United States
Environmental Protection Agency

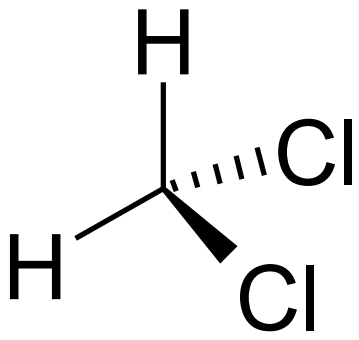
Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for Methylene Chloride

Systematic Review Supplemental File:

Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Studies

CASRN: 75-09-2



June 2020

Table Listing

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

Study Citation:	Lash, AA; Becker, CE; So, Y; Shore, M (1991). Neurotoxic effects of methylene chloride: Are they long lasting in humans? Occupational and Environmental Medicine, 48(6), 418-426
Data Type:	methylene chloride_retired workers_delayed verbal memory_exposed-Neurological/Behavior
HERO ID:	13509

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Participants were retired airline mechanics who had worked for the same, single airline and who were members of the same labor union. Both the airline and the union provided information about the study population and historical occupational methylene chloride exposures. Retirees had to have worked a minimum of 6 years in one or more of 14 target jobs in order to be eligible. Medical and demographic criteria for participants were well-documented in the study report. Follow-ups with survey non-respondents/non-participants revealed that a higher percentage of them had been diagnosed with heart disease and/or gout compared to survey respondents/participants, suggesting a bias toward lower frequency of heart disease in the study population. Additionally, the authors say that retirees that had suffered strokes were excluded, but Table 3 shows that 4 participants had had strokes.
	Metric 2: Attrition	Low	× 0.4	1.2	Of the 91 potential study participants who met all the medical and demographic criteria and were invited to participate in the field study, only 46 (25 solvent-exposed, 21 unexposed) participated. The low participation rate is not explicitly explained, although a logical assumption may be that these eligible subjects elected not to participate.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	The unexposed comparison group consisted of retired airline mechanics who had worked in low- or no-solvent-exposure jobs (jet engine assembly or routine aircraft maintenance). The unexposed comparison group differed from the solvent-exposed group in some demographic criteria (e.g., ethnic minority, English-speaking), but models were not adjusted accordingly.
Domain 2: Exposure Characterization					

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Study Citation:	Lash, AA; Becker, CE; So, Y; Shore, M (1991). Neurotoxic effects of methylene chloride: Are they long lasting in humans? Occupational and Environmental Medicine, 48(6), 418-426
Data Type:	methylene chloride_retired workers_delayed verbal memory_exposed-Neurological/Behavior
HERO ID:	13509

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Job-exposure matrices was determined using occupational/historical exposure information from both the airline and the labor union. Exposure was confirmed by industrial hygiene assessments (personal and area air monitoring from 1975 through 1986), observation of current workplace practices, and interviews with long-term employees. Additionally, the study population consisted of retirees who had worked for the same, single airline throughout their careers, and thus their full work histories were known.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	The study examines two levels of exposure (solvent-exposed and unexposed), based on occupational and historical exposure information provided by the airline and the labor union.
	Metric 6:	Temporality	High	× 0.4	0.4	Study participants the solvent-exposed group worked in these jobs for an average of 11.6 years during the target years of 1970 to 1984, and for an average of 23.8 years in all. For most, employment in these jobs was continuous. Participants were assessed for neurological outcomes including grip strength, motor speed, and memory.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Participants were tested for a number of psychophysical and psychological endpoints (grip strength, sensory responses, motor speed, short-term visual memory, etc.) through seven test stations at the field site. Tests were administered by specially trained examiners (e.g., physicians, psychologists, nurses) who were blind to the participants' exposure group.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Means and standard deviations were reported for each physiological and psychological test (along with p values).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The statistical analyses were adjusted only for age.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Questionnaires, standardized tests, and interviews by the research team and/or physicians were used to determine participation eligibility and assess potential confounders.

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Study Citation:	Lash, AA; Becker, CE; So, Y; Shore, M (1991). Neurotoxic effects of methylene chloride: Are they long lasting in humans? Occupational and Environmental Medicine, 48(6), 418-426
Data Type:	methylene chloride_retired workers_delayed verbal memory_exposed-Neurological/Behavior
HERO ID:	13509

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The issue of potential co-exposures was not addressed in the study, but there's also no evidence that there were co-exposures that were improperly adjusted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	A small occupational cohort of airline mechanic retirees with long-term methylene chloride exposure was assessed for neurological outcomes. Data presented as means/standard deviations evaluated with t-tests.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study had limited sample size (25 exposed, 21 unexposed), but showed statistically significant results. Statistical power appears sufficient to detect large effects.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Results of neurological assessments were reported as means/standard deviations. Analysis of effect estimates is clearly described, and reproducible.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Continuous dependent variables analyzed using t-tests. Composite scores for memory and attention tests were standardized for the pooled group of subjects.
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 2: **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_DCM-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_DCM-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_DCM-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_DCM-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 3: **Infante-Rivard 2005: Evaluation of Cancer Outcomes**

Study Citation:	Infante-Rivard, C; Siemiatycki, J; Lakhani, R; Nadon, L (2005). Maternal exposure to occupational solvents and childhood leukemia Environmental Health Perspectives, 113(6,6), 787-792
Data Type:	DCM_Case-Control_Children_2 Years Before Pregnancy_ALL-Cancer
HERO ID:	630639

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Included 848 eligible cases. Cases of acute lymphoblastic leukemia diagnosed between 1980 and 2000 in the province of Quebec, Canada were recruited from tertiary care centers. Between 1980 and 1993 cases 0-9 yrs. at diagnosis were recruited, between 1994 and 2000 cases included up to 14 yrs. at diagnosis. 790 parents were interviewed.
	Metric 2: Attrition	High	× 0.4	0.4	Children who were adopted, lived in foster families, families spoke neither English or French, who did not reside in Canada, whose parents were both unavailable for interviews were excluded. Reasons for nonparticipation were confidential phone number, refusal to participate, or inability to trace the family.
	Metric 3: Comparison Group	High	× 0.2	0.2	Population based controls were matched on sex and age at the same time of diagnosis. They were concurrently selected. From 1980 to 1993 population-based controls were chosen from family allowance files, Regie des Rentes du Quebec, Quebec, Canada. This data was the most complete census of children. Between 1994 and 2000, they used provincial universal health insurance files, Regie de l'Assurance Maldie du Quebac, Quebec, Canada, for controls. They switched to this source because family allowances were more often directly deposited in the mother's bank account. 916 eligible controls were found.
Domain 2: Exposure Characterization					

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Study Citation:	Infante-Rivard, C; Siemiatycki, J; Lakhani, R; Nadon, L (2005). Maternal exposure to occupational solvents and childhood leukemia Environmental Health Perspectives, 113(6,6), 787-792
Data Type:	DCM_Case-Control_Children_2 Years Before Pregnancy_ALL-Cancer
HERO ID:	630639

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposure coding was used. Carried out by assigning each occupation a standard Canadian industrial title and job titles. Job information was acquired through questionnaires that asked for each job held by the mother from 2 yrs. Before pregnancy and up to birth of the index child. They determined whether there was or was not exposure to specific solvents or chemical mixtures with solvents. Questionnaire included items to assess exposure to solvents at home. For each question, they asked who carried out the activity and during what time period, specified as 1 yr. before pregnancy, during pregnancy, and from birth to the reference date.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	For exposure period ranging from 2 years before pregnancy up to birth, they repeated analysis contrasting 'any exposure' and 'no exposure'. Exposure was coded as level 0 (baseline), no exposure (defined as none coded or 'possible' confidence); level 1, some exposure (exposure resulting in concentration x frequency < 4), and level 2, greater exposure (concentration x frequency >= 4).
	Metric 6:	Temporality	Medium	× 0.4	0.8	Study provides appropriate temporality between exposure to methylene chloride and childhood acute lymphoblastic leukemia of either 2 years before pregnancy or exposure while pregnant.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Acute lymphoblastic leukemia was assessed in cases using well-established methods. Cases were determined to have acute lymphoblastic leukemia (International Classification of Diseases, 9th Revision, code 204.0) on the basis of clinical diagnosis by an oncologist or hematologist.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Chemists who carried out the exposure coding were blind to the case/control status. Description of measured acute lymphoblastic leukemia is reported in the methods section. Number of cases and controls are reported for each analysis. Effect estimates are reported with sufficient details (odds ratios and 95% confidence intervals.) to allow for data extraction.
Domain 4: Potential Counfounding/Variable Control						

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Study Citation:	Infante-Rivard, C; Siemiatycki, J; Lakhani, R; Nadon, L (2005). Maternal exposure to occupational solvents and childhood leukemia Environmental Health Perspectives, 113(6,6), 787-792
Data Type:	DCM_Case-Control_Children_2 Years Before Pregnancy_ALL-Cancer
HERO ID:	630639

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Analyses were adjusted for maternal age and level of schooling in addition to age and sex which were matching covariates. .Data on general risk factors and potential confounders were also obtained from questionnaires. There is no information on why only two additional covariates were included in the final models.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Data on general risk factors and potential confounders were obtained from structured questionnaire administered by telephone. There is no information on the reliability of the data obtained from questionnaires.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	No indication of unbalanced co exposures. Co-exposures were appropriately measured or either directly or indirectly adjusted for.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control design was appropriate for this study. Description of analysis is sufficient for understanding and the reproducibility of the data.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Number of cases and controls is adequate. Identified 848 cases and interviewed 790 case parents. 916 eligible controls were identified and interviewed 790 control parents.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Study design and methods can be reproducible with information provided. Provided reasoning on how categories were created for exposure levels, why covariates were used.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Conditional logistic regression was used to estimate odds ratio and 95% confidence intervals. Each agent, mixture, and family were analyzed in a separate model and analyses.
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:	Infante-Rivard, C; Siemiatycki, J; Lakhani, R; Nadon, L (2005). Maternal exposure to occupational solvents and childhood leukemia Environmental Health Perspectives, 113(6,6), 787-792
Data Type:	DCM_Case-Control_Children_2 Years Before Pregnancy_ALL-Cancer
HERO ID:	630639

Domain	Metric	Rating†	MWF⋆	Score	Comments††
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 4: **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 DCM 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 DCM 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 DCM 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 5: **Costantini et al. 2008: Evaluation of Cancer Outcomes**

Study Citation:	Costantini, AS; Benvenuti, A; Vineis, P; Kriebel, D; 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, G; Mendico, I; Maltoni, S; Miligi, L (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian Multicenter Case-control study American Journal of Industrial Medicine, 51(11,11), 803-811
Data Type:	DCM_population-based case-control_leukemia low-Cancer
HERO ID:	699230

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	In this case-control study in 11 areas of Italy, all cases of hematolymphopoietic malignancies in males and females ages 20-74 years in the years 1991-1993 were identified. A total of 2,737 cases of malignancies were interviewed and the control group consisted of 1,779 subjects randomly selected through the demographic files of municipalities in each of the areas under study, stratified by sex and 5-year age group. Table 1 presents information on the characteristics of the cases and controls, showing that the demographic characteristics were similar.
	Metric 2: Attrition	High	× 0.4	0.4	Table 1 indicates that outcome data was generally complete. Any missing information was minimal and is not likely to appreciably bias the results.
	Metric 3: Comparison Group	High	× 0.2	0.2	The cases and controls were recruited from the same populations (11 areas in Italy) and were of the same age range and sex. The authors state that the control group was selected through demographic files of the municipalities in each of the areas under study. The authors do not describe how the cases were identified, but refer to Costantini et al. 2001. Potential confounders were considered and analyzed and presented in Table 1, several covariates were adjusted for in the final model.
Domain 2: Exposure Characterization					

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Study Citation:	Costantini, AS; Benvenuti, A; Vineis, P; Kriebel, D; 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, G; Mendico, I; Maltoni, S; Miligi, L (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian Multicenter Case-control study American Journal of Industrial Medicine, 51(11,11), 803-811
Data Type:	DCM_population-based case-control_leukemia low-Cancer
HERO ID:	699230

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure assessments were based on the utilization of job or industry-specific questionnaires and subsequent expert ratings in order to assign a level of exposure to the chemicals. Industrial hygiene experts from each geographic area were selected to examine questionnaires and assess a level of probability and intensity of exposure to chemicals. The assessment was blind with respect to case/control status. Exposure was rated on two scales: probability, which was classified into 3 levels (low, medium, and high), and intensity, which was measured on a 4-point scale (very low, low, medium, and high). To ensure a standardized approach, the assessors were centrally trained prior to and periodically during their independent evaluation of questionnaires.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Only two levels of exposure were assessed in the analysis: very low/low, and medium/high. These limited exposure levels are not sufficient to provide a high degree of accuracy in the exposure-response assessment analysis. Analyses for duration of exposure considered two levels: less than 15, and 15 or more years.
	Metric 6:	Temporality	Medium	× 0.4	0.8	The outcomes assessed were leukemia and multiple myeloma identified in the years 1991-1993. Exposure to the chemicals was assessed based on job or industry-specific questionnaires. It is unclear whether the exposures fall within the relevant exposure time-frame for development of leukemia and multiple myeloma.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Table 2 of the study report presents the ICD-9 codes (leukemia, 204-208; chrnoic lymphatic leukemia, 204.1) that were used to identify cases of leukemia or multiple myeloma in the study, details on case ascertainment were not discussed in the current reference but are included in Costantini et al. 2001 (Not found in HERO).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The results for the association between leukemia or multiple myeloma with DCM and other chemicals were reported in Table 2.

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Study Citation:	Costantini, AS; Benvenuti, A; Vineis, P; Kriebel, D; 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, G; Mendico, I; Maltoni, S; Miligi, L (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian Multicenter Case-control study American Journal of Industrial Medicine, 51(11,11), 803-811
Data Type:	DCM_population-based case-control_leukemia low-Cancer
HERO ID:	699230

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 4: Potential Counfounding/Variable Control					
Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Information on education, tobacco smoking, beverage consumption, occupational history, extra-occupational exposure to solvents and pesticides, hair dye use, lifelong residential history, previous diseases, use of diagnostic or therapeutic X-rays, specific medications, family medical history, and reproductive history was obtained by person-to-person interviews that used a specific questionnaire administered by trained personnel. The study adjusted for gender, age, education, and study area in the final analysis. The study also examined the education and smoking status of the cases and controls to ensure the two groups were comparable.
Metric 10:	Covariate Characterization	High	× 0.25	0.25	The information on covariates was obtained by person-to-person interviews that used a specific questionnaire done by trained personnel.
Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	The information on co-exposures was obtained by person-to-person interviews that used a specific questionnaire done by trained personnel.
Domain 5: Analysis					
Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study used an appropriate design to assess the relationship between chemical exposure and hematolymphopoietic malignancies. The study calculated odds ratios and the corresponding 95% confidence limits using multiple logistic regression models, taking into account relevant potential confounders.
Metric 13:	Statistical power	Medium	× 0.2	0.4	The study examined (in total) 355 cases and 811 controls (leukemia), 133 cases and 911 controls (acute myeloid leukemia), 103 cases and 925 controls (chronic lymphatic leukemia), and 163 cases and 674 controls (multiple myeloma). This is a sufficient number of cases and controls to detect an effect in the exposed population. However, the number of cases and controls exposed to DCM was quite small (2-28) and may not have been sufficient 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 and to be conceptually reproducible with access to the analytic data.

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Study Citation:	Costantini, AS; Benvenuti, A; Vineis, P; Kriebel, D; 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, G; Mendico, I; Maltoni, S; Miligi, L (2008). Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian Multicenter Case-control study American Journal of Industrial Medicine, 51(11,11), 803-811
Data Type:	DCM_population-based case-control_leukemia low-Cancer
HERO ID:	699230

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The use of the odds ratio for calculating the risk estimates was transparent and was presented in the paper in sufficient detail.
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 6: **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_DCM_BreastCancer_Females-Cancer
HERO ID:	699234

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

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

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

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 7: **Radican et al. 2008: Evaluation of Respiratory Outcomes**

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

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

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

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

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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: **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_DCM_exposed workers_cancer_10yrlag_1-7 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_DCM_exposed workers_cancer_10yrlag_1-7 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, but the number in the subsets are small.
	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_DCM_exposed workers_cancer_10yrlag_1-7 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 9: **Cocco et al. 1999: Evaluation of Cancer Outcomes**

Study Citation:	Cocco, P; Heineman, EF; Dosemeci, M (1999). Occupational risk factors for cancer of the central nervous system (CNS) among US women American Journal of Industrial Medicine, 36(1), 70-74
Data Type:	Case-Control_Occupational_DCM_MeningiomaMortality_Dichotomous-Cancer
HERO ID:	730500

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Low	× 0.4	1.2	Identified cases of cancer of the brain and other parts of the CNS among women who died in 24 states between 1984 – 1992 via occupation and industry listed on death certificate.
	Metric 2: Attrition	Medium	× 0.4	0.8	No mention of subject withdrawal. Specific inclusion criteria implemented into study design.
	Metric 3: Comparison Group	Low	× 0.2	0.6	For each case, four controls were selected among women who died from nonmalignant diseases, excluding neurological disorders, frequency-matched by state, race, and 5-year age groups.
Domain 2: Exposure Characterization					

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Study Citation:	Cocco, P; Heineman, EF; Dosemeci, M (1999). Occupational risk factors for cancer of the central nervous system (CNS) among US women American Journal of Industrial Medicine, 36(1), 70-74
Data Type:	Case-Control_Occupational_DCM_MeningiomaMortality_Dichotomous-Cancer
HERO ID:	730500

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Job-exposure matrices for 11 occupational hazards were designed. An estimate of intensity level of exposure and probability of exposure to each hazard was developed by two authors (M.D. and P.C.) for each 3-digit occupation and each 3-digit industry U.S. Census code. The final intensity score and probability score was developed for each occupation/industry combination appearing in study subjects' death certificates. The final probability and intensity score was created by combining the occupation and industry scores in the following ways: 1) If both occupation and industry involved exposure to hazard, then the final intensity score was equal to the product of the individual intensity scores. The final probability score was that attributed to the industry code alone. 2) If exposure was related only to occupation, regardless of industry, only the intensity and probability scores related to occupation were used to derive the final scores. Intensity score was squared in these instances to maintain consistency in units. The final intensity and probability scores were then grouped into four levels (unexposed, low, medium, and high). Low, medium, or high probability and intensity of exposure are meant as comparisons within a given exposure and are not comparable across exposures. Occupation and industry listed on the death certificate represent only a fraction of the work history for each subject, either the "usual" or the last occupation. The 3-digit US Census code may have not been specific enough to accurately identify exposures. Thus, there is potential for exposure misclassification that may have impaired the specificity of the job-exposure matrix and weakened positive associations.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range of exposure is sufficient. Some analyses used three levels of exposure, but some only included exposed and unexposed
	Metric 6:	Temporality	Medium	× 0.4	0.8	It is assumed that exposure occurred before outcome but it is unclear whether exposures fall within relevant exposure windows.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Obtained through death certificates and records. ICD-9 codes 192.1 and 192.3.

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Study Citation:	Cocco, P; Heineman, EF; Dosemeci, M (1999). Occupational risk factors for cancer of the central nervous system (CNS) among US women American Journal of Industrial Medicine, 36(1), 70-74
Data Type:	Case-Control_Occupational_DCM_MeningiomaMortality_Dichotomous-Cancer
HERO ID:	730500

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Diagnostic bias was likely to occur in death certificates in case-controls studies since mortality from all causes combined is generally greater and reliability of death certificate is poorer among low SES groups. Low SES occupations might be underrepresented in cases and overrepresented in controls. They controlled for SES.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Adjusted for marital status (never vs. ever married), SES (based on Green's Standardized Score for Specific Occupations, age (continuous), design (frequency matching) state, race, age and sex.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	To account for the uncertainty to control for confounding or effect modification by lifestyle factors or other occupational exposures with death certificates, they adjusted for marital status and residence in the analysis to reduce the effect of lifestyle factors. They adjusted for SES on three levels, based on Green's Standardized Score for Specific Occupations and age at death.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Introduces new analysis that was better designed for job-exposure matrices which was validated in another study. No indication of unbalanced co-exposures.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Case control is an appropriate study design for the research question; this study design is used to assess the association between exposure and rare diseases.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	OR and 95% CI were calculated with logistic regression for each workplace exposure adjusting for confounders mentioned above. ORs and 95% CI were calculated with Wald method using GMBO program in the Epicure software package. 13 cases and 3229 controls. Provided reasoning on how categories were created for exposure levels, why covariates were used, and what statistical analyses were put into place to gather comparative results for the analysis.

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Study Citation:	Cocco, P; Heineman, EF; Dosemeci, M (1999). Occupational risk factors for cancer of the central nervous system (CNS) among US women American Journal of Industrial Medicine, 36(1), 70-74
Data Type:	Case-Control_Occupational_DCM_MeningiomaMortality_Dichotomous-Cancer
HERO ID:	730500

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Study design and methods can be reproducible with information provided. Provided reasoning on how categories were created for exposure levels, why covariates were used. Covariates included in the regression models are reported explicitly.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Job-exposure matrices for the 11 occupational hazards (one being DCM). The categorization of exposure probability and intensity levels in the newly designed matrices resulted in greater sensitivity in identifying exposures particularly in the low probability/ low intensity groups. The number of people exposed in this study is greater than if they used the older matrices. OR and 95% CI were calculated with logistic regression for each workplace exposure adjusting for confounders mentioned above. ORs and 95% CI were calculated with Wald method using GMBO program in the Epicure software package
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 10: **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_DCM_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_DCM_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_DCM_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 11: **Bell et al. 1991: Evaluation of Growth (early life) and Development Outcomes**

Study Citation:	Bell, BP; Franks, P; Hildreth, N; Melius, J (1991). Methylene chloride exposure and birthweight in Monroe County, New York Environmental Research, 55(1,1), 31-39
Data Type:	DCM_birth weight of children of exposed residents_birth weight_Low vs no exposure-Growth (early life) and Development
HERO ID:	730515

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	The study examined data available on birth certificates of individuals near the Eastman Kodak Company at Kodak Park in Rochester, Monroe County, New York. They excluded multiple births and infants weighing less than 750 grams. Because of the few births among nonwhites in the areas of higher exposure, the study was restricted to white births. The study population included white singleton births weighing 750 g or more, born to mothers residing in Monroe County in 1976-1987.
	Metric 2:	Attrition	High	× 0.4	0.4	The study obtained and analyzed data included on birth certificates from all years 1976-1987. The study indicated that outcome data was complete, no attrition.
	Metric 3:	Comparison Group	High	× 0.2	0.2	Because of the known major differences in the distribution of birthweight and in the relationship of risk factors to birthweight between whites and nonwhites, the two groups were not considered together. The study was restricted to white births because of the few births among nonwhites in the areas of higher exposure. Women included in the analysis were recruited from the same geographical area.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure was determined using the Kodak Air Management Program (KAMP) on air dispersion modeling system, which predicts average annual ground level concentrations of substances in the surrounding community. Details on the model were minimal in the present reference and did not indicate that it had been validated.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The KAMP model was used to generate a map of the air dispersion pattern of point and nonpoint sources of DCM within Kodak Park, designating exposure of 50, 25, 10, and 2 ug/mˆ3 DCM in the community. Using the map, the study reported four exposure levels: high (50 ug/m), moderate (25 ug/m), low (10 ug/m), and none.

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Study Citation:	Bell, BP; Franks, P; Hildreth, N; Melius, J (1991). Methylene chloride exposure and birthweight in Monroe County, New York Environmental Research, 55(1,1), 31-39
Data Type:	DCM_birth weight of children of exposed residents_birth weight_Low vs no exposure-Growth (early life) and Development
HERO ID:	730515

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Census tract of residence at the time of birth of the infant, obtained from the birth certificate, was the surrogate measure of exposure to DCM during pregnancy. Temporality between exposure and outcome is established, but there is some remaining uncertainty using a cross-sectional measure of exposure. Study authors state they included an interaction term for 4-year intervals and exposure as well as seasons and exposure.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Birth weight data were obtained from birth certificates for all births in Monroe County in 1976-1987. This is a well-established method of obtaining birthweight data.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	The study reported regression coefficients and odds ratio for low birthweight with confidence intervals.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Multiple linear regression was used to examine the association between birthweight and multiple risk factors, such as maternal education, parity, previous losses, maternal age, late care, male sex, and complicated pregnancy. No information was available on smoking.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Potential confounders such as maternal age, parity, and maternal education were obtained and assessed from data available on birth certificates. This is a valid method of obtaining covariate information.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Any co-exposure to pollutants with potential to bias the results was not likely present because the study only included residents in Monroe County near the Eastman Kodak Company where DCM emissions occurred.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Cross-sectional study design was used to examine the relationship between birthweight and exposure to emissions of DCM. The study used t-tests, correlation coefficients, ANOVA, and multiple linear regression to analyze the association between birthweight and risk factors.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants were adequate for the analysis. The study included over 90,000 birth records from 1976 to 1987 for analysis.

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Study Citation:	Bell, BP; Franks, P; Hildreth, N; Melius, J (1991). Methylene chloride exposure and birthweight in Monroe County, New York Environmental Research, 55(1,1), 31-39
Data Type:	DCM_birth weight of children of exposed residents_birth weight_Low vs no exposure-Growth (early life) and Development
HERO ID:	730515

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of analysis is sufficient to reproduce the analysis. The study used the DCM isopleth map generated by the KAMP model, county census tracts were classified into four exposure categories, high (50 ug/m), moderate (25 ug/m), low (10ug/m), and none. Birthweight and risk factors were gathered from birth certificates of residents living in Monroe County.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The study used t-tests, correlation coefficients, and ANOVA to examine the relationship of birthweight to risk factors. Multiple linear regression was used to investigate the association between birthweight and multiple risk factors.
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 12: **Ott et al. 1983: Evaluation of Mortality Outcomes**

Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride Scandinavian Journal of Work, Environment and Health, 9(Suppl 1,Suppl 1), 1-38
Data Type:	DCM_occupational_retrospective cohort_mortality-Mortality
HERO ID:	29149

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	Participants were employees of a cellulose triacetate and cellulose diacetate fiber manufacturing plant in South Carolina who had worked in preparation or extrusion areas for at least 3 months between 1954 and 1977. A total of 1271 employees from this plant were included in the mortality study. Control group participants (948) were drawn from a non-DCM-exposure reference acetate fiber manufacturing plant in Virginia. Because work assignments at this plant varied and day-to-day assignment records were not kept, employees who worked in comparable areas of the plant (preparation or extrusion areas) could not be identified.
Metric 2:	Attrition	Low	× 0.4	1.2	Attrition was not reported/addressed in this report.
Metric 3:	Comparison Group	Medium	× 0.2	0.4	Because of an absence of work records for employees of the reference plant, it could not be ascertained whether participants from this plant worked in similar areas/operations as those of the participants from the DCM-exposure plant. Additionally, details on participants (e.g., race, sex, age, etc.) were reportedly collected, but not reported in the study report.
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Eight-hr TWA concentrations and peak concentrations were determined for both plants. Personal air monitoring (>350 samples), area sampling (170 samples), and short-term excursion sampling (20 samples) were performed over the course of a 3.5-month survey period in late 1977-early 1978. Details of the personal air sampling methods are described in an appendix to the study report.
Metric 5:	Exposure levels	Medium	× 0.2	0.4	Occupational DCM exposure was categorized into three levels across a sufficient range.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride Scandinavian Journal of Work, Environment and Health, 9(Suppl 1,Suppl 1), 1-38
Data Type:	DCM_occupational_retrospective cohort_mortality-Mortality
HERO ID:	29149

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Low	× 0.4	1.2	The time frame between assessed employee exposures and mortality is unclear, but likely to be adequate since this is a mortality study. Causes of death were determined from death certificates. Mortality within the exposed cohort was compared with that of the reference population and the general U.S. population.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Cause of death was determined from copies death certificates of death certificates obtained through company insurance records or state vital statistics agencies. They were coded by a nosologist according to the Revision of the International Classification of Diseases in force at the time of death. Mortality within the exposed cohort was compared with that of both the corresponding United States population and the reference population. Outcomes of a priori interest were deaths due to ischemic heart disease and malignant neoplasms.
	Metric 8:	Reporting Bias	Low	× 0.333	1	Mortality information for participants is not reported in this study report. Only median exposures are reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Unacceptable	× 0.5	0.25	There is no discussion of covariate adjustments.
	Metric 10:	Covariate Characterization	Unacceptable	× 0.25	0.06	There is no discussion of covariate characterization.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The study report indicates that exposure to other chemicals (e.g., methanol, acetone) was possible at the South Carolina plant.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Unacceptable	× 0.667	0.44	Statistical analyses were not presented in this study report, and therefore it is difficult to determine acceptability on the basis of study design.
	Metric 13:	Statistical power	Medium	× 0.333	0.67	The study included 1,271 exposed employees and 948 unexposed employees, thus with a likely adequate sample size.
	Metric 14:	Reproducibility of analyses	Not Rated	NA	NA	Details of analyses are missing from this study report.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride Scandinavian Journal of Work, Environment and Health, 9(Suppl 1,Suppl 1), 1-38
Data Type:	DCM_occupational_retrospective cohort_mortality-Mortality
HERO ID:	29149

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 15: Statistical models	Not Rated	NA	NA	Details on statistical analyses were not presented in this 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‡		Unacceptable⋆⋆		2.8	
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 13: **Hearne and Pifer 1999: Evaluation of Cancer for Employees in Roll Coating Division Outcomes**

Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_dose-response analysis_total cancer-Cancer
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All key elements of the study design were reported and there is a low risk for selection bias. The total study population of the 1964-1970 roll coating cohort was 1013 men. Women were excluded because of the small number employed in film support operations during those years.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study. Only one death certificate was unavailable for the decedents.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Two referent populations were used in the analyses: the general population of New York State men (excluding NYC) and an occupational population of all Rochester-based Kodak hourly wage men (excluding the roll coating division). The authors reported that, "previous studies of Roll Coating men demonstrated no unusual smoking patterns compared with other employees or with the population at large." No other information was provided to indicate if the workers were similar to the referent population characteristics. There was no adjustment for race in the analyses. For calculation of SMRs, a computer program based on person-years by age, sex, and calendar period was used to calculate the number of expected deaths by cause. For dose-response analysis, the authors conducted Poisson regression modeling to estimate the effect of career exposure on cause-specific mortality rates while adjusting for age, calendar year, and time from first exposure.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Air sampling data were integrated with detailed occupational history to develop an index of career exposure for each individual for their entire work history. Air sampling methods are described in the companion paper Hearne et al. 1987 (HERO ID 730524). The rate estimates were adjusted for respiratory protection and were based on more than 1200 area samples and 1000 personal breathing zone samples collected over 5 decades.

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_dose-response analysis_total cancer-Cancer
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate. There were 4 exposure categories.
	Metric 6:	Temporality	High	× 0.4	0.4	The study population was followed from 24-30 years, depending on the date of entry. The median time from first exposure was ~35 years, which was sufficient for the development of cancer and other chronic illnesses. The employees were exposed to methylene chloride for about 24 years on average.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The vital status of workers was ascertained from the corporate human resources database, including death certificates collected for processing of life insurance claims. The Social Security Administration's Death Master File was searched through 1994 to determine the vital status of terminated employees. The underlying causes of death were coded by a nosologist according to ICD-8 (deaths through 1978) or ICD-9 (deaths after 1978). Causes of death were not confirmed with medical records, but there was no evidence of outcome misclassification.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Effect estimates are reported with confidence intervals in Table 5 which reports SMRs for the entire cohort. Table 6 reports SMRs for different exposure categories but does not include confidence intervals. All results tables include number of observed and expected deaths for each outcome.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjustments are briefly described. The results were age- and sex-adjusted, but not adjusted or stratified by race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Sex and age were ascertained from work records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence of co-exposures in some cohort members and the co-exposures were not addressed in the analysis. Approximately one third of the subjects in the roll coating cohort were employed in that division before the mid-1940s when methylene chloride was introduced, as thus received occupational exposure to other solvents, primarily acetone and methanol.
Domain 5: Analysis						

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_dose-response analysis_total cancer-Cancer
HERO ID:	730525

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and appropriate statistical methods were used to address the research question (a computer program was used to calculate the number of deaths expected by cause; Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs). Exposure-response relationship was also evaluated (tests for trend were conducted using X2 statistics for both internally and externally standardized rates; Poisson regression modelling was performed to assess the relationship between cause-specific mortality and career exposure, adjusting for age, calendar year, and time from first exposure). The Software used for calculations was EGRET which was developed by the Statistics and Epidemiology Research Corporation.
	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 a total of 1013 subjects, and the total observational period generated 26,251 person-years of follow-up.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible. SMRs were calculated using the person-years method. Numbers of observed and expected deaths were provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method used for calculating SMRs is transparent. Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs. Tests for trend were conducted using X2 statistics with P value as probability of observed results, given no trend. Poisson regression modeling was used to assess the relationship between cause-specific mortality and career exposure.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_dose-response analysis_total cancer-Cancer
HERO ID:	730525

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 14: **Hearne and Pifer 1999: Evaluation of Cancer for All Employees Outcomes**

Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1946-1970 cohort_liver and biliary-Cancer
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All key elements of the study design were reported and there is a low risk for selection bias. The total study population of the 1946-1970 methylene chloride cohort was 1311 men. Women were excluded because of the small number employed in film support operations during those years. The authors stated that, "to address the issue of potential selectivity bias, we included all individuals who were hired by, or transferred to, the Roll Coating Division between 1946 and 1970, including those who died, terminated employment, or transferred to other departments before 1964."
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study. The follow-up rate was >99%. Death certificates were unavailable for four decedents.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The referent population was New York state men residing outside of NYC from 1945-1990. The authors reported that, "previous studies of Roll Coating men demonstrated no unusual smoking patterns compared with other employees or with the population at large." No other information was provided to indicate if the workers were similar to the referent population characteristics. The study population (all male) was described as "almost all white," but no other baseline characteristics were provided. There was no adjustment for race in the analyses. For calculation of SMRs, a computer program based on person-years by age, sex, and calendar period was used to calculate the number of expected deaths by cause. For dose-response analysis, the authors also used an internal comparison (expected numbers of death based on intra-cohort distribution of person-years) in addition to the New York state external comparison and conducted Poisson regression modeling to estimate the effect of career exposure on cause-specific mortality rates while adjusting for age, calendar year, and time from first exposure.
Domain 2: Exposure Characterization						

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1946-1970 cohort_liver and biliary-Cancer
HERO ID:	730525

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Air sampling data were integrated with detailed occupational history to develop an index of career exposure for each individual for their entire work history. Air sampling methods are described in the companion paper Hearne et al. 1987 (HERO ID 730524). The rate estimates were adjusted for respiratory protection and were based on more than 1500 area samples and 2500 personal breathing zone samples collected over 5 decades.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate. There were 4 exposure categories.
	Metric 6:	Temporality	High	× 0.4	0.4	The study population was followed from 25-49 years, depending on the date of entry. The average time from first exposure was ~34 years, which was sufficient for the development of cancer and other chronic illnesses. The employees were exposed to methylene chloride for about 17 years on average (range 1-42 years).
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The vital status of workers was ascertained from the corporate human resources database, including death certificates collected for processing of life insurance claims. The Social Security Administration's Death Master File was searched through 1994 to determine the vital status of terminated employees. The underlying causes of death were coded by a nosologist according to ICD-8 (deaths through 1978) or ICD-9 (deaths after 1978). Causes of death were not confirmed with medical records, but there was no evidence of outcome misclassification.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Effect estimates are reported with confidence intervals in Table 2 which reports SMRs for the entire cohort. Table 4 reports SMRs for different exposure categories but does not include confidence intervals. All results tables include number of observed and expected deaths for each outcome.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjustments are briefly described. The results were age- and sex-adjusted, but not adjusted or stratified by race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Sex and age were ascertained from work records.

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1946-1970 cohort_liver and biliary-Cancer
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Any co-exposure to pollutants that are not the target exposure that would likely bias the results were not likely to be present. The authors stated that, "to ensure that methylene chloride was the cohort's primary solvent exposure, we selected employees who were hired after the Roll Coating Division began using this material in the mid-1940s." Prior to the mid-1940s, acetone and methanol were the major solvents used in film support manufacturing.
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 appropriate statistical methods were used to address the research question (a computer program was used to calculate the number of deaths expected by cause; Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs). Exposure-response relationship was also evaluated (tests for trend were conducted using X2 statistics for both internally and externally standardized rates; Poisson regression modelling was performed to assess the relationship between cause-specific mortality and career exposure, adjusting for age, calendar year, and time from first exposure). The Software used for calculations was EGRET which developed by the Statistics and Epidemiology Research Corporation.
	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 a total of 1311 subjects with over 200 people in each quartile of exposure. The total observational period generated 46,112 person-years of follow-up.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible. SMRs were calculated using the person-years method. Numbers of observed and expected deaths were provided.

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1946-1970 cohort_liver and biliary-Cancer
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method used for calculating SMRs is transparent. Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs. Tests for trend were conducted using X2 statistics with P value as probability of observed results, given no trend. Poisson regression modeling was used to assess the relationship between cause-specific mortality and career exposure.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			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 15: **Hearne and Pifer 1999: Evaluation of Respiratory Outcomes**

Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_allrespiratorydiseases-Respiratory
HERO ID:	730525

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	All key elements of the study design were reported and there is a low risk for selection bias. The total study population of the 1964-1970 roll coating cohort was 1013 men. Women were excluded because of the small number employed in film support operations during those years.
	Metric 2: Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study. Only one death certificate was unavailable for the decedents.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Two referent populations were used in the analyses: the general population of New York State men (excluding NYC) and an occupational population of all Rochester-based Kodak hourly wage men (excluding the roll coating division). The authors reported that, "previous studies of Roll Coating men demonstrated no unusual smoking patterns compared with other employees or with the population at large." No other information was provided to indicate if the workers were similar to the referent population characteristics. There was no adjustment for race in the analyses. For calculation of SMRs, a computer program based on person-years by age, sex, and calendar period was used to calculate the number of expected deaths by cause. For dose-response analysis, the authors conducted Poisson regression modeling to estimate the effect of career exposure on cause-specific mortality rates while adjusting for age, calendar year, and time from first exposure.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Air sampling data were integrated with detailed occupational history to develop an index of career exposure for each individual for their entire work history. Air sampling methods are described in the companion paper Hearne et al. 1987 (HERO ID 730524). The rate estimates were adjusted for respiratory protection and were based on more than 1200 area samples and 1000 personal breathing zone samples collected over 5 decades.

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_allrespiratorydiseases-Respiratory
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate. There were 4 exposure categories.
	Metric 6:	Temporality	High	× 0.4	0.4	The study population was followed from 24-30 years, depending on the date of entry. The median time from first exposure was ~35 years, which was sufficient for the development of cancer and other chronic illnesses. The employees were exposed to methylene chloride for about 24 years on average.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The vital status of workers was ascertained from the corporate human resources database, including death certificates collected for processing of life insurance claims. The Social Security Administration's Death Master File was searched through 1994 to determine the vital status of terminated employees. The underlying causes of death were coded by a nosologist according to ICD-8 (deaths through 1978) or ICD-9 (deaths after 1978). Causes of death were not confirmed with medical records, but there was no evidence of outcome misclassification.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Effect estimates are reported with confidence intervals in Table 5 which reports SMRs for the entire cohort. Table 6 reports SMRs for different exposure categories but does not include confidence intervals. All results tables include number of observed and expected deaths for each outcome.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjustments are briefly described. The results were age- and sex-adjusted, but not adjusted or stratified by race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Sex and age were ascertained from work records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence of co-exposures in some cohort members and the co-exposures were not addressed in the analysis. Approximately one third of the subjects in the roll coating cohort were employed in that division before the mid-1940s when methylene chloride was introduced, as thus received occupational exposure to other solvents, primarily acetone and methanol.
Domain 5: Analysis						

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_allrespiratorydiseases-Respiratory
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and appropriate statistical methods were used to address the research question (a computer program was used to calculate the number of deaths expected by cause; Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs). Exposure-response relationship was also evaluated (tests for trend were conducted using X2 statistics for both internally and externally standardized rates; Poisson regression modelling was performed to assess the relationship between cause-specific mortality and career exposure, adjusting for age, calendar year, and time from first exposure). The Software used for calculations was EGRET which was developed by the Statistics and Epidemiology Research Corporation.
	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 a total of 1013 subjects, and the total observational period generated 26,251 person-years of follow-up.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible. SMRs were calculated using the person-years method. Numbers of observed and expected deaths were provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method used for calculating SMRs is transparent. Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs. Tests for trend were conducted using X2 statistics with P value as probability of observed results, given no trend. Poisson regression modeling was used to assess the relationship between cause-specific mortality and career exposure.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_allrespiratorydiseases-Respiratory
HERO ID:	730525

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 16: **Hearne and Pifer 1999: Evaluation of Hematological and Immune Outcomes**

Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_infection_mortality-Hematological and Immune
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All key elements of the study design were reported and there is a low risk for selection bias. The total study population of the 1964-1970 roll coating cohort was 1013 men. Women were excluded because of the small number employed in film support operations during those years.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study. Only one death certificate was unavailable for the decedents.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Two referent populations were used in the analyses: the general population of New York State men (excluding NYC) and an occupational population of all Rochester-based Kodak hourly wage men (excluding the roll coating division). The authors reported that, "previous studies of Roll Coating men demonstrated no unusual smoking patterns compared with other employees or with the population at large." No other information was provided to indicate if the workers were similar to the referent population characteristics. There was no adjustment for race in the analyses. For calculation of SMRs, a computer program based on person-years by age, sex, and calendar period was used to calculate the number of expected deaths by cause. For dose-response analysis, the authors conducted Poisson regression modeling to estimate the effect of career exposure on cause-specific mortality rates while adjusting for age, calendar year, and time from first exposure.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Air sampling data were integrated with detailed occupational history to develop an index of career exposure for each individual for their entire work history. Air sampling methods are described in the companion paper Hearne et al. 1987 (HERO ID 730524). The rate estimates were adjusted for respiratory protection and were based on more than 1200 area samples and 1000 personal breathing zone samples collected over 5 decades.

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_infection_mortality-Hematological and Immune
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate. There were 4 exposure categories.
	Metric 6:	Temporality	High	× 0.4	0.4	The study population was followed from 24-30 years, depending on the date of entry. The median time from first exposure was ~35 years, which was sufficient for the development of cancer and other chronic illnesses. The employees were exposed to methylene chloride for about 24 years on average.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The vital status of workers was ascertained from the corporate human resources database, including death certificates collected for processing of life insurance claims. The Social Security Administration's Death Master File was searched through 1994 to determine the vital status of terminated employees. The underlying causes of death were coded by a nosologist according to ICD-8 (deaths through 1978) or ICD-9 (deaths after 1978). Causes of death were not confirmed with medical records, but there was no evidence of outcome misclassification.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Effect estimates are reported with confidence intervals in Table 5 which reports SMRs for the entire cohort. Table 6 reports SMRs for different exposure categories but does not include confidence intervals. All results tables include number of observed and expected deaths for each outcome.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Adjustments are briefly described. The results were age- and sex-adjusted, but not adjusted or stratified by race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Sex and age were ascertained from work records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence of co-exposures in some cohort members and the co-exposures were not addressed in the analysis. Approximately one third of the subjects in the roll coating cohort were employed in that division before the mid-1940s when methylene chloride was introduced, as thus received occupational exposure to other solvents, primarily acetone and methanol.
Domain 5: Analysis						

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_infection_mortality-Hematological and Immune
HERO ID:	730525

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and appropriate statistical methods were used to address the research question (a computer program was used to calculate the number of deaths expected by cause; Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs). Exposure-response relationship was also evaluated (tests for trend were conducted using X2 statistics for both internally and externally standardized rates; Poisson regression modelling was performed to assess the relationship between cause-specific mortality and career exposure, adjusting for age, calendar year, and time from first exposure). The Software used for calculations was EGRET which was developed by the Statistics and Epidemiology Research Corporation.
	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 a total of 1013 subjects, and the total observational period generated 26,251 person-years of follow-up.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible. SMRs were calculated using the person-years method. Numbers of observed and expected deaths were provided.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method used for calculating SMRs is transparent. Poisson probability distribution was used to test the statistical significance and to calculate confidence intervals for the SMRs. Tests for trend were conducted using X2 statistics with P value as probability of observed results, given no trend. Poisson regression modeling was used to assess the relationship between cause-specific mortality and career exposure.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	

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Study Citation:	Hearne, FT; Pifer, JW (1999). Mortality study of two overlapping cohorts of photographic film base manufacturing employees exposed to methylene chloride Journal of Occupational and Environmental Medicine, 41(12), 1154-1169
Data Type:	Occupational_DCM_1964-1970 roll coating cohort_infection_mortality-Hematological and Immune
HERO ID:	730525

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 17: **Gibbs et al. 1996: Evaluation of Cancer Outcomes**

Study Citation:	Gibbs, GW; Amsel, J; Soden, K (1996). A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride Journal of Occupational and Environmental Medicine, 38(7,7), 693-697
Data Type:	DCM_exposed workers_Mortality_Prostate Cancer_No Exposed-Cancer
HERO ID:	730533

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All workers were included in the study, all key elements were included. No loss was reported "The workers included in the Amcelle cohort comprised all individuals who were on the payroll on or after January 1, 1970 and who had worked at the plant for 3 or more months. The cohort consisted of 3211 white employees (2187 men and 1024 women)." The plant and production process were described in detail, including history of use and production.
	Metric 2:	Attrition	High	× 0.4	0.4	No indication of loss from the 3211 initial participants. Outcome and covariate data were complete.
	Metric 3:	Comparison Group	High	× 0.2	0.2	There were male and female workers in all exposure groups, all where white. The study authors state they present SMRs using Allegany County, MD as a reference group as these are "preferred because they, in effect, adjust for social, economic, ethnic, and cultural factors related to disease."
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposures were measured as reported in Ott et al. 1983 (HERO ID 29149). They describe personal sampling and area sampling, but the exact method and number of samples at the Amcelle plant is unclear. This is a direct exposure measurement, but the method is not entirely clear.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Exposure monitoring data, first reported by Ott et al 4 for the Celriver plant, were used to establish high and low exposure ranges, which were 350 to 700 ppm and 50 to 100 ppm, respectively. Because there were operations that did not involve methylene chloride exposure, a "0" exposure category was created as an internal control. The distribution of workers according to exposure is shown in Table 1.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Cause of death was determined and compared to earlier exposures. Workers were followed for 9 years after the closing of the plant. This sufficiently establishes temporality between exposure and outcome.
Domain 3: Outcome Assessment						

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Study Citation:	Gibbs, GW; Amsel, J; Soden, K (1996). A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride Journal of Occupational and Environmental Medicine, 38(7,7), 693-697
Data Type:	DCM_exposed workers_Mortality_Prostate Cancer_No Exposed-Cancer
HERO ID:	730533

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	"Vital status was determined as of December 31, 1989. The follow-up included searching company personnel records and pension files for persons still living. Often, plant records could be used for identifying former employees who had died. In addition, the National Death Index was searched and Social Security Death Master Files were examined ... causes of death were determined from death certificates and coded to the ninth revision of the International Classification of Diseases by a qualified nosologist." This is a well-established method of determining mortality and cause of death.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All measured outcomes were reported. The study authors state they published SMRs using the local population as a reference only. This was thought to be the most representative comparison.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates were assessed in the analysis. "The ratio of observed to expected deaths in each 5-year interval from 1970 through 1989 was determined for 62 causes of death, and standardized mortality ratios (SMRs) were calculated and controlled for age, race, gender, and calendar period."
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariate characterization was not explicitly discussed. It is assumed age, race, and gender were obtained from Amcelle employment records.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Exposures to acetone and finishing oils were present and may have varied by task. There is no indication that co-exposures were accounted for. More details can be found in HERO ID 29149.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This study looks at an causes of death in an occupational cohort with approximately 9 years of follow-up. This is appropriate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were over 3000 employees in this cohort. This is sufficient to see an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Categorization of exposure levels was adequately described. Other details on the analysis were included so that the work could be reproduced.

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Study Citation:	Gibbs, GW; Amsel, J; Soden, K (1996). A cohort mortality study of cellulose triacetate-fiber workers exposed to methylene chloride Journal of Occupational and Environmental Medicine, 38(7,7), 693-697
Data Type:	DCM_exposed workers_Mortality_Prostate Cancer_No Exposed-Cancer
HERO ID:	730533

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	"The ratio of observed to expected deaths in each 5-year interval from 1970 through 1989 was determined for 62 causes of death, and standardized mortality ratios (SMRs) were calculated and controlled for age, race, gender, and calendar period. Statistical analyses were done using OCMAP." The choice of a reference population was adequately described.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			High		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 18: **Lanes et al. 1990: Evaluation of Mortality Outcomes**

Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR all cause-Mortality
HERO ID:	730554

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Study setting and participants are described as an occupational cohort of 1271 employees, assembled in 1977. Employees worked for at least three months between 1954 and 1977 in areas identified as having methylene chloride exposure from an IH survey. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2: Attrition	High	× 0.4	0.4	Death certificates were obtained for 118/122 deaths. The authors note that use of "the national death index and the records of the Social Security Administration may fail to ascertain mortality by approximately 10-20%"
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Race and sex of the cohort are stratified in a table. The chosen reference population was York County, SC, the county in which 95% of the cohort resided but only constituted <4% of the county population.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	The cohort was comprised of employees that worked specifically in the two areas with concern for DCM exposure—the preparation and extrusion areas. Detailed work histories were only available for a small subset of this cohort. An IH survey in 1977 reported a time-weighted average for these two areas and it is assumed that exposure was constantly present prior to this survey.
	Metric 5: Exposure levels	Low	× 0.2	0.6	As an SMR study, there are presumed to be two levels of exposure. Those in the cohort are exposed to DCM in the preparation and extrusion areas while the reference population is unexposed.
	Metric 6: Temporality	High	× 0.4	0.4	Mortality was assessed for a follow-up period after employment at this facility of approximately 10 years (cohort formed in Jan 1977, follow-up until Sep 1986). Length of employment was assessed in select cancer-related mortality outcomes.
Domain 3: Outcome Assessment					

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR all cause-Mortality
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Mortality was assessed by searching the national death index and records from the Social Security Administration. This is not a gold standard method and the authors note there may be a 10-20% margin of error when assessing mortality by Social Security Administration records.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Race, age, sex, and calendar period were all considered in the SMR calculation. There is also indirect evidence to suggest the demographic distribution in the sample population is similar to that of the reference population. Employees in the cohort were reported to have worked in the preparation and extrusion areas; it is unclear whether there would be any differential distribution of SES status in this sample (i.e., managers vs non-managers).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates such as age, sex, and race were obtained through employment records. There is no evidence to suggest this method has poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The industrial hygiene survey conducted in 1977 revealed 8-hour TWAs for three chemicals present in these two areas of the textile manufacturing plant. There were detectable concentrations of DCM (1700 ppm), acetone (1600 ppm), and methanol (140 ppm). This indicates the presence of co-exposure, but the distribution of this exposure among the cohort is unknown.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The occupational cohort contained over 1000 employees and was sufficiently large to detect an effect of DCM.

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR all cause-Mortality
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Mortality among the cohort was compared to that of the York County, SC population to generate standardized mortality ratios. Reference population death rates from 1962 were used for non-cancer outcomes, as these rates were unavailable for the reference population for 1954-1961.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
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 19: **Lanes et al. 1990: Evaluation of Respiratory Outcomes**

Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR respiratory disease-Respiratory
HERO ID:	730554

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Study setting and participants are described as an occupational cohort of 1271 employees, assembled in 1977. Employees worked for at least three months between 1954 and 1977 in areas identified as having methylene chloride exposure from an IH survey. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2: Attrition	High	× 0.4	0.4	Death certificates were obtained for 118/122 deaths. The authors note that use of "the national death index and the records of the Social Security Administration may fail to ascertain mortality by approximately 10-20%"
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Race and sex of the cohort are stratified in a table. The chosen reference population was York County, SC, the county in which 95% of the cohort resided but only constituted <4% of the county population.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	The cohort was comprised of employees that worked specifically in the two areas with concern for DCM exposure—the preparation and extrusion areas. Detailed work histories were only available for a small subset of this cohort. An IH survey in 1977 reported a time-weighted average for these two areas and it is assumed that exposure was constantly present prior to this survey.
	Metric 5: Exposure levels	Low	× 0.2	0.6	As an SMR study, there are presumed to be two levels of exposure. Those in the cohort are exposed to DCM in the preparation and extrusion areas while the reference population is unexposed.
	Metric 6: Temporality	High	× 0.4	0.4	Mortality was assessed for a follow-up period after employment at this facility of approximately 10 years (cohort formed in Jan 1977, follow-up until Sep 1986). Length of employment was assessed in select cancer-related mortality outcomes.
Domain 3: Outcome Assessment					

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR respiratory disease-Respiratory
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Mortality was assessed by searching the national death index and records from the Social Security Administration. This is not a gold standard method and the authors note there may be a 10-20% margin of error when assessing mortality by Social Security Administration records.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Race, age, sex, and calendar period were all considered in the SMR calculation. There is also indirect evidence to suggest the demographic distribution in the sample population is similar to that of the reference population. Employees in the cohort were reported to have worked in the preparation and extrusion areas; it is unclear whether there would be any differential distribution of SES status in this sample (i.e., managers vs non-managers).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates such as age, sex, and race were obtained through employment records. There is no evidence to suggest this method has poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The industrial hygiene survey conducted in 1977 revealed 8-hour TWAs for three chemicals present in these two areas of the textile manufacturing plant. There were detectable concentrations of DCM (1700 ppm), acetone (1600 ppm), and methanol (140 ppm). This indicates the presence of co-exposure, but the distribution of this exposure among the cohort is unknown.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The occupational cohort contained over 1000 employees and was sufficiently large to detect an effect of DCM. The effect estimate is based on a small number of cases.

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR respiratory disease-Respiratory
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Mortality among the cohort was compared to that of the York County, SC population to generate standardized mortality ratios. Reference population death rates from 1962 were used for non-cancer outcomes, as these rates were unavailable for the reference population for 1954-1961.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
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 20: **Lanes et al. 1990: Evaluation of Cancer Outcomes**

Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR lung cancer-Cancer
HERO ID:	730554

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Study setting and participants are described as an occupational cohort of 1271 employees, assembled in 1977. Employees worked for at least three months between 1954 and 1977 in areas identified as having methylene chloride exposure from an IH survey. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2:	Attrition	High	× 0.4	0.4	Death certificates were obtained for 118/122 deaths. The authors note that use of "the national death index and the records of the Social Security Administration may fail to ascertain mortality by approximately 10-20%"
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Race and sex of the cohort are stratified in a table. The chosen reference population was York County, SC, the county in which 95% of the cohort resided but only constituted <4% of the county population.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	The cohort was comprised of employees that worked specifically in the two areas with concern for DCM exposure—the preparation and extrusion areas. Detailed work histories were only available for a small subset of this cohort. An IH survey in 1977 reported a time-weighted average for these two areas and it is assumed that exposure was constantly present prior to this survey.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	As an SMR study, there are presumed to be two levels of exposure. Those in the cohort are exposed to DCM in the preparation and extrusion areas while the reference population is unexposed.
	Metric 6:	Temporality	High	× 0.4	0.4	Mortality was assessed for a follow-up period after employment at this facility of approximately 10 years (cohort formed in Jan 1977, follow-up until Sep 1986). Length of employment was assessed in select cancer-related mortality outcomes.
Domain 3: Outcome Assessment						

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR lung cancer-Cancer
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Mortality was assessed by searching the national death index and records from the Social Security Administration. This is not a gold standard method and the authors note there may be a 10-20% margin of error when assessing mortality by Social Security Administration records.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Race, age, sex, and calendar period were all considered in the SMR calculation. There is also indirect evidence to suggest the demographic distribution in the sample population is similar to that of the reference population. Employees in the cohort were reported to have worked in the preparation and extrusion areas; it is unclear whether there would be any differential distribution of SES status in this sample (i.e., managers vs non-managers).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates such as age, sex, and race were obtained through employment records. There is no evidence to suggest this method has poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The industrial hygiene survey conducted in 1977 revealed 8-hour TWAs for three chemicals present in these two areas of the textile manufacturing plant. There were detectable concentrations of DCM (1700 ppm), acetone (1600 ppm), and methanol (140 ppm). This indicates the presence of co-exposure, but the distribution of this exposure among the cohort is unknown.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The occupational cohort contained over 1000 employees and was sufficiently large to detect an effect of DCM.

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR lung cancer-Cancer
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Mortality among the cohort was compared to that of the York County, SC population to generate standardized mortality ratios. Reference population death rates from 1962 were used for non-cancer outcomes, as these rates were unavailable for the reference population for 1954-1961.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
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 21: **Lanes et al. 1990: Evaluation of Cardiovascular Outcomes**

Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR cerebrovascular disease-Cardiovascular
HERO ID:	730554

Domain	Metric	Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Study setting and participants are described as an occupational cohort of 1271 employees, assembled in 1977. Employees worked for at least three months between 1954 and 1977 in areas identified as having methylene chloride exposure from an IH survey. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2: Attrition	High	× 0.4	0.4	Death certificates were obtained for 118/122 deaths. The authors note that use of "the national death index and the records of the Social Security Administration may fail to ascertain mortality by approximately 10-20%"
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Race and sex of the cohort are stratified in a table. The chosen reference population was York County, SC, the county in which 95% of the cohort resided but only constituted <4% of the county population.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	The cohort was comprised of employees that worked specifically in the two areas with concern for DCM exposure—the preparation and extrusion areas. Detailed work histories were only available for a small subset of this cohort. An IH survey in 1977 reported a time-weighted average for these two areas and it is assumed that exposure was constantly present prior to this survey.
	Metric 5: Exposure levels	Low	× 0.2	0.6	As an SMR study, there are presumed to be two levels of exposure. Those in the cohort are exposed to DCM in the preparation and extrusion areas while the reference population is unexposed.
	Metric 6: Temporality	High	× 0.4	0.4	Mortality was assessed for a follow-up period after employment at this facility of approximately 10 years (cohort formed in Jan 1977, follow-up until Sep 1986). Length of employment was assessed in select cancer-related mortality outcomes.
Domain 3: Outcome Assessment					

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR cerebrovascular disease-Cardiovascular
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Mortality was assessed by searching the national death index and records from the Social Security Administration. This is not a gold standard method and the authors note there may be a 10-20% margin of error when assessing mortality by Social Security Administration records.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Race, age, sex, and calendar period were all considered in the SMR calculation. There is also indirect evidence to suggest the demographic distribution in the sample population is similar to that of the reference population. Employees in the cohort were reported to have worked in the preparation and extrusion areas; it is unclear whether there would be any differential distribution of SES status in this sample (i.e., managers vs non-managers).
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates such as age, sex, and race were obtained through employment records. There is no evidence to suggest this method has poor validity.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The industrial hygiene survey conducted in 1977 revealed 8-hour TWAs for three chemicals present in these two areas of the textile manufacturing plant. There were detectable concentrations of DCM (1700 ppm), acetone (1600 ppm), and methanol (140 ppm). This indicates the presence of co-exposure, but the distribution of this exposure among the cohort is unknown.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The occupational cohort contained over 1000 employees and was sufficiently large to detect an effect of DCM. The effect estimate is based on a small number of observed cases thus caution should be taken in interpreting the SMR.

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Study Citation:	Lanes, SF; Cohen, A; Rothman, KJ; Dreyer, NA; Soden, KJ (1990). Mortality of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 16(4), 247-251
Data Type:	DCM Rock Hill occupational cohort SMR cerebrovascular disease-Cardiovascular
HERO ID:	730554

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Mortality among the cohort was compared to that of the York County, SC population to generate standardized mortality ratios. Reference population death rates from 1962 were used for non-cancer outcomes, as these rates were unavailable for the reference population for 1954-1961.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
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 22: **Lanes et al. 1993: Evaluation of Respiratory Outcomes**

Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_nonmalignant respiratory disease mortality-Respiratory
HERO ID:	730555

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cohort was assembled in 1977 for the purpose of investigating potential health effects of exposure to DCM. It included all 1271 workers employed in the preparation and extrusion areas of the plant for at least 3 months between January 1, 1954 and January 1, 1977. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2:	Attrition	High	× 0.4	0.4	There does not appear to be any attrition.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Adjustment or stratification are not specifically described. SMRs were calculated using the local population of York County, South Carolina controlled for age, race, gender, and calendar period.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Workers included worked in specific areas where DCM exposure would have occurred. Industrial monitoring in 1977 revealed 8-h time weighted average concentrations of below detection to 1700 ppm with median levels in the three areas of 140, 280, and 475 ppm. Respirators were not used until 1984 so exposure is likely, although levels of exposure were not determined. Detailed work history was only available for 356 active employees and 119 employees who terminated employment after 1979.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was only assessed as exposed in the occupational cohort compared to unexposed in the local population.
	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.
Domain 3: Outcome Assessment						

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_nonmalignant respiratory disease mortality-Respiratory
HERO ID:	730555

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Subjects vital status was identified through National Death Index and the Social Security Administration's Death Master Files. Previous assessment (HERO ID 730554) indicates that a nosologist reviewed the death certificates and coded the underlying cause of death in accordance with the ninth revision of the ICD codes. Employees not identified as deceased were assumed to be living at the end of the study period. Previous assessment identified 122 deaths through September 1986 with this study following up through December 1990.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	SMRs accounted for age, race, gender, and calendar period. Smoking was not discussed, but may not be an issue as there was no increase in lung cancer.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Not reported, but likely obtained from death records and the local rates.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Although DCM was the principal solvent used (and noted to be at the highest concentrations), methanol and acetone were also present. Although methanol was considerably lower with the upper concentration of 140 ppm compared to the 1700 pp, for DCM, acetone reached as high as 1600 ppm.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There are sufficient subjects for statistical power overall, however many of the listed causes of death have a small number of observed cases..
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient details were reported to be reproducible including the observed and expected numbers.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_nonmalignant respiratory disease mortality-Respiratory
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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 23: **Cherry et al. 1983: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Cherry, N; Venables, H; Waldron, HA (1983). The acute behavioural effects of solvent exposure Occupational Medicine, 33(1), 13-18
Data Type:	Cohort_Occupational_DCM_Behavior-Neurological/Behavior
HERO ID:	74582

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 presented, but available information indicates a low risk of selection bias. Factory C was the factory with methylene chloride exposure. Some details provided (type of shift work, age). There were three different shifts and controls were selected from all three shifts. However, participation rates and recruitment methods were not reported.
	Metric 2: Attrition	Unacceptable	× 0.4	0.16	Table II indicates loss of over half of the subjects, with no explanations. Methods indicated that there were 56 exposed subjects and 36 control subjects from factory C, but results in Table II indicate a sample size of 44. It was also not indicated if the 44 were exposed subjects only or if they included the control subjects. In addition, although they selected subjects from all three shifts, there is no information to indicate that those included in the results were still from all three shifts.
	Metric 3: Comparison Group	Low	× 0.2	0.6	No information about the similarity between groups nor was there information to indicate that controls were matched. Although it was noted that controls were selected from each shift so that they worked the same shift pattern as the exposed subjects. No other information was provided including if the controls were all men like the exposed workers. The mean age of the exposed workers was stated to be 43.8 years old, but no age was provided for the 36 controls. In addition, only 12 of the controls were from the areas of Factory C where there was no contact with solvents. The other 24 were from another factory belonging to the same parent group on a film making process identical to the exposed me without solvent exposure.
Domain 2: Exposure Characterization					

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Study Citation: Cherry, N; Venables, H; Waldron, HA (1983). The acute behavioural effects of solvent exposure Occupational Medicine, 33(1), 13-18
Data Type: Cohort_Occupational_DCM_Behavior-Neurological/Behavior
HERO ID: 74582

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Atmospheric solvent concentration was measured on a sub-group of men using individual pumps sampling onto charcoal tubes. The solvent was desorbed in carbon disulphide and solvent concentration was analyzed using gas chromatography with a 2 m 8% carbowax column. Blood samples were taken and measured as well. There is no information provided on QC methods or recovery rates for these methods.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	The range of exposure reported was 28-173 ppm. Blood solvent levels were not reported. Some results were presented as only exposed vs. unexposed, but combined the results for the different factories and controls and were not specific for methylene chloride exposure (i.e., Factory C)
	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. Blood samples (used in the analysis) were obtained at the beginning and end of the shift. These appear to be the same times that the outcome was tested. So although the subjects likely worked around methylene chloride prior to the outcomes, there is not enough information provided on how long or when and measurements were made at the same time as the outcome. However, the study authors appear to be looking at the acute effects indicating that the timing may be appropriate.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Three tests were completed at the beginning and the end of shift (i.e., visual analogue scales to reflect mood, the digit symbol substitution test from the Wescsler Adult Intelligence Scale, and a test of simple reaction time. Visual analogue scales are self-reported rating scales that were noted to have been shown to provide reliable and valid measure of mood. Some details were provided on the other measures, but it is not clear what the criteria being measured were.

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Study Citation: Cherry, N; Venables, H; Waldron, HA (1983). The acute behavioural effects of solvent exposure Occupational Medicine, 33(1), 13-18
Data Type: Cohort_Occupational_DCM_Behavior-Neurological/Behavior
HERO ID: 74582

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Low	× 0.333	1	Correlations were provided for methylene chloride and 4 mood changes noted as part of the visual analogue scales. No results were provided for simple reaction time in methylene chloride workers. Although results were stated to be in Table III and may have evaluated methylene chloride separate from the styrene workers, there was no Table III in the report nor is there a discussion of findings for this test in methylene chloride workers. Digit symbol scores were just noted to show no difference.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.667	2	All the subjects were presumably male (not clear that all the controls were male) and subjects in both exposed and control group were selected from all three shifts, but no other confounding variables were discussed. Although subjects were noted in the methods to be selected from all three shifts, not all subjects appear to have been included in the analysis and it is not clear that this was still accounted for in the results. Age was mentioned for the exposed workers, but was not mentioned for the control subjects.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	N/A because no covariates were discussed.
	Metric 11:	Co-exposure Confounding	Low	× 0.333	1	Co-exposed to methanol (DCM:methanol 9:1), but the co-exposures were not adjusted for. This co-exposure would also likely bias results away from the null, as it might contribute to effects seen. In addition, controls were exposed to other unspecified compounds as part of the film making process that could also have contributed to results in the control and may bias the results towards the null.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate. The study was evaluating acute neurobehavioral effects and was designed to test subjects before and after exposure. It also contained controls that were from the same plant and unexposed, which would also help address if the exposure had a chronic effect on the subjects (thus lowering their initial score) and if the differences were just based on working 8 hours and not an effect of exposure.

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Study Citation:	Cherry, N; Venables, H; Waldron, HA (1983). The acute behavioural effects of solvent exposure Occupational Medicine, 33(1), 13-18
Data Type:	Cohort_Occupational_DCM_Behavior-Neurological/Behavior
HERO ID:	74582

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population. The initial study group was 56 exposed and 36 controls. The results showed 44 subjects.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	It is apparent that the authors made several comparisons including correlations, but the specific methods used to determine significance or correlations was not provided. Therefore, they could not be replicated.
	Metric 15:	Statistical models	Low	× 0.2	0.6	It is apparent that the authors made several comparisons including correlations, but the specific methods used to determine significance or correlations was not provided. Therefore, they could not be replicated.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Low	× 0.167	0.5	Methylene chloride was reported to be tested in blood using a head space analyser and a 2 m 8% carbowax column. Blood carboxyhaemoglobin concentration was also measured as noted by the study authors carbon monoxide is a metabolite of methylene chloride. There is no information provided for QC or recovery rates. Nor is there any information on how the metabolite information was included if at all in the assessment of methylene chloride exposure. This is probably not a very accurate method.
	Metric 17:	Effect biomarker	Not Rated	NA	NA	No biomarker of effect was measured..
	Metric 18:	Method Sensitivity	Low	× 0.167	0.5	LOD/LOQ values are not stated
	Metric 19:	Biomarker stability	Low	× 0.167	0.5	There is no information on the storage or stability of the samples nor was there information provided on when the samples were tested in comparison to when they were collected.
	Metric 20:	Sample contamination	Low	× 0.167	0.5	There is no information about the collection and storage of the sample in regards to contamination.
	Metric 21:	Method requirements	Low	× 0.167	0.5	Sigma H6 head space analyser was used.
	Metric 22:	Matrix adjustment	Low	× 0.167	0.5	There was no information about adjustments (or not) for the matrix. There are no units provided so it cannot be determined if there was any adjustments or how the exposure was presented.
Overall Quality Determination[‡]			Unacceptable[⋆⋆]		2.7	
Extracted			No			

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Study Citation:	Cherry, N; Venables, H; Waldron, HA (1983). The acute behavioural effects of solvent exposure Occupational Medicine, 33(1), 13-18
Data Type:	Cohort_Occupational_DCM_Behavior-Neurological/Behavior
HERO ID:	74582

Domain	Metric	Rating†	MWF⋆	Score	Comments††

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 24: **Lanes et al. 1993: Evaluation of Cardiovascular Outcomes**

Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_ischemic heart disease mortality-Cardiovascular
HERO ID:	730555

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cohort was assembled in 1977 for the purpose of investigating potential health effects of exposure to DCM. It included all 1271 workers employed in the preparation and extrusion areas of the plant for at least 3 months between January 1, 1954 and January 1, 1977. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2:	Attrition	High	× 0.4	0.4	There does not appear to be any attrition.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Adjustment or stratification are not specifically described. SMRs were calculated using the local population of York County, South Carolina controlled for age, race, gender, and calendar period.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Workers included worked in specific areas where DCM exposure would have occurred. Industrial monitoring in 1977 revealed 8-h time weighted average concentrations of below detection to 1700 ppm with median levels in the three areas of 140, 280, and 475 ppm. Respirators were not used until 1984 so exposure is likely, although levels of exposure were not determined. Detailed work history was only available for 356 active employees and 119 employees who terminated employment after 1979.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was only assessed as exposed in the occupational cohort compared to unexposed in the local population.
	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.
Domain 3: Outcome Assessment						

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_ischemic heart disease mortality-Cardiovascular
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Subjects vital status was identified through National Death Index and the Social Security Administration's Death Master Files. Previous assessment (HERO ID 730554) indicates that a nosologist reviewed the death certificates and coded the underlying cause of death in accordance with the ninth revision of the ICD codes. Employees not identified as deceased were assumed to be living at the end of the study period. Previous assessment identified 122 deaths through September 1986 with this study following up through December 1990.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	SMRs accounted for age, race, gender, and calendar period. Smoking was not discussed, but may not be an issue as there was no increase in lung cancer.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Not reported, but likely obtained from death records and the local rates.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Although DCM was the principal solvent used (and noted to be at the highest concentrations), methanol and acetone were also present. Although methanol was considerably lower with the upper concentration of 140 ppm compared to the 1700 pp, for DCM, acetone reached as high as 1600 ppm.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There are sufficient subjects for statistical power overall, however many of the listed causes of death have a small number of observed cases..
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient details were reported to be reproducible including the observed and expected numbers.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_ischemic heart disease mortality-Cardiovascular
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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 25: **Lanes et al. 1993: Evaluation of Cancer Outcomes**

Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_breast cancer mortality-Cancer
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cohort was assembled in 1977 for the purpose of investigating potential health effects of exposure to DCM. It included all 1271 workers employed in the preparation and extrusion areas of the plant for at least 3 months between January 1, 1954 and January 1, 1977. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2:	Attrition	High	× 0.4	0.4	There does not appear to be any attrition.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Adjustment or stratification are not specifically described. SMRs were calculated using the local population of York County, South Carolina controlled for age, race, gender, and calendar period.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Workers included worked in specific areas where DCM exposure would have occurred. Industrial monitoring in 1977 revealed 8-h time weighted average concentrations of below detection to 1700 ppm with median levels in the three areas of 140, 280, and 475 ppm. Respirators were not used until 1984 so exposure is likely, although levels of exposure were not determined. Detailed work history was only available for 356 active employees and 119 employees who terminated employment after 1979.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was only assessed as exposed in the occupational cohort compared to unexposed in the local population.
	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.
Domain 3: Outcome Assessment						

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_breast cancer mortality-Cancer
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Subjects vital status was identified through National Death Index and the Social Security Administration's Death Master Files. Previous assessment (HERO ID 730554) indicates that a nosologist reviewed the death certificates and coded the underlying cause of death in accordance with the ninth revision of the ICD codes. Employees not identified as deceased were assumed to be living at the end of the study period. Previous assessment identified 122 deaths through September 1986 with this study following up through December 1990.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	SMRs accounted for age, race, gender, and calendar period. Smoking was not discussed, but may not be an issue as there was no increase in lung cancer.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Not reported, but likely obtained from death records and the local rates.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Although DCM was the principal solvent used (and noted to be at the highest concentrations), methanol and acetone were also present. Although methanol was considerably lower with the upper concentration of 140 ppm compared to the 1700 pp, for DCM, acetone reached as high as 1600 ppm.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There are sufficient subjects for statistical power overall, however many of the listed causes of death have a small number of observed cases.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient details were reported to be reproducible including the observed and expected numbers.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_breast cancer mortality-Cancer
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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: **Lanes et al. 1993: Evaluation of Mortality Outcomes**

Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_all causes mortality-Mortality
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cohort was assembled in 1977 for the purpose of investigating potential health effects of exposure to DCM. It included all 1271 workers employed in the preparation and extrusion areas of the plant for at least 3 months between January 1, 1954 and January 1, 1977. Demographic details on the cohort are provided in-text. Information regarding participation rate is provided in companion publication (Ott et al. 1983).
	Metric 2:	Attrition	High	× 0.4	0.4	There does not appear to be any attrition.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Adjustment or stratification are not specifically described. SMRs were calculated using the local population of York County, South Carolina controlled for age, race, gender, and calendar period.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Workers included worked in specific areas where DCM exposure would have occurred. Industrial monitoring in 1977 revealed 8-h time weighted average concentrations of below detection to 1700 ppm with median levels in the three areas of 140, 280, and 475 ppm. Respirators were not used until 1984 so exposure is likely, although levels of exposure were not determined. Detailed work history was only available for 356 active employees and 119 employees who terminated employment after 1979.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure was only assessed as exposed in the occupational cohort compared to unexposed in the local population.
	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.
Domain 3: Outcome Assessment						

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_all causes mortality-Mortality
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Subjects vital status was identified through National Death Index and the Social Security Administration's Death Master Files. Previous assessment (HERO ID 730554) indicates that a nosologist reviewed the death certificates and coded the underlying cause of death in accordance with the ninth revision of the ICD codes. Employees not identified as deceased were assumed to be living at the end of the study period. Previous assessment identified 122 deaths through September 1986 with this study following up through December 1990.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Mortality outcomes with a difference in observed vs expected of more than one were included in the results. SMRs were presented with confidence intervals in an easily read table.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	SMRs accounted for age, race, gender, and calendar period. Smoking was not discussed, but may not be an issue as there was no increase in lung cancer.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Not reported, but likely obtained from death records and the local rates.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Although DCM was the principal solvent used (and noted to be at the highest concentrations), methanol and acetone were also present. Although methanol was considerably lower with the upper concentration of 140 ppm compared to the 1700 pp, for DCM, acetone reached as high as 1600 ppm.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The design of this study was appropriate for the question of association between DCM and excess mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There are sufficient subjects for statistical power overall, however many of the listed causes of death have a small number of observed cases.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient details were reported to be reproducible including the observed and expected numbers.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The choice of an SMR was appropriate and transparent to investigate the question of exposure to DCM and excess mortality.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	Lanes, S. F., Rothman, K. J., Dreyer, N. A., Soden, K. J. (1993). Mortality update of cellulose fiber production workers Scandinavian Journal of Work, Environment and Health, 19(6), 426-428
Data Type:	Cellulose fiber production workers DCM_all causes mortality-Mortality
HERO ID:	730555

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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 27: **Taskinen et al. 1986: Evaluation of Reproductive Outcomes**

Study Citation:	Taskinen, H., Lindbohm, M.L., Hemminki, K. (1986). Spontaneous abortions among women working in the pharmaceutical industry British Journal of Industrial Medicine, 43(3,3), 199-205
Data Type:	DCM_exposed workers_cases vs. controls_spontaneous abortion-Reproductive
HERO ID:	730584

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Women were employed in 8 Finnish pharmaceutical factories from 1973-1980 were matched to hospital records for pregnancy outcomes during and after employment (1973-1981). The total number of pregnancies was 1795, which included 1179 deliveries, 142 spontaneous abortions, and 474 induced abortions. General population and matched controls were used. A subset of 44 cases (spontaneous abortion) and 130 controls (delivery) who worked in these factories for at least 1 week in the first trimester of pregnancy and completed questionnaires were used in a case-control analysis. The authors stated that there were 8 factories, but only 4 were included in 1975; it is unclear why these 4 factories were selected and if the same factories employed the cases and the matched controls.
	Metric 2: Attrition	Medium	× 0.4	0.8	Only subjects with completed exposure questionnaires were included in the case-control study. Thus, 3 cases (6.8%) and 9 controls (6.9%) were excluded. This loss of subjects does not appear to be significant and was adequately addressed in the study.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Cases and controls were employed in the same pharmaceutical factories during the first trimester of pregnancy, but job titles may have differed. Controls were matched on age at time of conception (within two and a half years). However, they were not matched on any other characteristics and no adjustments were made in the statistical analyses.
Domain 2: Exposure Characterization					

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Study Citation:	Taskinen, H., Lindbohm, M.L., Hemminki, K. (1986). Spontaneous abortions among women working in the pharmaceutical industry British Journal of Industrial Medicine, 43(3,3), 199-205
Data Type:	DCM_exposed workers_cases vs. controls_spontaneous abortion-Reproductive
HERO ID:	730584

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Factory physician and nurses completed questionnaires on subjects of the case-control study based on health cards, labor protection chiefs, and foremen of departments. The questionnaire form requested information on the individual worker's occupation and main tasks, and exposure to solvents, including DCM, antineoplastic agents and carcinogens, hormones, and antibiotics. Coders were blinded to outcome status. Since exposure was estimated based on professional judgement, there is uncertainty in the reliability of the exposure classification.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Exposure to DCM was classified based on frequency of exposure (less than once a week or greater than once a week). The intensity of solvent exposure was evaluated based on frequency of collective solvent use. Duration of exposure was not considered or discussed in this assessment. These limited exposure levels are not sufficient to provide a high degree of accuracy in the exposure-response assessment analysis.
	Metric 6:	Temporality	Low	× 0.4	1.2	Pregnancy outcomes were assessed based on hospital records for women working in pharmaceutical factories in Finland for at least one week during the first trimester of pregnancy. While exposure during the first trimester is anticipated to be an appropriate window of exposure, it is unclear if the length of exposure (1 week) is sufficient to detect an effect. No details are provided regarding the average length of employment or how that related to pregnancy outcomes.
Domain 3: Outcome Assessment						

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Study Citation:	Taskinen, H., Lindbohm, M.L., Hemminki, K. (1986). Spontaneous abortions among women working in the pharmaceutical industry British Journal of Industrial Medicine, 43(3,3), 199-205
Data Type:	DCM_exposed workers_cases vs. controls_spontaneous abortion-Reproductive
HERO ID:	730584

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Pregnancy outcomes (delivery, spontaneous abortion, induced abortion) were linked to workers were linked by personal identity number to a nation-wide hospital discharge register and hospital polyclinic data for 1973 to 1981. The reliability of the register was described in a references (Lindbohm 1984, Hemminki 1985, and Niemi 1985). Women treated for spontaneous abortions (ICD-8 codes 643 and 645) were defined as cases. If the woman had one or more spontaneous abortions, only one was randomly selected. Three controls were selected for every case from women who had given birth (ICD-8 codes 650-662) but only one pregnancy per woman was included. Unclear if women with both spontaneous abortions and healthy pregnancies were in the original subject pool.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Outcomes for case-control study fully presented, including distribution by occupation (Table 1) and frequency of DCM exposure (Table 2). Odds ratios (OR) for spontaneous abortions presented in Table 3 and Table 5 by DCM exposure (never/ever) and by frequency of exposure to DCM, respectively. No results were presented in the tables for the odds ratio for spontaneous abortions by intensity of exposure to DCM or for the rate of spontaneous abortions based on the year of employment (the authors' stated in the text that the spontaneous abortion rate decreased from about 15% to 9.5% for all employees during the study).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	The authors did not adjust for any covariates in the analysis of the association between DCM and spontaneous abortions. However, separate analysis of the odds ratio of spontaneous abortions and diseases and medications, type of work (sedentary, varying and standing), and amount of heavy lifting were presented; heavy lifting was significantly associated with spontaneous abortions. Information on smoking and previous pregnancies was available for only 25% and 41% of the women, respectively, and not presented. No consideration of alcohol intake or socioeconomic status was presented.

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Study Citation:	Taskinen, H., Lindbohm, M.L., Hemminki, K. (1986). Spontaneous abortions among women working in the pharmaceutical industry British Journal of Industrial Medicine, 43(3,3), 199-205
Data Type:	DCM_exposed workers_cases vs. controls_spontaneous abortion-Reproductive
HERO ID:	730584

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	Confounders were determined from the same occupational questionnaire used to determine exposure status. Few details are provided, but the low capture rate for smoking and previous pregnancy status indicates this was not a reliable method.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Occupational co-exposure information was collected from questionnaires completed by the occupational physician or nurses at the factory. Exposure to a number of solvents (aliphatic hydrocarbons, alicyclic hydrocarbons, benzene, toluene, xylene, chloroform), antieoplatic agents, oestrogens, progestogens, androgens, antibiotics, and known carcinogens were determined for these pharmaceutical factory workers. Correlations between these additional contaminates was not evaluated.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The case-control study design was used to assess the relationship between exposure to solvents and spontaneous abortions. The study calculated odds ratios for exposure with a logistic regression model for individual matched data based on the conditional maximum likelihood. The p values for separate variables were evaluated by comparing the respective standardized regression coefficients with normal distribution. This is an appropriate statistical model.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The case-control study examined 44 women who had a spontaneous abortion who were matched with 130 women who had a normal birth. This number of cases and controls is not large, but is adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Odds ratios for DCM exposure and pregnancy outcomes were determined with logistic regression. The description of the analysis was sufficient to understand what was done and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratio were calculated using logistic regression, which was transparent and presented in the paper in sufficient detail.
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:	Taskinen, H., Lindbohm, M.L., Hemminki, K. (1986). Spontaneous abortions among women working in the pharmaceutical industry British Journal of Industrial Medicine, 43(3,3), 199-205
Data Type:	DCM_exposed workers_cases vs. controls_spontaneous abortion-Reproductive
HERO ID:	730584

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‡			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 28: **Soden 1993: Evaluation of Cardiovascular Outcomes**

Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_unexposed workers_irregular heartbeat-Cardiovascular
HERO ID:	730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	There is a low risk for selection bias. Methods of participant selection and inclusion/exclusion criteria are reported. The exposed group consisted of all of the 150 employees at the Rock Hill plant as of December 31, 1986 who had worked for at least 10 years in the high methylene chloride exposure area and had also participated in the company's health monitoring program between 1984 and 1986. It is unclear how many highly-exposed employees were excluded because they had not participated in the health monitoring program.
	Metric 2: Attrition	Medium	× 0.4	0.8	Outcome data were incomplete, especially for the blood test parameters (hematological and hepatic outcomes). The missing outcome data were explained by the author and were balanced across study groups with similar reasons for the missing data. Outcome data were missing because not all of the employees responded to every health history question and not all of the employees underwent every blood test during the study period because of varying frequencies of examinations offered to employees based on age. There were a total of 150 exposed employees, and blood test data were only reported for 90-103 of them depending on the test. There were a total of 260 control subjects, and blood test data were only reported for 120-126 of them. The health history questionnaire data (neurological and cardiovascular outcomes) were nearly complete with 137-150/150 exposed employees responding to the various questions and 247-258/260 of the controls responding.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	There is only indirect evidence from the author that the exposed and control groups were similar. Workers at another plant within the same company (a polyester staple plant in Salisbury, NC) were chosen as the non-exposed controls. The two plants were reportedly "socioeconomically and demographically similar as well as geographically proximate." The controls were randomly selected and matched for age, sex, and race.

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Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_unexposed workers_irregular heartbeat-Cardiovascular
HERO ID:	730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The methods used to quantify exposure were not fully described in this publication. The author states, "Exposure assessment for both cohorts was performed routinely as part of the HCC industrial hygiene monitoring program. All monitoring was done using standard, validated in hospital measuring techniques and analysis was done by national certified laboratories." The exposed workers were chosen from a larger cohort of workers (n=1271) that had been followed for mortality with results reported in Ott et al., 1983 (not in HERO) and Lanes et al. 1990 (HERO ID 730554). The current study reports that the average methylene chloride exposure of the employees was 475 ppm (8-hour TWA) for at least ten years. No further details are provided.
Metric 5:	Exposure levels	Low	× 0.2	0.6	There were only 2 levels of exposure (exposed vs. non-exposed).
Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established and the interval between exposure and outcomes has an appropriate consideration of relevant exposure windows for the outcomes of interest. The study population was followed from 1984-1986, and exposure occurred for at least 10 years as of December 31, 1986.
Domain 3: Outcome Assessment					
Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The outcome assessment method used for cardiovascular and neurological outcomes is an insensitive measure. These results were taken from self-reported information in a health history questionnaire. The hematological and liver outcomes were assessed using well-established methods. The methods used for drawing blood were not described, however it was part of the company's health monitoring program that involved physicians and nurse practitioners. All blood work was performed by a biomedical laboratory.

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Study Citation: Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type: DCM_unexposed workers_irregular heartbeat-Cardiovascular
HERO ID: 730597

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All of the measured outcomes outlined in the methods are reported in a way that allows for data extraction. Incidence, prevalence, and samples sizes are reported for the cardiovascular and neurological outcomes. Sample sizes, means, standard deviations, and the results of statistical analyses are reported only for the hematological and hepatic outcomes (continuous outcomes). Statistical significance for comparison of prevalence measures are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate considerations were made for potential confounders. Two controls were selected at random for each exposed cohort member matching for age, sex, and race. The author points out that no attempt was made to control for the potential confounding effects of alcohol on the liver parameters studied. However, the researchers found from previous studies utilizing the same health monitoring data base that the socioeconomics and demographics of both plants are similar. Since no differences were found in the health parameters between the two plants, more specific analysis including any potential confounders was not considered necessary.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	All of the chosen cohort members and controls participated in the corporate health monitoring program that would have collected information on age, sex, and race.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence that there were unbalanced co-exposures across the study groups which were not adjusted for. The exposed employees were also exposed to acetone and methanol. The researchers considered the potential impacts of these co-exposures on the results and determined it was not an issue because significant differences were not found between the two groups. "Theoretically, we could postulate that the acetone and methanol exposure in the exposed group might potentiate any effects from the methylene chloride exposure because of their potential impact on the same target organs, ie, liver, blood, and central nervous system but this was clearly not the case as there were no clinically significant differences found between the two groups. This synergism or potentiation is not an issue based upon the results of this study."
Domain 5: Analysis						

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Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_unexposed workers_irregular heartbeat-Cardiovascular
HERO ID:	730597

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study used an appropriate statistical method to address the research question. For the hematological and hepatic outcomes, the Student's t-test was used to compare the means. For the cardiovascular and neurological outcomes, the prevalence of responses was compared between the two groups, but the statistical method was not described.
	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 150 exposed subjects and 260 controls.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The statistical test used to compare the responses on the health history questionnaire (cardiovascular and neurological outcomes) was not described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The method (one sided t-test) used for comparing the means for the hematological and hepatic outcomes is transparent. The statistical analyses are not described for the cardiovascular and neurological outcome measures.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		2.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 29: **Soden 1993: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_memory loss-Neurological/Behavior
HERO ID:	730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	There is a low risk for selection bias. Methods of participant selection and inclusion/exclusion criteria are reported. The exposed group consisted of all of the 150 employees at the Rock Hill plant as of December 31, 1986 who had worked for at least 10 years in the high methylene chloride exposure area and had also participated in the company's health monitoring program between 1984 and 1986. It is unclear how many highly-exposed employees were excluded because they had not participated in the health monitoring program.
	Metric 2: Attrition	Medium	× 0.4	0.8	Outcome data were incomplete, especially for the blood test parameters (hematological and hepatic outcomes). The missing outcome data were explained by the author and were balanced across study groups with similar reasons for the missing data. Outcome data were missing because not all of the employees responded to every health history question and not all of the employees underwent every blood test during the study period because of varying frequencies of examinations offered to employees based on age. There were a total of 150 exposed employees, and blood test data were only reported for 90-103 of them depending on the test. There were a total of 260 control subjects, and blood test data were only reported for 120-126 of them. The health history questionnaire data (neurological and cardiovascular outcomes) were nearly complete with 137-150/150 exposed employees responding to the various questions and 247-258/260 of the controls responding.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	There is only indirect evidence from the author that the exposed and control groups were similar. Workers at another plant within the same company (a polyester staple plant in Salisbury, NC) were chosen as the non-exposed controls. The two plants were reportedly "socioeconomically and demographically similar as well as geographically proximate." The controls were randomly selected and matched for age, sex, and race.

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Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_memory loss-Neurological/Behavior
HERO ID:	730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The methods used to quantify exposure were not fully described in this publication. The author states, "Exposure assessment for both cohorts was performed routinely as part of the HCC industrial hygiene monitoring program. All monitoring was done using standard, validated in hospital measuring techniques and analysis was done by national certified laboratories." The exposed workers were chosen from a larger cohort of workers (n=1271) that had been followed for mortality with results reported in Ott et al., 1983 (not in HERO) and Lanes et al. 1990 (HERO ID 730554). The current study reports that the average methylene chloride exposure of the employees was 475 ppm (8-hour TWA) for at least ten years. No further details are provided.
Metric 5:	Exposure levels	Low	× 0.2	0.6	There were only 2 levels of exposure (exposed vs. non-exposed).
Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established and the interval between exposure and outcomes has an appropriate consideration of relevant exposure windows for the outcomes of interest. The study population was followed from 1984-1986, and exposure occurred for at least 10 years as of December 31, 1986.
Domain 3: Outcome Assessment					
Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The outcome assessment method used for cardiovascular and neurological outcomes is an insensitive measure. These results were taken from self-reported information in a health history questionnaire. The hematological and liver outcomes were assessed using well-established methods. The methods used for drawing blood were not described, however it was part of the company's health monitoring program that involved physicians and nurse practitioners. All blood work was performed by a biomedical laboratory.

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Study Citation: Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type: DCM_exposed workers_memory loss-Neurological/Behavior
HERO ID: 730597

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All of the measured outcomes outlined in the methods are reported in a way that allows for data extraction. Incidence, prevalence, and samples sizes are reported for the cardiovascular and neurological outcomes. Sample sizes, means, standard deviations, and the results of statistical analyses are reported only for the hematological and hepatic outcomes (continuous outcomes). Statistical significance for comparison of prevalence measures are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate considerations were made for potential confounders. Two controls were selected at random for each exposed cohort member matching for age, sex, and race. The author points out that no attempt was made to control for the potential confounding effects of alcohol on the liver parameters studied. However, the researchers found from previous studies utilizing the same health monitoring data base that the socioeconomics and demographics of both plants are similar. Since no differences were found in the health parameters between the two plants, more specific analysis including any potential confounders was not considered necessary.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	All of the chosen cohort members and controls participated in the corporate health monitoring program that would have collected information on age, sex, and race.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence that there were unbalanced co-exposures across the study groups which were not adjusted for. The exposed employees were also exposed to acetone and methanol. The researchers considered the potential impacts of these co-exposures on the results and determined it was not an issue because significant differences were not found between the two groups. "Theoretically, we could postulate that the acetone and methanol exposure in the exposed group might potentiate any effects from the methylene chloride exposure because of their potential impact on the same target organs, ie, liver, blood, and central nervous system but this was clearly not the case as there were no clinically significant differences found between the two groups. This synergism or potentiation is not an issue based upon the results of this study."
Domain 5: Analysis						

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Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_memory loss-Neurological/Behavior
HERO ID:	730597

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study used an appropriate statistical method to address the research question. For the hematological and hepatic outcomes, the Student's t-test was used to compare the means. For the cardiovascular and neurological outcomes, the prevalence of responses was compared between the two groups, but the statistical method was not described.
	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 150 exposed subjects and 260 controls.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The statistical test used to compare the responses on the health history questionnaire (cardiovascular and neurological outcomes) was not described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The method (one sided t-test) used for comparing the means for the hematological and hepatic outcomes is transparent. The statistical analyses are not described for the cardiovascular and neurological outcome measures.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		2.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 30: **Soden 1993: Evaluation of Hepatic Outcomes**

Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_SGOT-Hepatic
HERO ID:	730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	There is a low risk for selection bias. Methods of participant selection and inclusion/exclusion criteria are reported. The exposed group consisted of all of the 150 employees at the Rock Hill plant as of December 31, 1986 who had worked for at least 10 years in the high methylene chloride exposure area and had also participated in the company's health monitoring program between 1984 and 1986. It is unclear how many highly-exposed employees were excluded because they had not participated in the health monitoring program.
	Metric 2: Attrition	Medium	× 0.4	0.8	Outcome data were incomplete, especially for the blood test parameters (hematological and hepatic outcomes). The missing outcome data were explained by the author and were balanced across study groups with similar reasons for the missing data. Outcome data were missing because not all of the employees responded to every health history question and not all of the employees underwent every blood test during the study period because of varying frequencies of examinations offered to employees based on age. There were a total of 150 exposed employees, and blood test data were only reported for 90-103 of them depending on the test. There were a total of 260 control subjects, and blood test data were only reported for 120-126 of them. The health history questionnaire data (neurological and cardiovascular outcomes) were nearly complete with 137-150/150 exposed employees responding to the various questions and 247-258/260 of the controls responding.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	There is only indirect evidence from the author that the exposed and control groups were similar. Workers at another plant within the same company (a polyester staple plant in Salisbury, NC) were chosen as the non-exposed controls. The two plants were reportedly "socioeconomically and demographically similar as well as geographically proximate." The controls were randomly selected and matched for age, sex, and race.

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Study Citation: Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type: DCM_exposed workers_SGOT-Hepatic
HERO ID: 730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The methods used to quantify exposure were not fully described in this publication. The author states, "Exposure assessment for both cohorts was performed routinely as part of the HCC industrial hygiene monitoring program. All monitoring was done using standard, validated in hospital measuring techniques and analysis was done by national certified laboratories." The exposed workers were chosen from a larger cohort of workers (n=1271) that had been followed for mortality with results reported in Ott et al., 1983 (not in HERO) and Lanes et al. 1990 (HERO ID 730554). The current study reports that the average methylene chloride exposure of the employees was 475 ppm (8-hour TWA) for at least ten years. No further details are provided.
Metric 5:	Exposure levels	Low	× 0.2	0.6	There were only 2 levels of exposure (exposed vs. non-exposed).
Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established and the interval between exposure and outcomes has an appropriate consideration of relevant exposure windows for the outcomes of interest. The study population was followed from 1984-1986, and exposure occurred for at least 10 years as of December 31, 1986.
Domain 3: Outcome Assessment					
Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The outcome assessment method used for cardiovascular and neurological outcomes is an insensitive measure. These results were taken from self-reported information in a health history questionnaire. The hematological and liver outcomes were assessed using well-established methods. The methods used for drawing blood were not described, however it was part of the company's health monitoring program that involved physicians and nurse practitioners. All blood work was performed by a biomedical laboratory.

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Study Citation: Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type: DCM_exposed workers_SGOT-Hepatic
HERO ID: 730597

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All of the measured outcomes outlined in the methods are reported in a way that allows for data extraction. Incidence, prevalence, and samples sizes are reported for the cardiovascular and neurological outcomes. Sample sizes, means, standard deviations, and the results of statistical analyses are reported only for the hematological and hepatic outcomes (continuous outcomes). Statistical significance for comparison of prevalence measures are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate considerations were made for potential confounders. Two controls were selected at random for each exposed cohort member matching for age, sex, and race. The author points out that no attempt was made to control for the potential confounding effects of alcohol on the liver parameters studied. However, the researchers found from previous studies utilizing the same health monitoring data base that the socioeconomics and demographics of both plants are similar. Since no differences were found in the health parameters between the two plants, more specific analysis including any potential confounders was not considered necessary.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	All of the chosen cohort members and controls participated in the corporate health monitoring program that would have collected information on age, sex, and race.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence that there were unbalanced co-exposures across the study groups which were not adjusted for. The exposed employees were also exposed to acetone and methanol. The researchers considered the potential impacts of these co-exposures on the results and determined it was not an issue because significant differences were not found between the two groups. "Theoretically, we could postulate that the acetone and methanol exposure in the exposed group might potentiate any effects from the methylene chloride exposure because of their potential impact on the same target organs, ie, liver, blood, and central nervous system but this was clearly not the case as there were no clinically significant differences found between the two groups. This synergism or potentiation is not an issue based upon the results of this study."
Domain 5: Analysis						

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Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_SGOT-Hepatic
HERO ID:	730597

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study used an appropriate statistical method to address the research question. For the hematological and hepatic outcomes, the Student's t-test was used to compare the means. For the cardiovascular and neurological outcomes, the prevalence of responses was compared between the two groups, but the statistical method was not described.
	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 150 exposed subjects and 260 controls.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The statistical test used to compare the responses on the health history questionnaire (cardiovascular and neurological outcomes) was not described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The method (one sided t-test) used for comparing the means for the hematological and hepatic outcomes is transparent. The statistical analyses are not described for the cardiovascular and neurological outcome measures.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		2.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 31: **Soden 1993: Evaluation of Hematological and Immune Outcomes**

Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_hematocrit-Hematological and Immune
HERO ID:	730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	There is a low risk for selection bias. Methods of participant selection and inclusion/exclusion criteria are reported. The exposed group consisted of all of the 150 employees at the Rock Hill plant as of December 31, 1986 who had worked for at least 10 years in the high methylene chloride exposure area and had also participated in the company's health monitoring program between 1984 and 1986. It is unclear how many highly-exposed employees were excluded because they had not participated in the health monitoring program.
	Metric 2: Attrition	Medium	× 0.4	0.8	Outcome data were incomplete, especially for the blood test parameters (hematological and hepatic outcomes). The missing outcome data were explained by the author and were balanced across study groups with similar reasons for the missing data. Outcome data were missing because not all of the employees responded to every health history question and not all of the employees underwent every blood test during the study period because of varying frequencies of examinations offered to employees based on age. There were a total of 150 exposed employees, and blood test data were only reported for 90-103 of them depending on the test. There were a total of 260 control subjects, and blood test data were only reported for 120-126 of them. The health history questionnaire data (neurological and cardiovascular outcomes) were nearly complete with 137-150/150 exposed employees responding to the various questions and 247-258/260 of the controls responding.
	Metric 3: Comparison Group	Medium	× 0.2	0.4	There is only indirect evidence from the author that the exposed and control groups were similar. Workers at another plant within the same company (a polyester staple plant in Salisbury, NC) were chosen as the non-exposed controls. The two plants were reportedly "socioeconomically and demographically similar as well as geographically proximate." The controls were randomly selected and matched for age, sex, and race.

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Study Citation: Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type: DCM_exposed workers_hematocrit-Hematological and Immune
HERO ID: 730597

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	The methods used to quantify exposure were not fully described in this publication. The author states, "Exposure assessment for both cohorts was performed routinely as part of the HCC industrial hygiene monitoring program. All monitoring was done using standard, validated in hospital measuring techniques and analysis was done by national certified laboratories." The exposed workers were chosen from a larger cohort of workers (n=1271) that had been followed for mortality with results reported in Ott et al., 1983 (not in HERO) and Lanes et al. 1990 (HERO ID 730554). The current study reports that the average methylene chloride exposure of the employees was 475 ppm (8-hour TWA) for at least ten years. No further details are provided.
Metric 5:	Exposure levels	Low	× 0.2	0.6	There were only 2 levels of exposure (exposed vs. non-exposed).
Metric 6:	Temporality	Medium	× 0.4	0.8	Temporality is established and the interval between exposure and outcomes has an appropriate consideration of relevant exposure windows for the outcomes of interest. The study population was followed from 1984-1986, and exposure occurred for at least 10 years as of December 31, 1986.
Domain 3: Outcome Assessment					
Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The outcome assessment method used for cardiovascular and neurological outcomes is an insensitive measure. These results were taken from self-reported information in a health history questionnaire. The hematological and liver outcomes were assessed using well-established methods. The methods used for drawing blood were not described, however it was part of the company's health monitoring program that involved physicians and nurse practitioners. All blood work was performed by a biomedical laboratory.

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Study Citation: Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type: DCM_exposed workers_hematocrit-Hematological and Immune
HERO ID: 730597

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	All of the measured outcomes outlined in the methods are reported in a way that allows for data extraction. Incidence, prevalence, and samples sizes are reported for the cardiovascular and neurological outcomes. Sample sizes, means, standard deviations, and the results of statistical analyses are reported only for the hematological and hepatic outcomes (continuous outcomes). Statistical significance for comparison of prevalence measures are not reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Appropriate considerations were made for potential confounders. Two controls were selected at random for each exposed cohort member matching for age, sex, and race. The author points out that no attempt was made to control for the potential confounding effects of alcohol on the liver parameters studied. However, the researchers found from previous studies utilizing the same health monitoring data base that the socioeconomics and demographics of both plants are similar. Since no differences were found in the health parameters between the two plants, more specific analysis including any potential confounders was not considered necessary.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	All of the chosen cohort members and controls participated in the corporate health monitoring program that would have collected information on age, sex, and race.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence that there were unbalanced co-exposures across the study groups which were not adjusted for. The exposed employees were also exposed to acetone and methanol. The researchers considered the potential impacts of these co-exposures on the results and determined it was not an issue because significant differences were not found between the two groups. "Theoretically, we could postulate that the acetone and methanol exposure in the exposed group might potentiate any effects from the methylene chloride exposure because of their potential impact on the same target organs, ie, liver, blood, and central nervous system but this was clearly not the case as there were no clinically significant differences found between the two groups. This synergism or potentiation is not an issue based upon the results of this study."
Domain 5: Analysis						

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Study Citation:	Soden, K.J. (1993). An evaluation of chronic methylene chloride exposure Journal of Occupational Medicine, 35(3,3), 282-286
Data Type:	DCM_exposed workers_hematocrit-Hematological and Immune
HERO ID:	730597

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study used an appropriate statistical method to address the research question. For the hematological and hepatic outcomes, the Student's t-test was used to compare the means. For the cardiovascular and neurological outcomes, the prevalence of responses was compared between the two groups, but the statistical method was not described.
	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 150 exposed subjects and 260 controls.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The statistical test used to compare the responses on the health history questionnaire (cardiovascular and neurological outcomes) was not described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	The method (one sided t-test) used for comparing the means for the hematological and hepatic outcomes is transparent. The statistical analyses are not described for the cardiovascular and neurological outcome measures.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		2.2	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 32: **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:	DCM_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:	DCM_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:	DCM_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:	DCM_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 33: **Tomeson 2011: Evaluation of Cancer Outcomes**

Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_AllCancerMortality_Dichotomous-Cancer
HERO ID:	787813

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	A cohort study was conducted of male workers employed at a photographic film base plant in Brantham, UK from 1946 until its closure in 1988. 1,785 workers and of those, 1,473 has worked in jobs that had exposure to methylene chloride. Information was obtained through UK Medical Research Information Services. Exposed workers were predominantly manual workers. Females were excluded because few had worked in production areas and many had job titles where exposure was difficult to assess. Median follow up time for exposed individuals was 36.8 years (IQR: 28.2-43.1) and 29.9 (IQR: 21.4-39.1) for unexposed individuals.
	Metric 2: Attrition	Medium	× 0.4	0.8	Attrition among the final study population with exposure information was not significant. 59 workers emigrated, 10 were temporary foreign, and 10 were lost to follow-up. However, for 439 workers (30% of study population) employment histories were insufficiently precise to calculate reliable estimates of cumulative exposure-unspecified job histories and were excluded from the dose-response analysis (most were laborers and maintenance workers).
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Non-exposed group consisted of a variety of occupations, but all were unlikely to have been exposed either directly or indirectly, though very low concentrations may have existed. Most unexposed workers were office workers in the technical and commercial functions, and the unexposed group tended to be older when hired and followed up for fewer years. The exposed group consisted of mostly manual workers. Mortality statistics for England and Wales were used for comparison and a comparison with local mortalities was also made for selected causes by combining mortality information from four surrounding districts to calculate an SMR. Authors attempted to reduce potential for healthy worker effect by using a suitable internal reference group.
Domain 2: Exposure Characterization					

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_AllCancerMortality_Dichotomous-Cancer
HERO ID:	787813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Potential exposure to DCM was contained to the time period for which the Brantham site was open (1946-1988). Estimates of DCM exposure were generated for 20 work groups during four production periods (before 1960, 1960-1969, 1970-1979, 1980-1988) at an exposure duration of 8-h TWA, ppm. Lifetime cumulative DCM exposure was calculated by summing the products of mean level of exposure and duration of employment for each job held by a cohort member. A potential limitation is that personal monitoring data before 1980 and reliable area monitoring data before 1975 was not available; however, good historical information on the casting machines and working conditions was available, and information on the number of incidents where workers were affected by DCM vapors was consistent with the pattern of exposure estimated for jobs and time periods.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Levels of cumulative exposure to methylene chloride were categorized as 0, 0-399, 400-799, and greater than 800 ppm-years. These cut-off points were chosen to enable comparisons with studies of the Rochester film workers. Trend analyses were also performed using cut-off points (36.4 and 299.1 ppm-years) which gave equal numbers of deaths from all causes in the 3 cumulative exposure categories. Cumulative exposure was also modeled as a continuous variable in the Cox regression models.
	Metric 6:	Temporality	High	× 0.4	0.4	Study participants were unlikely to have been exposed to DCM after the Brantham site closed in 1988, which strengthens the validity of the exposure estimates occurring prior to the outcome assessed. Cumulative exposure was treated as a time-dependent variable, both as a continuous variable and grouped by increasing exposure. Time since hire was included in some models (not the regression analyses), and analyses were also performed with lagged cumulative exposure (15 years). Median follow up time for exposed individuals was 36.8 years (IQR: 28.2-43.1) and 29.9 (IQR: 21.4-39.1) for unexposed individuals. Long follow up times for the cohort should be sufficient for the long latency period of some chronic diseases assessed, including cancer.

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_AllCancerMortality_Dichotomous-Cancer
HERO ID:	787813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Main outcome of interest was mortality. Obtained information through occupational cohort mortality analysis program OCAMP-PLUC for specified causes of death including malignant neoplasms and ischemic heart disease. No cases of liver cancer mortality were reported. There were too few pancreatic cancers to calculate a relative risk, and this outcome was therefore later excluded.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Results from all analyses clearly reported. Observed number of deaths and SMR for all major causes of death reported with 95% CI. SMR results, including numbers of observed cases included, with corresponding p-value. Cox regression analyses results fully presented, including relative risks and 95% confidence intervals with p-values.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	SMRs were calculated to take into account the potential confounding effect of age. Regression models included age as the time variable. Time since hire was included in some models, and analyses were also performed with lagged cumulative exposure (15 years). A limitation of this study includes the lack of smoking histories for participants which suggests potential residual confounding by smoking could influence the effect estimates.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Covariates considered included age and time since hire. All were measured using appropriate, valid methods using information provided in the UK Medical Research Information Service database.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	No co-exposures were considered in this study, nor adjusted for in the analyses. It is unclear whether other potential unmeasured co-exposures could have influenced effect estimates.
Domain 5: Analysis						

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_AllCancerMortality_Dichotomous-Cancer
HERO ID:	787813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Cohort study design was conducted to follow workers potentially exposed to methylene chloride at a photographic film base plant in Brantham, United Kingdom. The outcome assessed included mortality due to different causes. The cohort study design was appropriate for the research question involving a relatively rare exposure, and the long follow up time was suitable for the chronic disease outcomes investigated.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study population of 1,785 male employees, including 1,473 exposed workers (1,034 exposed had an exposure estimate) and 312 unexposed workers, was sufficient to detect an effect for methylene chloride. Statistical power not reported, but p values show some statistically significant correlations. Pancreatic cancer was ultimately excluded from the regression analysis because too few cases were reported.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Methods of statistical analysis was clearly described and should be reproducible with information provided. Descriptions of the methods for calculating SMRs were clearly described, and methods for regression models were also described.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	SMRs were calculated for each mortality outcome of interest, using the internal referent group and mortality statistics for England and Wales, as well as local mortalities from four surrounding districts and two surrounding counties. For selected causes of death, a multivariate regression analysis based on Cox's proportional hazards model was conducted. 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		1.7	

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_AllCancerMortality_Dichotomous-Cancer
HERO ID:	787813

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 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_DCM_OR_Q4-Neurological/Behavior
HERO ID:	103522

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

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Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_DCM_OR_Q4-Neurological/Behavior
HERO ID:	103522

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

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Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_DCM_OR_Q4-Neurological/Behavior
HERO ID:	103522

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

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Study Citation:	Windham, GC; Zhang, L; Gunier, R; Croen, LA; Grether, JK (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay area Environmental Health Perspectives, 114(9,9), 1438-1444
Data Type:	California_case_control_autism_DCM_OR_Q4-Neurological/Behavior
HERO ID:	103522

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.7	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 35: **Tomeson 2011: Evaluation of Cardiovascular Outcomes**

Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_IschemicHeartDiseaseMortality_Dichotomous-Cardiovascular
HERO ID:	787813

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	A cohort study was conducted of male workers employed at a photographic film base plant in Brantham, UK from 1946 until its closure in 1988. 1,785 workers and of those, 1,473 has worked in jobs that had exposure to methylene chloride. Information was obtained through UK Medical Research Information Services. Exposed workers were predominantly manual workers. Females were excluded because few had worked in production areas and many had job titles where exposure was difficult to assess. Median follow up time for exposed individuals was 36.8 years (IQR: 28.2-43.1) and 29.9 (IQR: 21.4-39.1) for unexposed individuals.
	Metric 2: Attrition	Medium	× 0.4	0.8	Attrition among the final study population with exposure information was not significant. 59 workers emigrated, 10 were temporary foreign, and 10 were lost to follow-up. However, for 439 workers (30% of study population) employment histories were insufficiently precise to calculate reliable estimates of cumulative exposure-unspecified job histories and were excluded from the dose-response analysis (most were laborers and maintenance workers).
	Metric 3: Comparison Group	Medium	× 0.2	0.4	Non-exposed group consisted of a variety of occupations, but all were unlikely to have been exposed either directly or indirectly, though very low concentrations may have existed. Most unexposed workers were office workers in the technical and commercial functions, and the unexposed group tended to be older when hired and followed up for fewer years. The exposed group consisted of mostly manual workers. Mortality statistics for England and Wales were used for comparison and a comparison with local mortalities was also made for selected causes by combining mortality information from four surrounding districts to calculate an SMR. Authors attempted to reduce potential for healthy worker effect by using a suitable internal reference group.
Domain 2: Exposure Characterization					

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_IschemicHeartDiseaseMortality_Dichotomous-Cardiovascular
HERO ID:	787813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Potential exposure to DCM was contained to the time period for which the Brantham site was open (1946-1988). Estimates of DCM exposure were generated for 20 work groups during four production periods (before 1960, 1960-1969, 1970-1979, 1980-1988) at an exposure duration of 8-h TWA, ppm. Lifetime cumulative DCM exposure was calculated by summing the products of mean level of exposure and duration of employment for each job held by a cohort member. A potential limitation is that personal monitoring data before 1980 and reliable area monitoring data before 1975 was not available; however, good historical information on the casting machines and working conditions was available, and information on the number of incidents where workers were affected by DCM vapors was consistent with the pattern of exposure estimated for jobs and time periods.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Levels of cumulative exposure to methylene chloride were categorized as 0, 0-399, 400-799, and greater than 800 ppm-years. These cut-off points were chosen to enable comparisons with studies of the Rochester film workers. Trend analyses were also performed using cut-off points (36.4 and 299.1 ppm-years) which gave equal numbers of deaths from all causes in the 3 cumulative exposure categories. Cumulative exposure was also modeled as a continuous variable in the Cox regression models.
	Metric 6:	Temporality	High	× 0.4	0.4	Study participants were unlikely to have been exposed to DCM after the Brantham site closed in 1988, which strengthens the validity of the exposure estimates occurring prior to the outcome assessed. Cumulative exposure was treated as a time-dependent variable, both as a continuous variable and grouped by increasing exposure. Time since hire was included in some models (not the regression analyses), and analyses were also performed with lagged cumulative exposure (15 years). Median follow up time for exposed individuals was 36.8 years (IQR: 28.2-43.1) and 29.9 (IQR: 21.4-39.1) for unexposed individuals. Long follow up times for the cohort should be sufficient for the long latency period of some chronic diseases assessed, including cancer.

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_IschemicHeartDiseaseMortality_Dichotomous-Cardiovascular
HERO ID:	787813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Main outcome of interest was mortality. Obtained information through occupational cohort mortality analysis program OCAMP-PLUC for specified causes of death including malignant neoplasms and ischemic heart disease. No cases of liver cancer mortality were reported. There were too few pancreatic cancers to calculate a relative risk, and this outcome was therefore later excluded.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Results from all analyses clearly reported. Observed number of deaths and SMR for all major causes of death reported with 95% CI. SMR results, including numbers of observed cases included, with corresponding p-value. Cox regression analyses results fully presented, including relative risks and 95% confidence intervals with p-values.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Low	× 0.5	1.5	SMRs were calculated to take into account the potential confounding effect of age. Regression models included age as the time variable. Time since hire was included in some models, and analyses were also performed with lagged cumulative exposure (15 years). A limitation of this study includes the lack of smoking histories for participants which suggests potential residual confounding by smoking could influence the effect estimates.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Covariates considered included age and time since hire. All were measured using appropriate, valid methods using information provided in the UK Medical Research Information Service database.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	No co-exposures were considered in this study, nor adjusted for in the analyses. It is unclear whether other potential unmeasured co-exposures could have influenced effect estimates.
Domain 5: Analysis						

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_IschemicHeartDiseaseMortality_Dichotomous-Cardiovascular
HERO ID:	787813

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Cohort study design was conducted to follow workers potentially exposed to methylene chloride at a photographic film base plant in Brantham, United Kingdom. The outcome assessed included mortality due to different causes. The cohort study design was appropriate for the research question involving a relatively rare exposure, and the long follow up time was suitable for the chronic disease outcomes investigated.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study population of 1,785 male employees, including 1,473 exposed workers (1,034 exposed had an exposure estimate) and 312 unexposed workers, was sufficient to detect an effect for methylene chloride. Statistical power not reported, but p values show some statistically significant correlations. Pancreatic cancer was ultimately excluded from the regression analysis because too few cases were reported.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Methods of statistical analysis was clearly described and should be reproducible with information provided. Descriptions of the methods for calculating SMRs were clearly described, and methods for regression models were also described.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	SMRs were calculated for each mortality outcome of interest, using the internal referent group and mortality statistics for England and Wales, as well as local mortalities from four surrounding districts and two surrounding counties. For selected causes of death, a multivariate regression analysis based on Cox's proportional hazards model was conducted. 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		1.7	

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Study Citation:	Tomenson, J.A. (2011). Update of a cohort mortality study of workers exposed to methylene chloride employed at a plant producing cellulose triacetate film base International Archives of Occupational and Environmental Health, 84(8,8), 889-897
Data Type:	Cohort_exposed workers_DCM_IschemicHeartDiseaseMortality_Dichotomous-Cardiovascular
HERO ID:	787813

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 36: **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_DCM_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_DCM_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_DCM_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 37: **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; DCM kidney cancer-Cancer
HERO ID:	2127914

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	Medium	× 0.4	0.8	The presented work is a subset of the Montreal Cancer Case-Control Study, evaluating male Canadian citizens aged 35-70 years diagnosed from 1979-1985 at the 18 largest Montreal area hospitals. 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 to a variety of chlorinated solvents, including Perc, TCE, DCM and CCL4, was assessed based on self-reported job history translated into exposure by chemists and industrial hygienists. Authors reported that there was no indication that completeness or validity of job histories differed between cases and controls.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	DCM 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.

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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; DCM kidney cancer-Cancer
HERO ID:	2127914

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Data for all outcomes (cancer incidence) and exposure levels 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	The large case-control study design was appropriate for assessing risk of cancer with chlorinated solvent exposure.
	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	Unconditional logistic regression was used to determine odds ratios (ORs). 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						

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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; DCM kidney cancer-Cancer
HERO ID:	2127914

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		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 38: **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:	DCM_all_subjects_possibleexp_Glioma-Cancer
HERO ID:	2128240

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

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

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

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Study Citation:	Neta, G., Stewart, P.A., Rajaraman, P., Hein, M.J., Waters, M.A., Purdue, M.P., Samanic, C., Coble, J.B., Linet, M.S. (2012). Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults Occupational and Environmental Medicine, 69(11), 793-801
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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 39: **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_DCM_cumulative_include proxy_glioma-Cancer
HERO ID:	2128307

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

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Study Citation:	Ruder, A.M., Yiin, J.H., Waters, M.A., Carreon, T., Hein, M.J., Butler, M.A., Calvert, G.M., Davis-King, K.E., Schulte, P.A., Mandel, J.S., Morton, R.F., Reding, D.J., Rosenman, K.D., Stewart, P.A., Brain Cancer Collaborative Study Group (2013). The Upper Midwest Health Study: Gliomas and occupational exposure to chlorinated solvents Occupational and Environmental Medicine, 70(2), 73-80
Data Type:	Upper Midwest Health Study_DCM_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_DCM_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 40: **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 (DCM substantial 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 (DCM substantial 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 DCM 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 (DCM substantial 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 41: **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_DCM_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_DCM_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_DCM_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 42: **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_DCM_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_DCM_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	Medium	× 0.25	0.5	The study considered the correlated nature of the pollutant mixture. Specifically, perchloroethylene was highly correlated (>90%) with benzene, 1,3-butadiene, toluene and ortho-xylene. However, methylene chloride and trichloroethylene 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_DCM_Childhood_Autism___OR_5km-Neurological/Behavior
HERO ID:	2453135

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 5: Analysis					
	Metric 12: Study Design and Methods	Medium	× 0.4	0.8	Appropriate design (i.e., retrospective cohort for assessment of a rare disease in relation to PCE/TCE/DCM exposure, and appropriate statistical methods (i.e., unconditional logistic regression models) were employed to analyze data.
	Metric 13: Statistical power	Medium	× 0.2	0.4	Sufficient study size to detect an effect. In the analysis of risk of autism associated with exposures within a 5 km buffer, there were 619 cases exposed to PCE, 641 cases exposed to DCM, and 624 cases exposed to TCE (Table 2).
	Metric 14: Reproducibility of analyses	Medium	× 0.2	0.4	Sufficient detail to understand analysis and reproduce if provided with all data.
	Metric 15: Statistical models	Medium	× 0.2	0.4	Logistic regression modeling was used to generate ORs. Rationale for variable selection is stated. Model assumptions do not appear to be violated.
Domain 6: Other Considerations for Biomarker Selection and Measurement					
	Metric 16: Use of Biomarker of Exposure		NA	NA	
	Metric 17: Effect biomarker		NA	NA	
	Metric 18: Method Sensitivity		NA	NA	
	Metric 19: Biomarker stability		NA	NA	
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		High		1.4	
Extracted		Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 43: **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:	DCM_nested case-control_exposed workers_AML_cancer_moderate-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:	DCM_nested case-control_exposed workers_AML_cancer_moderate-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:	DCM_nested case-control_exposed workers_AML_cancer_moderate-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:	DCM_nested case-control_exposed workers_AML_cancer_moderate-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:	DCM_nested case-control_exposed workers_AML_cancer_moderate-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 44: **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 (DCM men CEI 1)-Cancer
HERO ID:	2799644

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

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

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

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 45: **Siemiatycki 1991: Evaluation of Cancer Outcomes**

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

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	High	× 0.4	0.4	Of 4576 eligible male cases from the Montreal metropolitan area were ascertained between 1979-1985, 3730 completed an interview during this study (initiated in 1979 as a case-control design). Each cancer was coded by the International Classification of Disease for Oncology. Of 541 eligible population male controls, 375 were interviewed and selected from random digit calling, the provincial election of 1981, were noncancer patients hospitalized in the same institutions as those with cancer - a subgroup of control cancer cases unrelated to occupational exposure or with cancer at another site deemed not occupationally relevant was also interviewed
	Metric 2: Attrition	High	× 0.4	0.4	81.5% of eligible cases completed interviews. 72% of controls. Nonresponses due to refusal, death, no next of kin found, patient discharged, no valid address, psychiatric cases, no translator, or physician refusal
	Metric 3: Comparison Group	High	× 0.2	0.2	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: DCM_worker any exposure_rectal cancer-Cancer
HERO ID: 157954

Domain		Metric	Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Histological or autopsy confirmation of primary tumor site.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	ORs with 90% CIs.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	For each association between occupational exposure and cancer type adjustments were made included age, height, place of birth, and race
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Confounders based on literature and questionnaire data.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Adjustments for other occupational exposure types, smoking, and alcohol intake were made.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This is a case-control study that collected cancer type and lifetime occupational history from cancer patients to determine if occupational history effected cancer risk
	Metric 13:	Statistical power	Medium	× 0.2	0.4	DCM was not included in Table 1 results, which included all associations where power was adequate to detect a 2-fold risk (based on # participants and at least 2% exposure). DCM was included in Table 2 which shows elevated ORs only (irrespective of power to detect excess risk).
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Analysis was fully described a Mantel-Haenszel analysis was performed to analyze odds ratios for the data.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Method was transparent. A Mantel-Haenszel analysis was performed to analyze odds ratios for the data. p-values were computed by the Mantel-Haenszel chi-square test
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.7	

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 46: **Brender et al. 2014: Evaluation of Cardiovascular 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_methylene chloride-Cardiovascular
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 DCM 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 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.
Domain 3: Outcome Assessment					

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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_methylene chloride-Cardiovascular
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 DCM 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						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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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_methylene chloride-Cardiovascular
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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 47: **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- oral cleft_methylene chloride-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 DCM 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 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.
Domain 3: Outcome Assessment					

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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- oral cleft_methylene chloride-Growth (early life) and Development
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 DCM 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						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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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- oral cleft_methylene chloride-Growth (early life) and Development
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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 48: **Brender et al. 2014: Evaluation of Neurological/Behavior 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- neural tube_methylene chloride-Neurological/Behavior
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 DCM 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 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.
Domain 3: Outcome Assessment					

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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- neural tube_methylene chloride-Neurological/Behavior
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 DCM 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						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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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- neural tube_methylene chloride-Neurological/Behavior
HERO ID:	2799700

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.8	
Extracted			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 49: **Silver et al. 2014: Evaluation of 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_DCM_BrainNervousSystemCancer_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_DCM_BrainNervousSystemCancer_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_DCM_BrainNervousSystemCancer_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 50: **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_DCM_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_DCM_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_DCM_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 51: **Silver et al. 2014: Evaluation of Hepatic 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_DCM_LiverDisease_SMR_malehourly-Hepatic
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_DCM_LiverDisease_SMR_malehourly-Hepatic
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_DCM_LiverDisease_SMR_malehourly-Hepatic
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 52: **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 DCM 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 DCM 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. 13 cases and 3 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 DCM 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		1.8	
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 53: **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_DCM_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_DCM_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_DCM_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_DCM_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 54: **Garcia et al. 2015: Evaluation of Cancer Outcomes**

Study Citation:	Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14
Data Type:	Cohort_DCM_CTS_BreastCancer_Q3-Cancer
HERO ID:	3014082

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

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Study Citation:	Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14
Data Type:	Cohort_DCM_CTS_BreastCancer_Q3-Cancer
HERO ID:	3014082

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

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Study Citation:	Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14
Data Type:	Cohort_DCM_CTS_BreastCancer_Q3-Cancer
HERO ID:	3014082

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 55: **Kumagi et al. 2016: Evaluation of Cancer Outcomes**

Study Citation:	Kumagai, S; Sobue, T; Makiuchi, T; Kubo, S; Uehara, S; Hayashi, T; Sato, KK; Endo, G (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers Occupational and Environmental Medicine, 73(8), 545-552
Data Type:	DCM Osaka printing cohort cholangiocarcinoma IRR 5-year lag-Cancer
HERO ID:	3419929

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Study setting and participant selection are reported in detail. Employees were chosen from a company list of workers in the proof-printing section of the factory where they would be exposed to both 1,2-DCP and DCM. There were some small differences between the sub-population exposed to DCM compared to the whole factory sample. Workers exposed to DCM were slightly older, a larger proportion male, and more likely to have a longer exposure (larger cumulative exposure)
	Metric 2: Attrition	High	× 0.4	0.4	Of 116 workers identified from the company list, eight were excluded due to incomplete demographic/employment information. Eleven other workers were excluded due to starting work after termination of 1,2-DCP (the main exposure in this study) use in the plant.
	Metric 3: Comparison Group	High	× 0.2	0.2	For SIRs, the expected number of cases was "calculated using sex, calendar year and age-specific incidence rates of cholangiocarcinoma in the general population in Japan." This demonstrates adjustment for relevant characteristics as well as a clear selection of an appropriate reference population.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Medium	× 0.4	0.8	Exposure was extrapolated back from a recreation of the factory environment in a 2012 JNIOSH experiment at one of the Osaka factories (Plant O-2). This recreation used the appropriate mixture of 1,2-DCP and DCM to obtain TWAs for a known quantity used per hour. This was extrapolated back with worker's histories and accounting records of purchased 1,2-DCP and DCM for each specific plant to calculate a cumulative exposure for each employee. In the JNIOSH recreation, measurements of exposure were also taken in the front office and delivery areas so as to be able to assign exposure to workers that fell into these categories.

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Study Citation:	Kumagai, S; Sobue, T; Makiuchi, T; Kubo, S; Uehara, S; Hayashi, T; Sato, KK; Endo, G (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers Occupational and Environmental Medicine, 73(8), 545-552
Data Type:	DCM Osaka printing cohort cholangiocarcinoma IRR 5-year lag-Cancer
HERO ID:	3419929

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 5:	Exposure levels	Low	× 0.2	0.6	For the SIR, there are only two levels of exposure which is defined by employment at the plants and no exposure in the general population. For the incident rate ratio, there was also only two levels of exposure as it was included as a dichotomous variable.
	Metric 6:	Temporality	High	× 0.4	0.4	This study evaluates a rare cancer in employees during a follow-up period (minimum 5 years) which establishes temporality between exposure and disease.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Health records were obtained for all employees from the Japanese Ministry of Health, Labour, and Welfare. These records were evaluated by one of the study authors (Kubo). For comparison with the general Japenese population, the specific ICD-9 codes used were 155.1 and 156.1 (C22.1 and C24.0 in ICD-10). This is not a gold standard, but there is no evidence to suggest this method would have poor validity.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All outcomes listed in the abstract, introduction, and methods were provided both in-text and in easily read and extractable tables. Either standardized incidence ratios or incidence rate ratios with 95% confidence intervals and person-years and number of subjects were reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Relevant demographic and employment characteristics were drawn from employment records. For SIRs, the expected number of cases was "calculated using sex, calendar year and age-specific incidence rates of cholangiocarcinoma in the general population in Japan."
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	Covariates were taken from employment records. This is not a gold standard method, but there is no evidence to indicate this method has poor validity.

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Study Citation:	Kumagai, S; Sobue, T; Makiuchi, T; Kubo, S; Uehara, S; Hayashi, T; Sato, KK; Endo, G (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers Occupational and Environmental Medicine, 73(8), 545-552
Data Type:	DCM Osaka printing cohort cholangiocarcinoma IRR 5-year lag-Cancer
HERO ID:	3419929

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	For the SIR, there was no adjustment for exposure to 1,2-DCP. All workers in the DCM exposed group were also exposed to 1,2-DCP. Other co-exposures in this setting include kerosene and potentially carcinogenic inks although the study authors indicate that these were present in low levels and were unlikely to influence the DCM-cholangiocarcinoma relationship.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design was appropriate for investigating the relationship between exposure to DCM and cholangiocarcinoma.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The number of subjects for DCM exposure was rather small (n=33), but there were a sufficient number of cases to detect an effect.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The analysis was described in detail. For exposure measurement, the calculation of cumulative exposure was moderately complex, but explained thoroughly.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The methods for calculating risk in both the case of SIRs and RRs was appropriate and transparent. No apparent issues.
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:	Kumagai, S; Sobue, T; Makiuchi, T; Kubo, S; Uehara, S; Hayashi, T; Sato, KK; Endo, G (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers Occupational and Environmental Medicine, 73(8), 545-552
Data Type:	DCM Osaka printing cohort cholangiocarcinoma IRR 5-year lag-Cancer
HERO ID:	3419929

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: **Cantor et al. 1995: Evaluation of Cancer Outcomes**

Study Citation:	Cantor, KP; Stewart, PA; Brinton, LA; Dosemeci, M (1995). Occupational exposures and female breast cancer mortality in the United States Journal of Occupational and Environmental Medicine, 37(3,3), 336-348
Data Type:	DCM_breast cancer_occupational_case-control_OR_black2-Cancer
HERO ID:	194130

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	Cases were women whose death certificates listed breast cancer as the cause of death (across 24 U.S. states). Controls were randomly selected from non-cancer deaths, and frequency-matched for age, gender, and race (four controls per case). Records were from years 1984 to 1989, from a database supported by the National Cancer Institute, NIOSH, and the National Center for Health Statistics. Cases for which 'homemaker' was the designated occupation were excluded, leaving 29,397 white women cases, 102,955 white women controls, 4,112 black women cases, and 14,839 black women controls.
	Metric 2:	Attrition	High	× 0.4	0.4	Only cases for which 'homemaker' was the designated occupation were excluded (45.1% of white women cases, 31.1% of black women cases; 51.7% of white women controls, 37.9% of black women controls).
	Metric 3:	Comparison Group	High	× 0.2	0.2	Controls were recruited from records from the same database and for the same time period as cases, and were frequency-matched for age, gender, and race.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Medium	× 0.4	0.8	Exposure was estimated using a job exposure matrix, based on the assigned occupational codes, and developed according to professional judgement of an industrial hygienist, information in the general literature on occupational exposure, and NIOSH and OSHA occupational exposure databases. Exposure probability and level was estimated for 31 occupational exposure categories, of which DCM exposure was one. Scores were assigned for probability and level of exposure. There were no detailed employment records used.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	Four levels of exposure are presented, including no exposure. Detailed ranges for exposure are not included in the present reference, but more details may be available in HERO ID's 707912 and 1188.

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Study Citation:	Cantor, KP; Stewart, PA; Brinton, LA; Dosemeci, M (1995). Occupational exposures and female breast cancer mortality in the United States Journal of Occupational and Environmental Medicine, 37(3,3), 336-348
Data Type:	DCM_breast cancer_occupational_case-control_OR_black2-Cancer
HERO ID:	194130

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	Medium	× 0.4	0.8	Exposure is likely to have occurred prior to the outcome, but the exact timeline of occupational exposures in relation to outcome isn't clear.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Outcome was assessed from causes of death listed on official death certificates. Mortality from breast cancer was determined using the underlying cause of death (ICD-9, code 174) listed on the death certificate.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	One outcome (breast cancer) was assessed, and is appropriately identified in the study report. The numbers of cases and controls included in the assessment are also reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Analyses were adjusted for age at time of death, and/or socioeconomic class. Results were stratified by race.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	The assignment of SES was described in the current reference as the SES status implied by the usual occupation listed for an individual. This is not a well-established method, but there is no evidence to suggest that it is not a valid method.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	The study authors discuss potential for "overlapping exposures" and state this as a limitation. of the study
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	This case-control study calculates odds ratios and 95% confidence intervals for probability and level of exposure to DCM among breast cancer deaths across 24 states, from 1984 to 1989. The design is appropriate for investigating the effects of DCM on breast cancer mortality.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	There were 29,397 white women cases, 102,955 white women controls, 4,112 black women cases, and 14,839 black women controls included in the analysis. This was sufficient to detect an effect.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	Some methods for covariate adjustments were not described. Assignment of SES was not fully described.

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Study Citation:	Cantor, KP; Stewart, PA; Brinton, LA; Dosemeci, M (1995). Occupational exposures and female breast cancer mortality in the United States Journal of Occupational and Environmental Medicine, 37(3,3), 336-348
Data Type:	DCM_breast cancer_occupational_case-control_OR_black2-Cancer
HERO ID:	194130

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 15:	Statistical models	Medium	× 0.2	0.4	Odds ratios were calculated for the odds of breast cancer mortality, by the method published in Gart (1970). Two models were presented (one age adjusted and the other age and SES adjusted). The reasoning for inclusion of SES was discussed.
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 57: **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_DCM_HeadNeckCancer_OR_EverExposure-Cancer
HERO ID:	3480125

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

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

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	Cases identified from cancer registries in 10 geographical regions of France. Histologically confirmed diagnosis from 2001-2007 in women aged 18-85. ICD-O-3 codes were used to identify squamous cell carcinomas in oral cavity, oropharynx, hypopharynx, oral cavity, and larynx (detailed list of codes in text).
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Quantitative description of relevant outcomes (head and neck cancers in women) from the abstract/methods are provided and extractable.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Analyses adjusted for geographical area, age, smoking status, tobacco consumption (pack-years) and alcohol consumption. Interaction terms for smoking and alcohol were also included. SES considered with last occupation and longest occupation, but did not impact ORs and were not presented.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	In person interviews with standardized questionnaire.
	Metric 11:	Co-exposure Confounding	Medium	× 0.25	0.5	Exposures to TCE, Perc, and DCM were strongly correlated. Rather than adjusting for co-exposures, exclusive exposure to individual and combinations of chlorinated solvents were analyzed.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was appropriate for the research questions. Logistic regression was used appropriately to estimate ORs and CIs.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The cohort contains sufficient participants to detect an effect for TCE, perc, and DCM. Insufficient data for carbon tetrachloride, so it was excluded from analysis beyond an ever/never OR.
	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_DCM_HeadNeckCancer_OR_EverExposure-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 58: **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 - DCM_50-89% 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 DCM 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	
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 - DCM_50-89% 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 59: **Celanese Fibers, Inc 1987: Evaluation of Hepatic Outcomes**

Study Citation:	Celanese Fibers Inc (1987). Methylene chloride analysis of liver function tests with attachments and cover letter dated 091887
Data Type:	Celriver Plant_DCM_exposed workers_Hepatic endpoint-Hepatic
HERO ID:	4213851

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	The study reported that all individuals were workers in the same company. Group A was employed for 10 or more years, and Group B 5 or more years. However it was not reported how long the unexposed controls were employed with the company. No other inclusion/exclusion criteria were reported (age, sex, health status etc.) nor was recruitment or participation rate reported.
	Metric 2:	Attrition	Low	× 0.4	1.2	Group A = 37, Group B =59, Controls = 32. Results on page 6 show minimal loss in each group (although the reason for loss was not reported) and the control group showed no loss.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	There is no direct evidence that the comparison groups were similar (characteristics not reported). However, all individuals were from the same company, and assumed to be tested within the same time frame, so there is indirect evidence of similar comparison groups.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Unacceptable	× 0.4	0.16	There is no information about how exposure was assessed (only that employees were exposed to DCM or not). It is reported that DCM levels in the exposed groups was greater than 250 ppm. There is no indication when this measure was taken (at the time of the study, over the 10 years of previous employment, what job functions this measure applies to. . .). Normal ranges of parameters seem to be obtained from Roche Biomedical Lab; no statistics were run on analysis, no measures of exposure taken, no details on population analyzed.
	Metric 5:	Exposure levels	Low	× 0.2	0.6	There are 3 levels of exposure (controls, exposed 5 years, exposed 10 years). Groups are divided by exposure duration is not by exposure level; both groups exposed to levels greater than 250ppm.
	Metric 6:	Temporality	Medium	× 0.4	0.8	Employees were exposed at least 5 or 10 years to DCM before outcome measurements were taken. It is unclear if exposures fall within relevant window.
Domain 3: Outcome Assessment						

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Study Citation:	Celanese Fibers Inc (1987). Methylene chloride analysis of liver function tests with attachments and cover letter dated 091887
Data Type:	Celriver Plant_DCM_exposed workers_Hepatic endpoint-Hepatic
HERO ID:	4213851

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 7:	Outcome measurement or characterization	Low	× 0.667	2	The study reported that the outcome assessments were "commonly used liver function tests (LD, SGOT, SGPT, TOT, BIL)." However, the methods were not reported. Time of sample collection was not reported nor was time from collection to analysis. Normal parameter values for these tests appear to be obtained from Roche Biomedical lab.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Means, SDs, and Ns are reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Not Rated	NA	NA	There are no reporting of confounders or confounder adjustments.
	Metric 10:	Covariate Characterization	Not Rated	NA	NA	No indication of covariate assessment
	Metric 11:	Co-exposure Confounding	Low	× 1	3	Although it is unclear what other chemicals these workers were exposed to (none are reported), it is likely that there were co-exposures working in this plant.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.667	1.33	There is no detailed information about study design, but it is acceptable. Statistics were not employed in this study.
	Metric 13:	Statistical power	Not Rated	NA	NA	Statistics were not employed in this study. Group A (n=37), Group B (n=59) and control (n=32) are small to apply to the general population
	Metric 14:	Reproducibility of analyses	Low	× 0.333	1	Details of the study design are not reported, and thus would be difficult to replicate.
	Metric 15:	Statistical models	Not Rated	NA	NA	No stats 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[‡]			Unacceptable[⋆⋆]		2.7	
Extracted			No			

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Study Citation:	Celanese Fibers Inc (1987). Methylene chloride analysis of liver function tests with attachments and cover letter dated 091887
Data Type:	Celriver Plant_DCM_exposed workers_Hepatic endpoint-Hepatic
HERO ID:	4213851

Domain	Metric	Rating†	MWF⋆	Score	Comments††

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 60: **General Electric, Co 1990: Evaluation of Hepatic Outcomes**

Study Citation:	General Electric Company (1990). Morbidity study of occupational exposure to methylene chloride using a computerized surveillance system (final report) with cover sheets and letter dated 041190
Data Type:	Occupational_DCM_Hepatic_GGT_HighExposure-Hepatic
HERO ID:	4213921

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
Metric 1:	Participant selection	Medium	× 0.4	0.8	Employees were grouped into one of four exposure categories, based on MeCL measurements from personal air monitoring. Only males who completed the medical exam and worked in key job functions were included in analysis; the only exception was in the analysis of breast cancer. However, there was no information about participation selection or rates.
Metric 2:	Attrition	Medium	× 0.4	0.8	There was very little information about attrition, however it was reported that "5 workers refused the medical examination entirely in 1984." It is unclear if this is the only attrition that occurred during the study. Final numbers were 896 males (19 workers in the high, 49 in the intermediate, 56 in the low, and 722 in the minimal/none).
Metric 3:	Comparison Group	Medium	× 0.2	0.4	There is no information about the similarity of groups, but they are from the same factories, so indirect evidence that they are similar..
Domain 2: Exposure Characterization					
Metric 4:	Measurement of Exposure	High	× 0.4	0.4	Exposures were determined by personal and area monitoring levels, duration of monitoring, work zone, job classification, and method of sampling. Exposure methods were well detailed.
Metric 5:	Exposure levels	Medium	× 0.2	0.4	There were 4 exposure groups: 1) low exposure (mean = 3.3 ppm), 2) medium exposure (mean = 10.9 ppm), 3) high exposures (mean = 49.0 ppm), 4) "other groups" with minimal or no exposure to MeCl (<1.0 ppm); all based on personal air monitoring conducted 1979-1985. Exposures known to reach up to 150 ppm during specific manufacturing steps.
Metric 6:	Temporality	Medium	× 0.4	0.8	Exposures occurred before medical examinations, however it is not clear how long workers were employed before examination
Domain 3: Outcome Assessment					

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Study Citation: General Electric Company (1990). Morbidity study of occupational exposure to methylene chloride using a computerized surveillance system (final report) with cover sheets and letter dated 041190
Data Type: Occupational_DCM_Hepatic_GGT_HighExposure-Hepatic
HERO ID: 4213921

Domain	Metric		Rating†	MWF*	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Medical data was collected by the plant physician (medical history and physical examination, and medical equipment results: sphygmo-manometer, spirometer, electrocardiographs, audiogram, self-reported family history which physician follow up with worker about.)
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	SD/SE are not reported; percentages were reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Sex was adjusted for in the final analysis (females analysis was removed. The study reported that the mean age was 35.3 years, predominantly white and male. All analysis were adjusted for age and race
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Age, race. sex were collected by a medical physician during an annual checkup
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposure to phenol around reaction vessels, high noise levels, and potentially other hazardous materials in small amounts at the BPA plant and phosgene, high noise level, and other catalysts at the resin plant are mentioned but not adjusted for. High noise level suggested to add to headaches
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was acceptable for this type of cross-sectional study; Workers at a BPA plant were categorized based on personal exposure and job titles into exposure categories (little/none, low, medium and high) and assessed for relationships with vertigo experience)
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Final numbers were 19 workers in the high, 49 in the intermediate, 56 in the low, and 722 in the minimal/none.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The methods of collection of exposure and outcome data were clearly described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Bivariate and multivariate analysis was achieved utilizing an ANOVA to observe for differences between groups, a cross-tabulation was performed using chi-square to identify associations with categorical variables from the medical exam; very minimal explanation of analysis provided
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure	Not Rated	NA	NA	

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Study Citation:	General Electric Company (1990). Morbidity study of occupational exposure to methylene chloride using a computerized surveillance system (final report) with cover sheets and letter dated 041190
Data Type:	Occupational_DCM_Hepatic_GGT_HighExposure-Hepatic
HERO ID:	4213921

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 17:	Effect biomarker	High	× 0.2	0.2	Well established biomarkers for hepatic health were used: serum gamma glutamyl transferase (GGT), serum total bilirubin, serum aspartate aminotransferase (AST), and serum alanine aminotransferase (ALT).
	Metric 18:	Method Sensitivity	Medium	× 0.2	0.4	Limits of detection not stated, but values reported for most of the subjects (missing some endpoints for 6 subjects out of the >800 presented).
	Metric 19:	Biomarker stability	Medium	× 0.2	0.4	Storage history not described, but do not have a high likelihood of biomarker instability.
	Metric 20:	Sample contamination	Low	× 0.2	0.6	No documentation of steps used to ensure contamination free from collection to measurement.
	Metric 21:	Method requirements	Medium	× 0.2	0.4	Method of quantification not stated, but standard clinical tests.
	Metric 22:	Matrix adjustment	Not Rated	NA	NA	
Overall Quality Determination‡			Medium		1.9	
Extracted			Yes			

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 61: **General Electric, Co 1990: Evaluation of Neurological/Behavior Outcomes**

Study Citation:	General Electric Company (1990). Morbidity study of occupational exposure to methylene chloride using a computerized surveillance system (final report) with cover sheets and letter dated 041190
Data Type:	Occupational_Neuro_DCM_High Exposed-Neurological/Behavior
HERO ID:	4213921

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Employees were grouped into one of four exposure categories, based on MeCL measurements from personal air monitoring. Only males who completed the medical exam and worked in key job functions were included in analysis; the only exception was in the analysis of breast cancer. However, there was no information about participation selection or rates.
	Metric 2: Attrition	Medium	× 0.4	0.8	There was very little information about attrition, however it was reported that "5 workers refused the medical examination entirely in 1984." It is unclear if this is the only attrition that occurred during the study. Final numbers were 896 males (19 workers in the high, 49 in the intermediate, 56 in the low, and 722 in the minimal/none).
	Metric 3: Comparison Group	Medium	× 0.2	0.4	There is no information about the similarity of groups, but they are from the same factories, so indirect evidence that they are similar.
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	High	× 0.4	0.4	Exposures were determined by personal and area monitoring levels, duration of monitoring, work zone, job classification, and method of sampling. Exposure methods were well detailed.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	There were 4 exposure groups: 1) low exposure (mean = 3.3 ppm), 2) medium exposure (mean = 10.9 ppm), 3) high exposures (mean = 49.0 ppm), 4) "other groups" with minimal or no exposure to MeCl (<1.0 ppm); all based on personal air monitoring conducted 1979-1985. Exposures known to reach up to 150 ppm during specific manufacturing steps.
	Metric 6: Temporality	Medium	× 0.4	0.8	Exposures occurred before medical examinations, however it is not clear how long workers were employed before examination
Domain 3: Outcome Assessment					

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Study Citation:	General Electric Company (1990). Morbidity study of occupational exposure to methylene chloride using a computerized surveillance system (final report) with cover sheets and letter dated 041190
Data Type:	Occupational_Neuro_DCM_High Exposed-Neurological/Behavior
HERO ID:	4213921

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Medical data was collected by the plant physician (medical history and physical examination, and medical equipment results: sphygmo-manometer, spirometer, electrocardiographs, audiogram, self-reported family history which physician follow up with worker about.)
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	SD/SE are not reported; percentages were reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Sex was adjusted for in the final analysis (females analysis was removed. The study reported that the mean age was 35.3 years, predominantly white and male. All analysis were adjusted for age and race
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	Age, race. sex were collected by a medical physician during an annual checkup
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposure to phenol around reaction vessels, high noise levels, and potentially other hazardous materials in small amounts at the BPA plant and phosgene, high noise level, and other catalysts at the resin plant are mentioned but not adjusted for. High noise level suggested to add to headaches
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design was acceptable for this type of cross-sectional study; Workers at a BPA plant were categorized based on personal exposure and job titles into exposure categories (little/none, low, medium and high) and assessed for relationships with vertigo experience)
	Metric 13:	Statistical power	Medium	× 0.2	0.4	Final numbers were 19 workers in the high, 49 in the intermediate, 56 in the low, and 722 in the minimal/none.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	The methods of collection of exposure and outcome data were clearly described.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Bivariate and multivariate analysis was achieved utilizing an ANOVA to observe for differences between groups, a cross-tabulation was performed using chi-square to identify associations with categorical variables from the medical exam; very minimal explanation of analysis provided
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	

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Study Citation:	General Electric Company (1990). Morbidity study of occupational exposure to methylene chloride using a computerized surveillance system (final report) with cover sheets and letter dated 041190
Data Type:	Occupational_Neuro_DCM_High Exposed-Neurological/Behavior
HERO ID:	4213921

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		1.9	
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 62: **Gibbs 1992: Evaluation of Cancer Outcomes**

Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_prostate_subcohort 1 high exposure_>20 years latency-Cancer
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All key elements of the study design are reported including the setting, methods of participant selection, participation rate at all steps of the study, and inclusion/exclusion criteria. The total study population including exposed and not exposed employees was n=3211 (2187 men, 1024 women).The authors report that 3220 persons were eligible for the study, but nine of those had inaccurate information concerning employment dates. The total number of exposed employees was n=2909 (1931 men, 978 women). The authors explain that the cohort could have included 4468 eligible employees if the initial protocol had been followed. The original protocol called for all eligible employees on the payroll in 1954 and subsequent years. However, there were some issues with missing employee records for the period 1954-1969. The issues are fully described by the authors including all of the efforts taken to find the missing records. In the end, the investigators chose to only include employees on the payroll on or after January 1, 1970.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study. Death certificates were obtained for 95.8% (252/263) of the decedents in the high exposure category ("subcohort 1"), 97% (350/361) of the decedents in the low exposure category ("subcohort 2"), and 98% (108/110) of the decedents in the not exposed category ("subcohort 3").
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The mortality of exposed employees was compared to three reference populations: the general populations of Allegany County and the State of Maryland, and the total white population of the U.S. (used for subcohort 1 only). The results were stratified by sex, and the calculation of SMRs incorporated the 5-year age and sex specific mortality rates for the reference populations. There were no adjustments for or stratification by race.

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_prostate_subcohort 1 high exposure_>20 years latency-Cancer
HERO ID:	4214006

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure was estimated solely using professional judgement. The authors report that "measurements of the concentrations of methylene chloride in the air of the plant were not available." Because of this, the authors used concentrations measured at another plant owned by the same company to estimate exposures for this study: "The median time-weighted average concentration for jobs in the "Extrusion and Preparation" areas at the Celriver plant (Ott et al 1983) was 475 ppm." Discussions with persons familiar with the Amcelle plant (current study) suggested that the concentrations in the extrusion area would have been about 7 times that in the bobbin shops and other low exposure areas. Based on those discussions and the industrial hygiene survey at the Celriver plant, the authors categorized departments with a range of 50-100 ppm as a "1" for exposure and the departments with concentrations in the range of 350-700 ppm as "7" for exposure. It was assumed that the same concentrations were present throughout the entire operation of the plant.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	There were three exposure levels (high, low, and not exposed). Each department was assigned a category of methylene chloride exposure (0, 1, or 7), and this was used to calculate an index representing the cumulative exposure of each worker. The main cohort was divided into three subcohorts on the basis of exposure: Subcohort 1 included all persons who ever worked in an area of the plant involving high (category 7) concentrations of methylene chloride (could have been in any department but had at least some time in a department considered high exposure); Subcohort 2 included persons who ever worked in an area of the plant with low (category 1) methylene chloride concentrations (never worked in high exposure department, but could have worked in non-exposure areas); Subcohort 3 included persons who according to their work histories never worked in any methylene chloride exposed departments or jobs.

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_prostate_subcohort 1 high exposure_>20 years latency-Cancer
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established and consideration was given to the interval between exposure and outcomes of interest. Employees were eligible if they were on the payroll or joined the company on or after January 1, 1970. In addition, they must have worked for more than 3 months at the plant. Follow-up was for the period 1970-1989. A latency of 20 years from first exposure to death was included in the analyses of malignant neoplasms.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The causes of death were determined from death certificates. The vital status of each employee was ascertained using a variety of different approaches including company records, the National Death Index, and social security file searches performed by two separate organizations. A nosologist reviewed the death certificates and assigned the underlying causes of death according to ICD-9. Medical records were not obtained.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Confidence intervals are not reported for the SMRs. The observed and expected numbers of deaths are reported for each cause of death in all data tables. The text and data tables indicate which effects were considered statistically significant with a p value < 0.05 or 0.01.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The SMRs were calculated with 5-year age and sex specific mortality rates. Results were stratified by sex, but were not adjusted for or stratified by race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	The age and gender of each employee were ascertained from company records.

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_prostate_subcohort 1 high exposure_>20 years latency-Cancer
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence of co-exposures in cohort members which may have been unbalanced across the study groups, and the co-exposures were not addressed in the analyses. The authors note that, "virtually all methylene chloride exposed workers were exposed to acetone, methanol and "finishing oils" and some workers were likely exposed to many other chemicals." In addition, the authors make the following comment regarding the significant excess in prostate cancer mortality observed in the highly-exposed employees: "Thus, while these men spent many years exposed to methylene chloride, they may have had even longer exposure to the cellulose acetate extrusion process and other associated chemicals."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study uses an appropriate statistical method to address the research question (the Occupational Cohort Mortality Analysis Program was used to perform mortality analyses).
	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 a total of 2909 exposed subjects with 602 deaths analyzed.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The authors provide no description of the statistical methods used to determine statistical significance.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method used for calculating SMRs is transparent. The number of observed and expected deaths in each 5 year interval from 1970 through 1989 inclusive were determined and SMRs were calculated using the OCMAP (Occupational Cohort Mortality Analysis Program) for personal computer. The 5-year age and sex specific mortality rates which were used in various analyses included those for the white population of the United States, State of Maryland, and Allegany county.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_prostate_subcohort 1 high exposure_>20 years latency-Cancer
HERO ID:	4214006

Domain	Metric	Rating†	MWF⋆	Score	Comments††
	Metric 20: Sample contamination		NA	NA	
	Metric 21: Method requirements		NA	NA	
	Metric 22: Matrix adjustment		NA	NA	
Overall Quality Determination‡		Medium		1.9	
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 63: **Gibbs 1992: Evaluation of Respiratory Outcomes**

Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_respiratory_subcohort 1 high exposure_>20 years latency-Respiratory
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation						
	Metric 1:	Participant selection	High	× 0.4	0.4	All key elements of the study design are reported including the setting, methods of participant selection, participation rate at all steps of the study, and inclusion/exclusion criteria. The total study population including exposed and not exposed employees was n=3211 (2187 men, 1024 women).The authors report that 3220 persons were eligible for the study, but nine of those had inaccurate information concerning employment dates. The total number of exposed employees was n=2909 (1931 men, 978 women). The authors explain that the cohort could have included 4468 eligible employees if the initial protocol had been followed. The original protocol called for all eligible employees on the payroll in 1954 and subsequent years. However, there were some issues with missing employee records for the period 1954-1969. The issues are fully described by the authors including all of the efforts taken to find the missing records. In the end, the investigators chose to only include employees on the payroll on or after January 1, 1970.
	Metric 2:	Attrition	High	× 0.4	0.4	There was minimal subject loss to follow up during the study. Death certificates were obtained for 95.8% (252/263) of the decedents in the high exposure category ("subcohort 1"), 97% (350/361) of the decedents in the low exposure category ("subcohort 2"), and 98% (108/110) of the decedents in the not exposed category ("subcohort 3").
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The mortality of exposed employees was compared to three reference populations: the general populations of Allegany County and the State of Maryland, and the total white population of the U.S. (used for subcohort 1 only). The results were stratified by sex, and the calculation of SMRs incorporated the 5-year age and sex specific mortality rates for the reference populations. There were no adjustments for or stratification by race.

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_respiratory_subcohort 1 high exposure_>20 years latency-Respiratory
HERO ID:	4214006

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 2: Exposure Characterization					
	Metric 4: Measurement of Exposure	Low	× 0.4	1.2	Exposure was estimated solely using professional judgement. The authors report that "measurements of the concentrations of methylene chloride in the air of the plant were not available." Because of this, the authors used concentrations measured at another plant owned by the same company to estimate exposures for this study: "The median time-weighted average concentration for jobs in the "Extrusion and Preparation" areas at the Celriver plant (Ott et al 1983) was 475 ppm." Discussions with persons familiar with the Amcelle plant (current study) suggested that the concentrations in the extrusion area would have been about 7 times that in the bobbin shops and other low exposure areas. Based on those discussions and the industrial hygiene survey at the Celriver plant, the authors categorized departments with a range of 50-100 ppm as a "1" for exposure and the departments with concentrations in the range of 350-700 ppm as "7" for exposure. It was assumed that the same concentrations were present throughout the entire operation of the plant.
	Metric 5: Exposure levels	Medium	× 0.2	0.4	There were three exposure levels (high, low, and not exposed). Each department was assigned a category of methylene chloride exposure (0, 1, or 7), and this was used to calculate an index representing the cumulative exposure of each worker. The main cohort was divided into three subcohorts on the basis of exposure: Subcohort 1 included all persons who ever worked in an area of the plant involving high (category 7) concentrations of methylene chloride (could have been in any department but had at least some time in a department considered high exposure); Subcohort 2 included persons who ever worked in an area of the plant with low (category 1) methylene chloride concentrations (never worked in high exposure department, but could have worked in non-exposure areas); Subcohort 3 included persons who according to their work histories never worked in any methylene chloride exposed departments or jobs.

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_respiratory_subcohort 1 high exposure_>20 years latency-Respiratory
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Temporality is established and consideration was given to the interval between exposure and outcomes of interest. Employees were eligible if they were on the payroll or joined the company on or after January 1, 1970. In addition, they must have worked for more than 3 months at the plant. Follow-up was for the period 1970-1989. A latency of 20 years from first exposure to death was included in the analyses of malignant neoplasms.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	The causes of death were determined from death certificates. The vital status of each employee was ascertained using a variety of different approaches including company records, the National Death Index, and social security file searches performed by two separate organizations. A nosologist reviewed the death certificates and assigned the underlying causes of death according to ICD-9. Medical records were not obtained.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	Confidence intervals are not reported for the SMRs. The observed and expected numbers of deaths are reported for each cause of death in all data tables. The text and data tables indicate which effects were considered statistically significant with a p value < 0.05 or 0.01.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	The SMRs were calculated with 5-year age and sex specific mortality rates. Results were stratified by sex, but were not adjusted for or stratified by race.
	Metric 10:	Covariate Characterization	High	× 0.25	0.25	The age and gender of each employee were ascertained from company records.

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_respiratory_subcohort 1 high exposure_>20 years latency-Respiratory
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	There is direct evidence of co-exposures in cohort members which may have been unbalanced across the study groups, and the co-exposures were not addressed in the analyses. The authors note that, "virtually all methylene chloride exposed workers were exposed to acetone, methanol and "finishing oils" and some workers were likely exposed to many other chemicals." In addition, the authors make the following comment regarding the significant excess in prostate cancer mortality observed in the highly-exposed employees: "Thus, while these men spent many years exposed to methylene chloride, they may have had even longer exposure to the cellulose acetate extrusion process and other associated chemicals."
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	The study design chosen was appropriate for the research question and the study uses an appropriate statistical method to address the research question (the Occupational Cohort Mortality Analysis Program was used to perform mortality analyses).
	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 a total of 2909 exposed subjects with 602 deaths analyzed.
	Metric 14:	Reproducibility of analyses	Low	× 0.2	0.6	The authors provide no description of the statistical methods used to determine statistical significance.
	Metric 15:	Statistical models	Medium	× 0.2	0.4	The method used for calculating SMRs is transparent. The number of observed and expected deaths in each 5 year interval from 1970 through 1989 inclusive were determined and SMRs were calculated using the OCMAP (Occupational Cohort Mortality Analysis Program) for personal computer. The 5-year age and sex specific mortality rates which were used in various analyses included those for the white population of the United States, State of Maryland, and Allegany county.
Domain 6: Other Considerations for Biomarker Selection and Measurement						
	Metric 16:	Use of Biomarker of Exposure		NA	NA	
	Metric 17:	Effect biomarker		NA	NA	
	Metric 18:	Method Sensitivity		NA	NA	
	Metric 19:	Biomarker stability		NA	NA	

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Study Citation:	Gibbs, GW (1992). Mortality or workers employed at a cellulose acetate & triacetate fibers plant in Cumberland, MD (final report) with cover letter dated 061792
Data Type:	Methylene chloride_occupational_respiratory_subcohort 1 high exposure_>20 years latency-Respiratory
HERO ID:	4214006

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 20:	Sample contamination		NA	NA	
	Metric 21:	Method requirements		NA	NA	
	Metric 22:	Matrix adjustment		NA	NA	
Overall Quality Determination‡			Medium		1.9	
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 64: **Dow Chem, Co 1976: Evaluation of Skin and Connective Tissue Outcomes**

Study Citation:	Dow Chemical Company (1976). In-use safety study with an aerosol spray deodorant #443181- 10 (633-65a) and an aerosol spray antiperspirant #d4247-41a with cover letter dated 042181
Data Type:	controlled randomized trial_DCM_Skin irritation-Skin and Connective Tissue
HERO ID:	4214072

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	There is no information on inclusion/exclusion criteria, or from what population the participants were selected.
	Metric 2:	Attrition	Medium	× 0.4	0.8	There is no information about attrition in this study, however, the study indicates no loss.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	The age range was from 18-60 years (although there was no indication of the age range of each group). Group 1 had 47 males/28 females, group 2 had 25 males/25 females. No other information was provided on the two groups. In addition, there was no control group that had a placebo spray.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	This was a controlled trial and there was no specific measurement of exposure. Samples tested contained similar amounts of DCM (21.5% in one compound and 20% in the other). However, exposures may have varied by subjects as they were instructed to spray the entire axillary vault of both arms for 2 seconds at a distance of 6 inches.
	Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	There is no control group with no DCM exposure, each formulation consisted of ~20% AEROTHENE MM which is 99.5% methylene chloride.
	Metric 6:	Temporality	High	× 0.4	0.4	For the response of skin irritation, the time frame (12 weeks) is sufficient to see responses
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	High	× 0.667	0.67	A standardized checklist of skin symptoms was used by a single dermatologist after 1, 2, 4, 8, and 12 weeks
	Metric 8:	Reporting Bias	High	× 0.333	0.33	All raw data are reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Age and sex were similar between the two groups.
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	No information was provided in how age and sex was obtained, but it was likely based on self-report from the subjects and there is little concern for self-reporting of age or sex.

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Study Citation:	Dow Chemical Company (1976). In-use safety study with an aerosol spray deodorant #443181- 10 (633-65a) and an aerosol spray antiperspirant #d4247-41a with cover letter dated 042181
Data Type:	controlled randomized trial_DCM_Skin irritation-Skin and Connective Tissue
HERO ID:	4214072

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposures from the other ingredients in the deodorants were not accounted for. There were no controls that received placebo without the DCM. In addition, there appears to have been differences in the concentrate used with one of the formulas using aluminum chlorohydrate.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Unacceptable	× 0.667	0.44	Although the study design may have been acceptable for the study purpose, it is not acceptable for the purpose of determining if DCM is a skin irritant. There were no control groups that did not receive DCM exposures and there were additional compounds that may have caused any irritation reported.
	Metric 13:	Statistical power	Medium	× 0.333	0.67	There were 125 subjects included, which would have had enough statistical power.
	Metric 14:	Reproducibility of analyses	Not Rated	NA	NA	The study did not conduct any analyses on the results. They just noted there was slight transient erythema , which was considered safe for marketing.
	Metric 15:	Statistical models	Not Rated	NA	NA	The study did not conduct any analyses on the results. They just noted there was slight transient erythema , which was considered safe for marketing.
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[⋆⋆]		2.3	
Extracted			No			

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Study Citation:	Dow Chemical Company (1976). In-use safety study with an aerosol spray deodorant #443181- 10 (633-65a) and an aerosol spray antiperspirant #d4247-41a with cover letter dated 042181
Data Type:	controlled randomized trial_DCM_Skin irritation-Skin and Connective Tissue
HERO ID:	4214072

Domain	Metric	Rating†	MWF⋆	Score	Comments††

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 65: **Dow Chem, Co 1972: Evaluation of Skin and Connective Tissue Outcomes**

Study Citation:	Dow Chemical Company (1972). Human repeated insult patch test with four aerosol antiperspirant products
Data Type:	Randomized controlled trial_DCM_Skin Irritation-Skin and Connective Tissue
HERO ID:	4214073

Domain	Metric		Rating[†]	MWF[⋆]	Score	Comments[††]
Domain 1: Study Participation						
	Metric 1:	Participant selection	Low	× 0.4	1.2	There is no information on participant selection (inclusion/exclusion etc), but likely all were from a the same population (same time frame, etc)
	Metric 2:	Attrition	Medium	× 0.4	0.8	No information on attrition, but no reports of loss during the study. Presumably all subjects noted to be tested were all those included in the study initially.
	Metric 3:	Comparison Group	Medium	× 0.2	0.4	Table 1 shows similar sex (1:1) and race ratio, all groups had similar age ranges (16-59). However, comparison was made for four samples of aerosol antiperspirant and there does not appear to be a control group.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	Low	× 0.4	1.2	Exposure via skin patches, there was a uniform way of making these patches, but no reporting of how much DCM was in each patch. It was noted that formula 14-2 and 14-4 contained 15% DCM.
	Metric 5:	Exposure levels	Unacceptable	× 0.2	0.04	Two of the samples contained 15% DCM. However, how this was applied to the skin was not reported. It was only noted that a patch was applied on Monday, Wednesday, and Thursday and allowed contact with the skin for 24 hours. Although there were 4 different formulas tests and two of the formulas contained DCM. There is in essence one exposure group with DCM at 15%.
	Metric 6:	Temporality	High	× 0.4	0.4	The time frame (4 days/24 hours) was an appropriate time frame for the outcome of skin irritation
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	A checklist of skin irritation is provided (table 2), but it is unclear if a dermatologist carried out the assessments.
	Metric 8:	Reporting Bias	High	× 0.333	0.33	Raw data reported.
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	Medium	× 0.5	1	Sex, age, race were similar. No other covariates were noted or considered.

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Study Citation: Dow Chemical Company (1972). Human repeated insult patch test with four aerosol antiperspirant products
Data Type: Randomized controlled trial_DCM_Skin Irritation-Skin and Connective Tissue
HERO ID: 4214073

Domain		Metric	Rating†	MWF⋆	Score	Comments††
	Metric 10:	Covariate Characterization	Medium	× 0.25	0.5	It was not reported how the sex, race, and age were obtained, but it is likely was self-report and there is little concern for the self-report for these variables.
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Co-exposures were present in the formulations, however, there is no information provided on what is in the different formulas so we do not know how any of them compare or if they may contain other compounds that are potential skin irritants. It is just noted that two of the 4 formulas contain 15% DCM.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Unacceptable	× 0.667	0.44	Although the study design may have been acceptable for the study purpose, it is not acceptable for the purpose of determining if DCM causes skin sensitization. There were no control groups that did not receive DCM exposures and there were additional compounds that may have caused any sensitization reported.
	Metric 13:	Statistical power	Medium	× 0.333	0.67	There were 50 subjects, which was likely of sufficient power. It is unclear if the 50 subjects were separated into 4 different groups, but this should still provide sufficient power to detect skin sensitization.
	Metric 14:	Reproducibility of analyses	Not Rated	NA	NA	The study did not conduct any analyses on the results. They just noted there was no evidence of skin sensitization
	Metric 15:	Statistical models	Not Rated	NA	NA	The study did not conduct any analyses on the results. They just noted there was no evidence of skin sensitization
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⋆⋆		2.4	
Extracted			No			

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Study Citation:	Dow Chemical Company (1972). Human repeated insult patch test with four aerosol antiperspirant products
Data Type:	Randomized controlled trial_DCM_Skin Irritation-Skin and Connective Tissue
HERO ID:	4214073

Domain	Metric	Rating†	MWF⋆	Score	Comments††

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 66: **Ott et al. 1983: Evaluation of Hematological and Immune Outcomes**

Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_exposed_white women_aspartate aminotransferase-Hematological and Immune
HERO ID:	5240267

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Study population was described in a methodological paper covering all aspects of the health surveillance project (Ref ID: 24149). Briefly, exposed participants were employees of a cellulose triacetate and cellulose diacetate fiber manufacturing plant in Rock Hill, South Carolina, exposed to were exposed to methylene chloride, acetone, and methanol, the methanol being present in a ratio of approximately 1 to 10 to methylene chloride. Unexposed participants were from a non-DCM-exposure acetate fiber manufacturing plant in Narrows, Virginia, who were exposed to similar concentrations of acetone but were not exposed to methylene chloride or ethanol. Participation in the health examination was on a volunteer basis and was estimated to cover about 61 % of the employees in the plant with methylene chloride exposure and 55 % of the employees in the reference plant.
	Metric 2: Attrition	Medium	× 0.4	0.8	Participation in the health examination was on a volunteer basis, with 266 exposed and 251 unexposed employees. There was no other specific mention of attrition reported/addressed in this report.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_exposed_white women_aspartate aminotransferase-Hematological and Immune
HERO ID:	5240267

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 3:	Comparison Group	High	× 0.2	0.2	Details on participants (e.g., race, sex, age, and cigarette smoking.) were reported in the study report. Cigarette smoking varied with sex and race; however, there were no differences between the exposed and reference groups within the sex-by race subgroups. Among the exposed volunteers only 9 of 266 (3.4 %) had been employed less than one year and 169 (63.5 %) had been employed for more than five years at the time of the examination. In the reference plant, the percentages were 13.9 and 55.1 %, respectively. In addition, the regression analyses controlled for sex, race, age, cigarette smoking history, time of venipuncture. The authors acknowledge potential differences in the collection and handling of the blood specimens between exposed and unexposed workers that might bias the results, and hence did not perform direct comparisons of laboratory findings between exposed and unexposed.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	The results of the industrial hygiene monitoring of the work environment are detailed in another report (Ref ID: 29149.) (Eight-hr TWA concentrations and peak concentrations were determined for both plants. Personal air monitoring (>350 samples), area sampling (170 samples), and short-term excursion sampling (20 samples) were performed over the course of a 3.5-month survey period in late 1977-early 1978. Details of the personal air sampling methods are described in an appendix to the study report.). Median time weighted average concentrations of methylene chloride for an 8-h day were presented in this report for exposed employees in various work areas.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Occupational DCM exposure was categorized into four levels across a sufficient range: unexposed, 60 and 140 ppm DCM, 280 ppm, and 475 ppm DCM.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_exposed_white women_aspartate aminotransferase-Hematological and Immune
HERO ID:	5240267

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Among the exposed volunteers only 3.4 % had been employed less than one year and 63.5% had been employed for more than five years at the time of the examination. In the reference plant, the percentages were 13.9 and 55.1%. Since the outcomes in the study concern hematological evaluations, the study presents an appropriate temporality between exposure and outcome.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Analyses of blood samples for both exposed ad unexposed employees were performed by the same laboratory. Analyses are described in detail and are adequate. However, there were differences in the collection (posture, time of day, altitude) and handling of the blood specimens between exposed and unexposed workers that might bias the results, and hence did not perform direct comparisons of laboratory findings between exposed and unexposed.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	The blood constituents examined were red cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, carboxyhemoglobin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin, and albumin. Regression results are mainly presented with effect estimates and p-values (lacking standard errors or confidence intervals).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates used in the analyses were sex, race,age, cigarette smoking history, time of venipuncture,. Additional variables evaluated as potential covariates were date of examination, and intensity of acetone exposure within the reference plant.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	There is no direct information in this report on covrariate characterization, however it is likely that the main source of information is the health evaluation and/or company records.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_exposed_white women_aspartate aminotransferase-Hematological and Immune
HERO ID:	5240267

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Intensity of acetone exposure within the reference plant. was evaluated as potential important covariate for blood constituents. The study report also indicates that exposure to other chemicals (e.g., methanol, acetone) was possible at the South Carolina plant.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design (retrospective cohort) and analyses were adequate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study included 266 exposed and 251 unexposed workers.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Statistical analyses are briefly described and likely to be conceptually reproducible given access to the analytic data.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Regression analyses and covariates considered are briefly described. There is no detail on model assumptions, model selection, or sensitivity analyses.
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 67: **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_DCM_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

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

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_DCM_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

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

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_DCM_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

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

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Study Citation:	Heineman, EF; Cocco, P; Gomez, MR; Dosemeci, M; Stewart, PA; Hayes, RB; Zahm, SH; Thomas, TL; Blair, A (1994). Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer American Journal of Industrial Medicine, 26(2), 155-169
Data Type:	Case-control_Occupational_DCM_AstrocyticBrainCancer_Q2-Cancer
HERO ID:	194131

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

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 68: **Ott et al. 1983: Evaluation of Hepatic Outcomes**

Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_total bilirubin_exposed_white women-Hepatic
HERO ID:	5240267

Domain	Metric	Rating†	MWF⋆	Score	Comments††
Domain 1: Study Participation					
	Metric 1: Participant selection	Medium	× 0.4	0.8	Study population was described in a methodological paper covering all aspects of the health surveillance project (Ref ID: 24149). Briefly, exposed participants were employees of a cellulose triacetate and cellulose diacetate fiber manufacturing plant in Rock Hill, South Carolina, exposed to were exposed to methylene chloride, acetone, and methanol, the methanol being present in a ratio of approximately 1 to 10 to methylene chloride. Unexposed participants were from a non-DCM-exposure acetate fiber manufacturing plant in Narrows, Virginia, who were exposed to similar concentrations of acetone but were not exposed to methylene chloride or ethanol. Participation in the health examination was on a volunteer basis and was estimated to cover about 61 % of the employees in the plant with methylene chloride exposure and 55 % of the employees in the reference plant.
	Metric 2: Attrition	Medium	× 0.4	0.8	Participation in the health examination was on a volunteer basis, with 266 exposed and 251 unexposed employees. There was no other specific mention of attrition reported/addressed in this report.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_total bilirubin_exposed_white women-Hepatic
HERO ID:	5240267

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 3:	Comparison Group	High	× 0.2	0.2	Details on participants (e.g., race, sex, age, and cigarette smoking.) were reported in the study report. Cigarette smoking varied with sex and race; however, there were no differences between the exposed and reference groups within the sex-by race subgroups. Among the exposed volunteers only 9 of 266 (3.4 %) had been employed less than one year and 169 (63.5 %) had been employed for more than five years at the time of the examination. In the reference plant, the percentages were 13.9 and 55.1 %, respectively. In addition, the regression analyses controlled for sex, race, age, cigarette smoking history, time of venipuncture. The authors acknowledge potential differences in the collection and handling of the blood specimens between exposed and unexposed workers that might bias the results, and hence did not perform direct comparisons of laboratory findings between exposed and unexposed.
Domain 2: Exposure Characterization						
	Metric 4:	Measurement of Exposure	High	× 0.4	0.4	The results of the industrial hygiene monitoring of the work environment are detailed in another report (Ref ID: 29149.) (Eight-hr TWA concentrations and peak concentrations were determined for both plants. Personal air monitoring (>350 samples), area sampling (170 samples), and short-term excursion sampling (20 samples) were performed over the course of a 3.5-month survey period in late 1977-early 1978. Details of the personal air sampling methods are described in an appendix to the study report.). Median time weighted average concentrations of methylene chloride for an 8-h day were presented in this report for exposed employees in various work areas.
	Metric 5:	Exposure levels	Medium	× 0.2	0.4	Occupational DCM exposure was categorized into four levels across a sufficient range: unexposed, 60 and 140 ppm DCM, 280 ppm, and 475 ppm DCM.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_total bilirubin_exposed_white women-Hepatic
HERO ID:	5240267

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 6:	Temporality	High	× 0.4	0.4	Among the exposed volunteers only 3.4 % had been employed less than one year and 63.5% had been employed for more than five years at the time of the examination. In the reference plant, the percentages were 13.9 and 55.1%. Since the outcomes in the study concern hematological evaluations, the study presents an appropriate temporality between exposure and outcome.
Domain 3: Outcome Assessment						
	Metric 7:	Outcome measurement or characterization	Medium	× 0.667	1.33	Analyses of blood samples for both exposed ad unexposed employees were performed by the same laboratory. Analyses are described in detail and are adequate. However, there were differences in the collection (posture, time of day, altitude) and handling of the blood specimens between exposed and unexposed workers that might bias the results, and hence did not perform direct comparisons of laboratory findings between exposed and unexposed.
	Metric 8:	Reporting Bias	Medium	× 0.333	0.67	The blood constituents examined were red cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, carboxyhemoglobin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin, and albumin. Regression results are mainly presented with effect estimates and p-values (lacking standard errors or confidence intervals).
Domain 4: Potential Counfounding/Variable Control						
	Metric 9:	Covariate Adjustment	High	× 0.5	0.5	Covariates used in the analyses were sex, race,age, cigarette smoking history, time of venipuncture,. Additional variables evaluated as potential covariates were date of examination, and intensity of acetone exposure within the reference plant.
	Metric 10:	Covariate Characterization	Low	× 0.25	0.75	There is no direct information in this report on covrariate characterization, however it is likely that the main source of information is the health evaluation and/or company records.

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Study Citation:	Ott, MG; Skory, LK; Holder, BB; Bronson, JM; Williams, PR (1983). Health evaluation of employees occupationally exposed to methylene chloride: Clinical laboratory evaluation Scandinavian Journal of Work, Environment and Health, 9(1) 17-25
Data Type:	DCM_occupational_retrospective cohort_total bilirubin_exposed_white women-Hepatic
HERO ID:	5240267

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	Metric 11:	Co-exposure Confounding	Low	× 0.25	0.75	Intensity of acetone exposure within the reference plant. was evaluated as potential important covariate for blood constituents. The study report also indicates that exposure to other chemicals (e.g., methanol, acetone) was possible at the South Carolina plant.
Domain 5: Analysis						
	Metric 12:	Study Design and Methods	Medium	× 0.4	0.8	Study design (retrospective cohort) and analyses were adequate for the research question.
	Metric 13:	Statistical power	Medium	× 0.2	0.4	The study included 266 exposed and 251 unexposed workers.
	Metric 14:	Reproducibility of analyses	Medium	× 0.2	0.4	Statistical analyses are briefly described and likely to be conceptually reproducible given access to the analytic data.
	Metric 15:	Statistical models	Low	× 0.2	0.6	Regression analyses and covariates considered are briefly described. There is no detail on model assumptions, model selection, or sensitivity analyses.
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 69: **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:	>175 ppm*yrs DCM_B-NHL-Cancer-Cancer
HERO ID:	194429

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

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Study Citation:	Seidler, A; Möhner, M; Berger, J; Mester, B; Deeg, E; Elsner, G; Nieters, A; Becker, N (2007). Solvent exposure and malignant lymphoma: A population-based case-control study in Germany Journal of Occupational Medicine and Toxicology, 2 2
Data Type:	>175 ppm*yrs DCM_B-NHL-Cancer-Cancer
HERO ID:	194429

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

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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:	>175 ppm*yrs DCM_B-NHL-Cancer-Cancer
HERO ID:	194429

Domain	Metric		Rating†	MWF⋆	Score	Comments††
	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 and controls.
	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 70: **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 DCM-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 DCM-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 DCM-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