. Registries drawn from reliable and verified sources (hospital reports, birth/death certificates). Birth defects were diagnosed in the first year of life. Defects were classified using ICD-9 codes for atrial septal defects, pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, congenital anomalies of the heart and circulatory system, and conotruncal heart defects.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Cardiac outcomes assessed are well described. Adjusted odds ratios are provided for each exposure group and chemical with number of cases in each group reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates were evaluated with a change-in-estimate approach. If change was >10%, variables were included in the model. A large number of covariates related to prenatal care, maternal health and background, infants, and water source were considered, which covered anticipated variations well.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Maternal and infant covariate information was obtained from birth records with the exception of income, which was estimated based on residence at birth. Some of these covariates (e.g. smoking during pregnancy, termination history) could be biased.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Trichloroethylene (TCE) was not directly determined in the water samples, only 3 biological metabolites. A range of chlorinated compounds were evaluated in the same water samples. Spearman correlation coefficients were as high as 0.79 between these TCE metabolites and other contaminants (chloroform); trichloroacetic acid and dichloroacetic acid showed a correlation of 0.85. Therefore, it is unclear to what degree the outcomes are associated with exposure to TCE.
Domain 5: Analysis						

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Study Citation:	J. M. Wright, A. Evans, J. A. Kaufman, Z. Rivera-Núñez, M. G. Narotsky (2017). Disinfection by-product exposures and the risk of specific cardiac birth defects Environmental Health Perspectives, 125(2,2), 269-277
Data Type:	Case-control_TCE_CVD_trichloraceticacid_low-Cardiovascular
HERO ID:	3671764

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design used was appropriate for evaluating cardiovascular birth defects. Logistic regression was used to determine the odds ratio (OR) for birth defects associated with prenatal exposure to halogenated compounds in drinking water. Since TCE was not evaluated directly, the study design is not suited to the research of this assessment.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The large sample size (904 cases, 9040 controls) and statistically significant associations for some compounds indicated sufficient statistical power.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Procedures for determining odds ratios are well described and data is presented in detail.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratios with 95% confidence intervals were determined using conditional logistic regression.
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: "The study lacks a direct assessment of trichloroethylene (TCE). Three of the evaluated compounds are known biological metabolites of TCE (Lash et al. 2000): monochloroacetic acid, dichloroacetic acid and trichloroacetic acid. However, no direct correlation was made to TCE exposure in this study and it is possible that these compounds originated from another source."

Table 99: **Thiokol Corp 1986: Evaluation of Genotoxicity Outcomes**

Study Citation:	Thiokol, Corp (1986). INITIAL SUBMISSION: REPORT TO MORTON THIOKOL, ELKTON DIVISION ON RESULTS OF THE SISTER CHROMATID EXCHANGE TESTING, 1986 (FINAL REPORT) WITH COVER LETTER
Data Type:	TCE_cohort_exposed workers_drinking water_genotoxicity-Other (please specify below)
HERO ID:	4215758

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.25	0.5	Participants were all only selected from Morton-Thiokol's Elkton Facility plant with known exposure to elevated levels of TCE in drinking water, dichotomized into low (n = 30 subjects) and high (n = 30 subjects) exposure groups based on self-reported drinking habits. Unclear how many other potential exposed individuals at the factory did not participate. Surveys were conducted in 1985 and 1986 to assess sister chromatid exchange.
	Metric 2:	Attrition	High	× 0.4	0.4	Attrition from initial survey in 1985 to follow-up in 1986 was 3 (one to death, one resigned, and one was absent on day of blood draw). All 3 individuals were in the high TCE exposure group.
	Metric 3:	Comparison Group	Unacceptable	× 0.2	0.04	No unexposed group was used in this study. There was a low and high TCE exposure group in initial study in 1985 (no difference in genotoxicity endpoint observed), but only the high exposure group was included in follow-up in 1986 (decreased significantly compared with both low and high exposure group in 1985). In order to properly interpret these data an unexposed group is needed as the comparison group.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Personal exposure was estimated using known water concentration and self-reported water consumption via a survey. Exposure levels of TCE in water supplies at the plan were reported as 4-6 ppm, but no measurement methods were reported.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Study had two exposure levels: low versus high exposed TCE, which was determined based on self-reported response on a survey on frequency of water consumption. The estimated exposure levels were not reported.

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Study Citation:	Thiokol, Corp (1986). INITIAL SUBMISSION: REPORT TO MORTON THIOKOL, ELKTON DIVISION ON RESULTS OF THE SISTER CHROMATID EXCHANGE TESTING, 1986 (FINAL REPORT) WITH COVER LETTER
Data Type:	TCE_cohort_exposed workers_drinking water_genotoxicity-Other (please specify below)
HERO ID:	4215758

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Measurement of TCE exposure was based on self-reported questionnaires on water consumption at a previous time point. In 1984, the wells with TCE in the plant were discovered and shutdown prior to the measurement of the outcome in 1985. However, "medium" was selected because it is unclear whether exposures fall within the relevant exposure windows for the outcome of interest.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Sister chromatid exchange was measured from blood samples taken from all participants. All testing was conducted blinded. Authors claim that the same procedures (with the same reagents, protocol and key technical staff) were conducted for outcome assessments in 1985 and 1986. Medium was selected because sister chromatid exchange was measured in unspecified cell type.
	Metric 8:	Reporting Bias	Low	× 0.333	1.0	Study fails to report estimated levels of TCE exposure per group. Descriptive statistics of the number of participants per exposure group, mean sister chromatid exchange, standard deviation and range are provided, with p values for significant differences reported. Study also reports individual sister chromatic exchange levels for each study participant, divided by high vs. low TCE exposure. Study also provides figures comparing relationships between 1985 and 1986 sister chromatid exchange levels in the high exposure group.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Evidence of consideration for covariates measured, including age, Chem-10, TCE consumption, alcohol, smoking and gender. However, none of these variables were found to be significant predictors of 1986 sister chromatid exchange, and therefore not included in model. Although no evidence of adjustment, reported parameters didn't differ significantly between groups.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Covariates were assessed using self-administered questionnaires. There is minimal reported information on the covariate characterization, including how alcohol or smoking were assessed.

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Study Citation:	Thiokol, Corp (1986). INITIAL SUBMISSION: REPORT TO MORTON THIOKOL, ELKTON DIVISION ON RESULTS OF THE SISTER CHROMATID EXCHANGE TESTING, 1986 (FINAL REPORT) WITH COVER LETTER
Data Type:	TCE_cohort_exposed workers_drinking water_genotoxicity-Other (please specify below)
HERO ID:	4215758

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Study reports general exposure to other chemicals (undefined) in last 10 years using a "Chem-10" score developed from answers to self-reported questionnaire. Study considered, but did not adjust analysis for this. Study did report distribution in low and high exposed, and an inverse relationship with outcome was reported.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Unacceptable	× 0.4	0.16	A cohort study was conducted on low and high occupationally exposed individuals to TCE in a plant. The relationship between TCE exposure and sister chromatid exchange was investigated. The lack of follow-up for any individuals in the low-exposure group is critical flaw, as there is no true control group.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Sample sizes are small (n = 30 for cases, n = 30 for controls), but sufficient to detect an effect as some statistical differences were observed. Note that as discussed above, a critical flaw is the lack of follow-up for the control group.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient description was provided describing the regression conducted looking at the relationship between the 1985 and 1986 sister chromatid exchange in high TCE exposed individuals. Variables tested for inclusion in the multivariate model were described (although that model was not ultimately reported). Method for testing differences in sister chromatid exchange levels for low vs. high individuals not reported.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Linear regression was conducted looking at the relationship between the 1985 and 1986 sister chromatid exchange in high TCE exposed individuals (reported intercept and R^2 value). Differences in sister chromatid exchange levels were conducted with p values reported (method not described). 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	

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Data Type:	TCE_cohort_exposed workers_drinking water_genotoxicity-Other (please specify below)
HERO ID:	4215758

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⋆⋆		2.5	
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