United States
Environmental Protection Agency

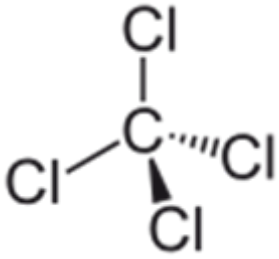
Office of Chemical Safety and
Pollution Prevention

# Final Risk Evaluation for Carbon Tetrachloride

## Systematic Review Supplemental File:

## Data Quality Evaluation of Human Health Hazard Studies – Epidemiological Studies

## CASRN: 56-23-5




*October 2020*

# Table Listing

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

| | | | | | | |
|---|---|---|---|---|---|---|
| Study Citation: | P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966 | | | | | |
| Data Type: | Davis_CCl4_controlled_inhalation_exposure_clinicalobs-Acute Toxicity/Poisoning | | | | | |
| HERO ID: | 3611 | | | | | |
| Domain | | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | Low | × 0.4 | 1.2 | Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided. |
| | Metric 2: | Attrition | Medium | × 0.4 | 0.8 | Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described. |
| | Metric 3: | Comparison Group | Low | × 0.2 | 0.6 | No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear. |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Low | × 0.4 | 1.2 | The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments. |
| | Metric 5: | Exposure Levels | Low | × 0.2 | 0.6 | Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration. |
| | Metric 6: | Temporality | Low | × 0.4 | 1.2 | This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride. |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome Measurement or Characterization | Low | × 0.667 | 2 | Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment. |
| | Metric 8: | Reporting Bias | Medium | × 0.333 | 0.67 | Outcomes were outlined throughout the paper and clinical observations were described. |
| Domain 4: Potential Confounding/Variable Control | | | | | | |

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

| Domain | | Metric | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 9: | Covariate Adjustment | Low | × 0.667 | 2 | A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for. |
| | Metric 10: | Covariate Characterization | Not Rated | NA | NA | Covariates, besides age, were not collected. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.333 | 0.67 | There was no indication of co-exposures being present or measured for during the controlled inhalation exposure. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.5 | 1 | This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results. |
| | Metric 13: | Statistical Power | Medium | × 0.25 | 0.5 | Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution. |
| | Metric 14: | Reproducibility of Analyses | Low | × 0.25 | 0.75 | The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported. |
| | Metric 15: | Statistical Models | Not Rated | NA | NA | Results were compared to reference values and described qualitatively only. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination‡ | | | Low | | 2.6 | |
| Extracted | | | Yes | | | |

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | This study consisted of an extended follow-up of the Hill Air Force Base occupational cohort through 2000. The cohort is composed of former civilian employees, who worked at this aircraft maintenance facility for at least 1 year between January 1, 1952 and December 31, 1956 (n=14,455). The key elements of the study design were reported. Selection into the study was not likely to be biased. The cohort was described in detail in previous publications (Spirtas et al., 1991; Stewart et al., 1991; Blair et al., 1998). |
| | Metric 2: | Attrition | High | × 0.4 | 0.4 | There was no loss of subjects to follow-up reported in the study (as of December 31, 2000, 8,580 subjects had died and 5,875 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 | | | | | | |
| | 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. |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Low | × 0.5 | 1.5 | Adjustments were made for age, race, and gender. However, there was indirect evidence that socioeconomic status (SES) was considerably different among exposed and non-exposed populations. The proportion of non-exposed persons that were salaried was 61% compared to < 1% in the exposed cohort, suggesting a dissimilar SES. This difference may affect the results for some specific cancer types/diseases. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Confounders were assessed using reliable methods (database of employees and NDI). However, other than age, gender, and race, data on other factors (disease history, SES) were not available. |
| | Metric 11: | Co-exposure Confounding | Low | × 0.25 | 0.75 | The study evaluated exposure to CCl4 and various other chemicals. Exposures were not mutually exclusive; therefore, it was not possible to evaluate the risk of death from exposure to a singular chemical while controlling for exposure to other chemicals. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The cohort design and calculation of hazard ratios were appropriate for determining the association between exposure to TCE, Perc, CCl4 and DCM, and all-cause, cancer, and non-cancer mortality. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | The cohort was large (adequate for statistical analyses). Despite the relatively large size of the cohort, the number of cases for many causes of death was small to evaluate associations. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | The analysis (exposure estimation and statistical modeling) is described in sufficient detail to understand what was done and is conceptually reproducible. |
| | 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 | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | This study consisted of an extended follow-up of the Hill Air Force Base occupational cohort through 2000. The cohort is composed of former civilian employees, who worked at this aircraft maintenance facility for at least 1 year between January 1, 1952 and December 31, 1956 (n=14,455). The key elements of the study design were reported. Selection into the study was not likely to be biased. The cohort was described in detail in previous publications (Spirtas et al., 1991; Stewart et al., 1991; Blair et al., 1998). |
| | Metric 2: | Attrition | High | × 0.4 | 0.4 | There was no loss of subjects to follow-up reported in the study (as of December 31, 2000, 8,580 subjects had died and 5,875 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 | | | | | | |
| | 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. |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Low | × 0.5 | 1.5 | Adjustments were made for age, race, and gender. However, there was indirect evidence that socioeconomic status (SES) was considerably different among exposed and non-exposed populations. The proportion of non-exposed persons that were salaried was 61% compared to < 1% in the exposed cohort, suggesting a dissimilar SES. This difference may affect the results for some specific cancer types/diseases. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Confounders were assessed using reliable methods (database of employees and NDI). However, other than age, gender, and race, data on other factors (disease history, SES) were not available. |
| | Metric 11: | Co-exposure Confounding | Low | × 0.25 | 0.75 | The study evaluated exposure to CCl4 and various other chemicals. Exposures were not mutually exclusive; therefore, it was not possible to evaluate the risk of death from exposure to a singular chemical while controlling for exposure to other chemicals. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The cohort design and calculation of hazard ratios were appropriate for determining the association between exposure to TCE, Perc, CCl4 and DCM, and all-cause, cancer, and non-cancer mortality. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | The cohort was large (adequate for statistical analyses). Despite the relatively large size of the cohort, the number of cases for many causes of death was small to evaluate associations. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | The analysis (exposure estimation and statistical modeling) is described in sufficient detail to understand what was done and is conceptually reproducible. |
| | 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 | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 11: | Co-exposure Confounding | Low | × 0.25 | 0.75 | Exposure to other chlorinated solvents was also assessed with JEM. Study authors note that they report the percentages of control subjects exposed to these chemicals alone and to two of these chemicals and provide an estimate of the association with multiple myeloma for subjects who were exposed to all four (TCE, CCl4, DCM, PERC). But analyses were not adjusted for these exposures. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The case-control study design chosen was appropriate for the exposure and outcome of interest. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | The overall number of cases and controls are adequate to detect an effect. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | The description of the analysis is sufficient to understand what has been done. |
| | Metric 15: | Statistical Models | Medium | × 0.2 | 0.4 | There is sufficient information on how the ORs were calculated. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination[‡] | | | High ⟶ Medium[§] | | 1.6 | |
| Extracted | | | Yes | | | |

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

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

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| 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, 22,098 controls. Reasons for excluding subjects were clearly detailed. There was minimal loss of subjects reported in results (325 cases/22,101 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)."<br><br>The erratum states that the authors did not use background exposures when determining the quintiles in 1996, so the quintiles are somewhat different than as reported. |
| | Metric 5: Exposure Levels | Medium | × 0.2 | 0.4 | Exposure levels ranged from 0.0006-41.9 ug/m$^3$, 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 | | | | | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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: 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 mothers from the study. |
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | All measured outcomes were outlined in the methods, and information could be fully extracted for analysis. Some information was provided in supplemental information. |
| Domain 4: Potential Confounding/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 | | | | | | |
| | 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. |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | |
| | Metric 1: Participant Selection | High | × 0.4 | 0.4 | Key elements of study are reported: participants were selected from the National Academy of Sciences/National Research Council WWII Veteran Twins Registry, an all-male twin cohort. Cases were selected through telephone screening of the entire reachable cohort; concurrently, searches of VA medical databases, the Health Care Financing Administration, and the National Death Index were undertaken to identify other cases. It was stated that age at PD diagnosis or interview was similar between those pairs that completed the interview and those pairs that did not complete the interview. As such, the reported information indicates selection in or out of the study and participation is not likely to be biased. |
| | Metric 2: Attrition | Medium | × 0.4 | 0.8 | Occupational histories were completed by 63.6% of twins with PD and 60.1% of twins without PD leading to a final total of 99 twin pairs. This is moderate exclusion from the analysis sample. Rates of completion were similar between twins with and without PD. |
| | Metric 3: Comparison Group | High | × 0.2 | 0.2 | In both paired and unpaired analysis, smoking was an included covariate. In unpaired analysis, an age index was also adjusted for. Other important demographic factors in the paired analysis would be highly controlled as the analysis was of twin pairs. The type of twin (monozygotic or dizygotic) was also included as a covariate in the paired analysis. |
| Domain 2: Exposure Characterization | | | | | |
| | Metric 4: Measurement of Exposure | Low | × 0.4 | 1.2 | This method relies on self-reported occupational histories. There may be some misclassification due recall bias in addition to any bias introduced by accuracy of response for participant proxies. |
| | Metric 5: Exposure Levels | Medium | × 0.2 | 0.4 | For logistic regression using duration of exposure or cumulative exposure indices, ORs addressed risk associated with a one tertile change in the respective marker of exposure. This represents three or more levels of exposure.<br>For the Ever/Never analysis, only two levels of exposure are used. Ever exposure was defined as exposure to a solvent for at least 2% of work time or 1 hour per week. |

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 6: | Temporality | High | × 0.4 | 0.4 | This study investigated occupational exposures beginning at a young age and their association with Parkinson's Disorder later in life. The interval between exposure and outcome measurement is appropriate to measure this association. |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome Measurement or Characterization | High | × 0.667 | 0.67 | Cases were identified through searches of records in the Department of Veteran's Affairs, the Health Care Financing Administration, and the National Death Index. Participants suspected of having Parkinson's underwent in-person examination with a trained movement disorder specialist. This outcome assessment represents a well-established method. Both neurologists followed standard criteria for PD diagnosis and made their diagnosis by video. There is no mention of blinding during this evaluation., although participants were unaware of study hypotheses. |
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | All outcomes mentioned in the abstract, introduction, and methods were presented clearly in the results. ORs are contained in easily extractable tables, including number of participants used in each analysis accompanied by summary measures of exposure in the analyses of cumulative exposure. |
| Domain 4: Potential Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | High | × 0.5 | 0.5 | In the paired analysis (paired twins), the conditional logistic regression model included terms for respondent type (monozygotic/dizygotic) and smoking. In the unpaired analysis, respondent type, smoking, and age were all included in the analysis. Models including head injury were stated to be similar to the results shown. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | In some cases, questionnaires/surveys were completed by proxies such as a spouse or sibling. For several covariates including head injury or smoking, this is not a well-established method, but there was little evidence that the method had poor validity. It should also be noted that results were presented for an analysis excluding twin pairs using proxy respondents. The results of this analysis were in agreement with the main analyses. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Co-exposures to other solvents was measured in this study. Overall, six different solvents were included in the exposure analysis: TCE, PERC, CCl4, n-hexane, toluene, and xylene. Several analysis strategies were presented to elucidate any effects of co-exposures. Analyses were done for the relationship between PD and exposure to TCE or PERC as well as an analysis of the relationship between exposure to any of the 4 solvents, excluding TCE and PERC. |

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The retrospective study design is appropriate to investigate long-term or chronic exposure to industrial solvents and development of the neurodegenerative Parkinson's Disease. Appropriate statistical methods (i.e., conditional logistical modeling) were employed to analyze the matched data. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | There is an adequate number of discordant twin pairs (n=99) for the pairwise analysis and an adequate number of participants in the unpaired analysis (n=126 cases exposed, n=110 controls exposed) to detect an effect in the exposed population. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | The description of the analysis is sufficient to reproduce the results if given original data. No apparent issues. |
| | Metric 15: | Statistical Models | Medium | × 0.2 | 0.4 | The method (logistic regression modeling) of calculating risk is transparent and appropriate. Rationale for variable selection is stated. Model assumptions do not appear to be violated. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

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

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | High rating: all of the study's measured outcomes are reported, effect estimates reported with confidence interval; number of exposed reported for each analysis. |
| Domain 4: Potential Confounding/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 o f 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, forever/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. |
| | 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 | | | | | | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | |
| | Metric 1: Participant Selection | High | × 0.4 | 0.4 | Subjects were selected from the same area during the same time frame. Cases were identified through participating medical facilities and neurosurgeon offices. Controls were identified from state driver's license records. 91.5% of cases or their next of kin participated and 70.4% of controls participated. Key elements of the study design are reported.. |
| | Metric 2: Attrition | High | × 0.4 | 0.4 | Study population consisted of 1,175 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). |
| | 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. |

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | Medium | × 0.4 | 0.8 | This was a population based case-control study in which subjects were restricted to Canadian citizens who were residents in the Montreal metropolitan area. This report did not describe case ascertainment, but cited references (Ramanakumar et al., 2011; Parent et al., 2007) 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 | | | | | | |
| | Metric 7: | Outcome Measurement or Characterization | High | × 0.667 | 0.67 | Cases were histologically confirmed. |

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

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

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

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 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 Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | High | × 0.5 | 0.5 | Confounders considered in adjusted analysis: age, sex, country, current smoking habit (cigarettes/day), alcohol intake, BMI, and education level. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Primary confounders were assessed using a less-established method with no reporting of validation against well-established methods. Specifically, covariates were determined from interviews. Next of kin completed interviews for 4 cases and 95 controls. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Co-exposures were not accounted for in this analysis, but no direct evidence that co-exposures differ across cases and controls. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | Case-control design was appropriate for investigating chlorinated solvents and a rare disease such as MF, and appropriate statistical methods (logistic regression) were employed to analyze data. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | 100 cases and 2,846 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 | |

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

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

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

| Domain | Metric | | Rating† | MWF* | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 7: | Outcome Measurement or Characterization | Medium | × 0.667 | 1.33 | Outcome assessed using International Classification of Childhood Cancer, version3 (ICCC-3) code 041 as reported in the California Cancer Registry, but diagnosis was not confirmed. It is not clear if absence of cancer diagnosis in controls was confirmed. |
| | Metric 8: | Reporting Bias | Medium | × 0.333 | 0.67 | For CCl4, both OR for IQR at different buffer sizes (2.5 km, 3 km, 4 km, and 5 km) and for each quartile (vs. 1st quartile) are reported; however, when reporting results for each quartile it is not clearly stated whether or not these are for the 5 km buffer size. For Perc and TCE, OR per interquartile increase reported only for two buffer sizes (2.5 km and 5 km) and results for each quartile are not reported. |
| Domain 4: Potential Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Medium | × 0.5 | 1 | Selection of potential confounders was based on literature review and relationship in sample between demographic and perinatal factors and outcome. Several relevant covariates were considered and retained in final a nalysis [ mother's age, mother's race/ethnicity, birth year, socioeconomic indicator (method of payment for prenatal care)]. However, other potential confounders noted as relevant by the authors in the Introduction section (e.g., birthweight, maternal and paternal alcohol intake and smoking status, paternal occupational exposures) were not evaluated. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Demographic and socio-economic data obtained from birth certificates ( mother's age, mother's race/ethnicity, birth y ear) and US Census data (socio-economic data). SES was assessed through both insurance type and census tract data. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Co-exposures to pollutants were measured but not adjusted for in the regression models. Authors state that, according to cited study (Heck et al., in press), they found that Perc was highly correlated with traffic-related toxics, while other air toxics "were not as strongly correlated with each other." No differences expected between exposure groups. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | A case-control study design was used to evaluate the relationship between prenatal exposure to air toxics (CCl4, PERC, TCE) and neuroblastoma (childhood cancer). Logistic regression was used to determine OR for IQR of increase in exposure to each air toxic and, for CCl4, the OR for each quartile relative to the lowest quartile of exposure was also evaluated. |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | Statistically significant effects were determined for some air toxics using each respective sample size, but no statistical power was reported. For CCl4, the analysis included 40 cases and 7,443 controls, for Perc 67 cases and 12,041 controls were included and for TCE 67 cases and 12,086 controls were included, for a 5 km radius around air pollution monitors. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | Detailed description of statistical analysis provided. The covariates adjusted for in the logistic regression explicitly stated for each model. Number of cases/controls used in each analysis presented for 5 km and 2.5 km radii. |
| | Metric 15: | Statistical Models | Medium | × 0.2 | 0.4 | Logistic regression appropriately used to determine ORs. Study presents models adjusted just for birth year, or for all confounders that were collected (birth year, maternal age, maternal race/ethnicity, and method of payment - SES). Potential confounders identified from literature and in a previous study (Heck 2009). |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

| | | | | | | |
|---|---|---|---|---|---|---|
| Study Citation: | P. A. Davis (1934). Carbon tetrachloride as an industrial hazard Journal of the American Medical Association, 103(13,13), 962-966 | | | | | |
| Data Type: | Davis_CCl4_controlled_inhalation_exposure_hematology-Hematological and Immune | | | | | |
| HERO ID: | 3611 | | | | | |
| Domain | | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | Low | × 0.4 | 1.2 | Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided. |
| | Metric 2: | Attrition | Medium | × 0.4 | 0.8 | Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described. |
| | Metric 3: | Comparison Group | Low | × 0.2 | 0.6 | No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear. |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Low | × 0.4 | 1.2 | The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments. |
| | Metric 5: | Exposure Levels | Low | × 0.2 | 0.6 | Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration. |
| | Metric 6: | Temporality | Low | × 0.4 | 1.2 | This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride. |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome Measurement or Characterization | Low | × 0.667 | 2 | Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment. |
| | Metric 8: | Reporting Bias | Medium | × 0.333 | 0.67 | Outcomes were outlined throughout the paper and clinical observations were described. |
| Domain 4: Potential Confounding/Variable Control | | | | | | |

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

| Domain | | Metric | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 9: | Covariate Adjustment | Low | × 0.667 | 2 | A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for. |
| | Metric 10: | Covariate Characterization | Not Rated | NA | NA | Covariates, besides age, were not collected. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.333 | 0.67 | There was no indication of co-exposures being present or measured for during the controlled inhalation exposure. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.5 | 1 | This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results. |
| | Metric 13: | Statistical Power | Medium | × 0.25 | 0.5 | Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution. |
| | Metric 14: | Reproducibility of Analyses | Low | × 0.25 | 0.75 | The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported. |
| | Metric 15: | Statistical Models | Not Rated | NA | NA | Results were compared to reference values and described qualitatively only. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination‡ | | | Low | | 2.6 | |
| Extracted | | | Yes | | | |

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

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

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

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

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | Sufficient details were provided. |
| Domain 4: Potential Confounding/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 | |
| 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | |
| | Metric 1: Participant Selection | High | × 0.4 | 0.4 | California Teachers Study including active and retired female teachers and administrators were enrolled in the California State Teachers Retirement System and completed a questionnaire. Study population was comprised on 5,676 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. |
| | 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 | | | | | |

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

| Domain | Metric | | Rating† | MWF* | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 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 Confounding/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 for 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 5,676 women. There were enough subjects to detect effects for some chemicals and for some trends. |
| | 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 | |

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | 296 cases of head and neck squamous cell carcinomas and 775 controls were drawn from ICARE, a French population-based case-control study (Luce 2011). 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 | | | | | | |
| | 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 Confounding/Variable Control | | | | | | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 9: | Covariate Adjustment | High | × 0.5 | 0.5 | Analyses adjusted for geographical area, age, smoking status, tobacco consumption (pack-years) and alcohol consumption. Interaction terms for smoking and alcohol were also included. SES considered with last occupation and longest occupation, but did not impact ORs and were not presented. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | In person interviews with standardized questionnaire. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Exposures to TCE, Perc, and DCM were strongly correlated. Rather than adjusting for co-exposures, exclusive exposure to individual and combinations of chlorinated solvents were analyzed. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | Study design was appropriate for the research questions. Logistic regression was used appropriately to estimate ORs and CIs. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | The cohort contains sufficient participants to detect an effect for TCE, perc, and DCM. Insufficient data for carbon tetrachloride, so it was excluded from analysis beyond an ever/never OR. For analysis involving ever exposure to CCL4, the number of cases and controls is relatively small. |
| | Metric 14: | Reproducibility of Analyses | Low | × 0.2 | 0.6 | Although the process of creating the regression models was described in detail, adjustments used for covariates were not explicitly stated. |
| | Metric 15: | Statistical Models | Medium | × 0.2 | 0.4 | Odds ratios and 95% confidence intervals were determined using unconditional logistic regression adjusted for key covariates. Models were transparent and assumptions were met. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination[‡] | | | Medium | | 1.8 | |
| Extracted | | | Yes | | | |

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|

[⋆] MWF = Metric Weighting Factor

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

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

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

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

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | Cohort of aging men of Japanese ancestry born between and 1900 and 1919 and between age 45-68 at time of initial examination (1965-1968). Participants identified through WWII selective service records. Of 14,426 men estimated to be Oahu residents, 11,148 were located and 8,006 completed a baseline examination (>70% of target population). |
| | Metric 2: | Attrition | High | × 0.4 | 0.4 | Participants followed through series of six follow-up examinations from 1968-2000, and less than 1% lost to follow-up (5/8,006). Occupational exposure data available for entire cohort based on information collected in first and third examinations. |
| | Metric 3: | Comparison Group | High | × 0.2 | 0.2 | Participants identified through WWII selective service records. All were born between 1900-1919 and were aged 45-68 at time of initial examination (1965-1968). There is no evidence that participants were not similar in health status. |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Low | × 0.4 | 1.2 | Participants reported present and usual jobs and years worked at these jobs during the first and third examinations. Jobs were coded according to U.S. Bureau of the Census and unique occupation/industry combinations were identified and independently assessed by three industrial hygienists. Likelihood of exposure was assigned by consensus as none, low, medium, and high. An intensity score was calculated using the likelihood of exposure multiplied by number of years worked in usual occupation. |
| | Metric 5: | Exposure Levels | Medium | × 0.2 | 0.4 | Exposure levels categorized as none, low or medium, and high, but corresponding numerical levels not presented. |
| | Metric 6: | Temporality | Medium | × 0.4 | 0.8 | Exposure based on responses during first and third examinations (1965-1968 and 1971-1974). GBM developed during the follow-up periods between 1974-1995. However, unclear whether exposures fall within relevant exposure window for outcome. |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome Measurement or Characterization | High | × 0.667 | 0.67 | All GBM cases were confirmed by histological examination. The source of initial diagnosis was not reported, but is assumed to have come from follow-up examinations, hospital discharge records, and/or death certificates or searches of the National Death Index. |

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | HR and 95% CI reported for outcome outlined. Number of cases and non-cases also reported for each analysis. All outlined statistical analyses were reported with sufficient detail. |
| Domain 4: Potential Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Medium | × 0.5 | 1 | Adjustment methods not explicitly described, but were made for other risk factors included in the model (age, education, triceps skinfold, sugar consumption, coffee consumption, tea consumption, chest surgery, blood transfusion). |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Basic demographic, occupational and socioeconomic data, medical history (chest surgery, blood transfusion, herpes), and lifestyle factors including usual physical activity, smoking habits, alcohol intake, and dietary habits identified from questionnaires completed from the first three examinations (self-reported), but no report of validation. Exposure based on self-report of jobs and classification by independent industrial hygienists. Additional risk factors (e.g., tricep skinfold thickness) were assessed during the first three examinations, but no detailed description of methods provided. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Cases and non-cases were similar in exposure to solvents, pesticides, and metals. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The study design (prospective cohort) and statistical methods (including a multivariate analysis to estimate the hazard ratio associated with exposure to CCl4, using the Cox proportional hazards regression model) were appropriate for the research question. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | Cohort size (8,006) is sufficient to detect an effect, but only 9 cases resulting in low statistical power. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | Exact logistic regression relating to each potential risk factor was performed to obtain exact p-values which were then used to assess linear trend. Multivariate analysis performed using Cox proportional hazards regression model to estimate hazard ratio. |
| | Metric 15: | Statistical Models | Medium | × 0.2 | 0.4 | Model assumptions were described and met. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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

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

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Dow Chemical, Co 1992: Evaluation of Cancer Outcomes**

| | | | | | | |
|---|---|---|---|---|---|---|
| Study Citation: | Dow Chemical Company (1992). Nested case-control study of lung cancer among chemical workers | | | | | |
| Data Type: | Occupational_case control_CCl4_lung cancer_High Exposure-Cancer | | | | | |
| HERO ID: | 4215786 | | | | | |
| Domain | | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | Any former male employee that had one or more years of service between 1940 and Dec 31, 1980. Cases were those who expired of primary lung cancer prior to Dec 1980. Two controls groups were chosen, deceased (died after the case, not more than 5 years) and living (survived at least as long as the case, but could die later), chosen from all other members of the cohort without cancer. Ages were reported. All men. All control cases were matched for age, race, and year of hire to each case. |
| | Metric 2: | Attrition | High | × 0.4 | 0.4 | Numbers used in the study were explained in detail. 81.9% completed interviews - 734 subjects. |
| | Metric 3: | Comparison Group | High | × 0.2 | 0.2 | Controls were matched with cases on race, year of birth (+/- 5) and year of hire. |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Medium | × 0.4 | 0.8 | Employee's Dow work history record served as the starting point for categorizing occupation exposures of interest. Used work area and chemical and physical agent exposure profiles. Chemical and physical agent exposure profiles were developed by a certified industrial hygienist for each case and control. |
| | Metric 5: | Exposure Levels | Medium | × 0.2 | 0.4 | For carbon tetrachloride a degree of exposure ranking (high, moderate, or low) was assigned to each job. This was based on limited industrial hygiene monitoring data and therefore was not possible to estimate exposure |
| | Metric 6: | Temporality | Medium | × 0.4 | 0.8 | Interviews conducted in 1984 on all employed >1 year between 1940 and 1980 who were selected for study; onset of disease is estimated to be 3-5 years from exposure. Analysis was also completed with incorporation of a 15 year latency period |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome Measurement or Characterization | High | × 0.667 | 0.67 | Death certificates and hospital records when available. Cases must have bronchus, lung or respiratory system as underlying cause, contributing cause, or as other significant condition |
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | Ns, ORs, and 95% CIs reported |
| Domain 4: Potential Confounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | High | × 0.5 | 0.5 | Adjusted for smoking, vitamin A consumption, migration patterns, occupational exposures outside the facility, vitamin supplements, education level. Collected confounding variables by telephone interviews with subject or next of kin; age, race, year of hire, death (+/-5 yr) all considered |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Telephone interview to collect information on participants from participant or next of kin (not as accurate as primary data) |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Attempts were made to adjust for confounding exposures; these were collected from phone interviews (smoking status and duration, vitamin A intake, occupational exposures outside the facility, education level) |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The study design is appropriate for the population/outcomes studied. Eligible workers who worked at the plant for over 1 year between 1940-1980, those who died of or with respiratory disease were assessed for exposures to chemicals and development of lung cancer. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | 308 and 616-28 overlapping individuals; exposure determined from job titles and bucketed into high, medium and low exposures. Odds ratios determined for CCl4 exposure with 15 year latency and without regard to year of death as well as across levels of occupational exposure. |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | Methods are clearly laid out and can be reproduced. Cases and controls were compared with traditional stratification and conditional logistic regression. The observation period for each matched set ended at the time of each death of case. |
| | Metric 15: | Statistical Models | Low | × 0.2 | 0.6 | Statistical methods were not outlined, but indirect evidence shows they are adequate (OR reporting, confounder adjustments) |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination[‡] | | | High | | 1.5 | |
| Extracted | | | Yes | | | |

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|

⋆ MWF = Metric Weighting Factor

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

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

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

where High: $\geq 1$ to $< 1.7$; Medium: $\geq 1.7$ to $< 2.3$; Low: $\geq 2.3$ to $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Davis 1934: Evaluation of Renal Outcomes**

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | |
| | Metric 1: Participant Selection | Low | × 0.4 | 1.2 | Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided. |
| | Metric 2: Attrition | Medium | × 0.4 | 0.8 | Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described. |
| | Metric 3: Comparison Group | Low | × 0.2 | 0.6 | No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear. |
| Domain 2: Exposure Characterization | | | | | |
| | Metric 4: Measurement of Exposure | Low | × 0.4 | 1.2 | The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments. |
| | Metric 5: Exposure Levels | Low | × 0.2 | 0.6 | Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration. |
| | Metric 6: Temporality | Low | × 0.4 | 1.2 | This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride. |
| Domain 3: Outcome Assessment | | | | | |
| | Metric 7: Outcome Measurement or Characterization | Low | × 0.667 | 2 | Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment. |
| | Metric 8: Reporting Bias | Medium | × 0.333 | 0.67 | Outcomes were outlined throughout the paper and clinical observations were described. |
| Domain 4: Potential Confounding/Variable Control | | | | | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 9: | Covariate Adjustment | Low | × 0.667 | 2 | A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for. |
| | Metric 10: | Covariate Characterization | Not Rated | NA | NA | Covariates, besides age, were not collected. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.333 | 0.67 | There was no indication of co-exposures being present or measured for during the controlled inhalation exposure. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.5 | 1 | This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results. |
| | Metric 13: | Statistical Power | Medium | × 0.25 | 0.5 | Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution. |
| | Metric 14: | Reproducibility of Analyses | Low | × 0.25 | 0.75 | The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported. |
| | Metric 15: | Statistical Models | Not Rated | NA | NA | Results were compared to reference values and described qualitatively only. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination[‡] | | | Low | | 2.6 | |
| Extracted | | | Yes | | | |

[⋆] MWF = Metric Weighting Factor

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

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

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

where High: $\geq 1$ to $< 1.7$; Medium: $\geq 1.7$ to $< 2.3$; Low: $\geq 2.3$ to $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Davis 1934: Evaluation of Cardiovascular Outcomes**

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | |
| | Metric 1: Participant Selection | Low | × 0.4 | 1.2 | Eight controlled experiments were conducted in total. Each experiment consisted of three to four individuals and one group of individuals was used for two experiments. Age and basic clinical measurements were provided for each subject. Some subjects may have been used for multiple experiments, but this is unclear. The method of recruitment was not described and demographic details, including sex, were not provided. |
| | Metric 2: Attrition | Medium | × 0.4 | 0.8 | Subjects differed for all experiments but one. The reason for this change from experiment to experiment is not fully described. |
| | Metric 3: Comparison Group | Low | × 0.2 | 0.6 | No control group was used in this study. The measured outcomes were presumably compared to reference values, but the details are not clear. |
| Domain 2: Exposure Characterization | | | | | |
| | Metric 4: Measurement of Exposure | Low | × 0.4 | 1.2 | The inhalation chamber was adequately described. The method of creating the inhalation exposure and the method to monitor the exposure level were not described. Source and purity of the test article are not reported. Exposure duration varied by exposure level. The seventh experiment described determining the carbon tetrachloride concentration by the alcohol potassium hydroxide and combustion method, but it is unclear if this was used for other experiments. |
| | Metric 5: Exposure Levels | Low | × 0.2 | 0.6 | Multiple exposure levels were examined in this study including 76 ppm, 158 ppm, 317 ppm, 1191 ppm, 2300 ppm and additional unreported levels, but exposure duration varied by exposure concentration. |
| | Metric 6: Temporality | Low | × 0.4 | 1.2 | This study was a controlled inhalation exposure. The timing of outcome measurement was not fully described in the text and remains unclear, although it is presumed that measurements were taken after controlled exposure to carbon tetrachloride. |
| Domain 3: Outcome Assessment | | | | | |
| | Metric 7: Outcome Measurement or Characterization | Low | × 0.667 | 2 | Clinical observations were described, if present. Hematology, urinalysis, and vital measurements were taken, but the methods or other details on outcome measurement were not reported. It was not reported whether outcome investigators were blinded to exposure during treatment. |
| | Metric 8: Reporting Bias | Medium | × 0.333 | 0.67 | Outcomes were outlined throughout the paper and clinical observations were described. |
| Domain 4: Potential Confounding/Variable Control | | | | | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 9: | Covariate Adjustment | Low | × 0.667 | 2 | A statistical analysis was not conducted. Age of the test subjects was provided, but no other demographic information was presented or adjusted for. |
| | Metric 10: | Covariate Characterization | Not Rated | NA | NA | Covariates, besides age, were not collected. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.333 | 0.67 | There was no indication of co-exposures being present or measured for during the controlled inhalation exposure. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.5 | 1 | This study utilized an inhalation chamber to examine the effects of acute inhalation exposures to carbon tetrachloride. No concurrent control group was used and clinical measurements were presumably compared to reference standards. No statistical analysis was applied to the results. |
| | Metric 13: | Statistical Power | Medium | × 0.25 | 0.5 | Three to four subjects were used in each controlled inhalation experiment. This is a low number of individuals per experiment and results should be interpreted with caution. |
| | Metric 14: | Reproducibility of Analyses | Low | × 0.25 | 0.75 | The inhalation chamber is described, but the method of used to achieve the inhalation exposure and ensure maintenance of an accurate dose are not described. Also, timings of exposure and measured outcomes were not reported. |
| | Metric 15: | Statistical Models | Not Rated | NA | NA | Results were compared to reference values and described qualitatively only. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination[‡] | | | Low | | 2.6 | |
| Extracted | | | Yes | | | |

[⋆] MWF = Metric Weighting Factor

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

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

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

where High: $\geq 1$ to $< 1.7$; Medium: $\geq 1.7$ to $< 2.3$; Low: $\geq 2.3$ to $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Siemiatycki 1991: Evaluation of Cancer Outcomes**

| | | | | | | |
|---|---|---|---|---|---|---|
| Study Citation: | Siemiatycki, J (1991). Risk factors for cancer in the workplace | | | | | |
| Data Type: | CCL4_worker andy exposure_rectal cancer-Cancer | | | | | |
| HERO ID: | 157954 | | | | | |
| Domain | | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | Of the 4,576 eligible male cases from the Montreal metropolitan area that were ascertained between 1979-1985, 3,730 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 sub-group 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. Non-responses due to refusal, death, no next of kin found, patient discharged, no valid address, psychiatric cases, no translator, or physician refusal. |
| | Metric 3: | Comparison Group | High | × 0.2 | 0.2 | Population controls, hospital controls and cancer controls (cancer control preferred). Baseline characteristics were collected from participants and adjusted for. Cases and controls were similar in that they were selected from Montreal, Canada, between 35-70 years old, male and recruited from 1979-1985. |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Low | × 0.4 | 1.2 | Exposure determined by questionnaire, no occupational records. Chemist-hygienists interview consultants to better grasp the workings of particular industries, occupations were selected and coded as low medium or high concentrations of exposure to a host of chemicals based on job title. |
| | Metric 5: | Exposure Levels | Medium | × 0.2 | 0.4 | Any or substantial exposure was assigned to each job title and patients were assigned to one of the two categories for analysis. Assignments made by a chemist-hygienist. |
| | Metric 6: | Temporality | Low | × 0.4 | 1.2 | Cases aged 35-70, time since first exposure not estimated; study was initiated in 1979 with exposures occurring before or between 1945-1975. |
| Domain 3: Outcome Assessment | | | | | | |
| | 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 Confounding/Variable Control | | | | | | |

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

| Domain | | Metric | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 9: | Covariate Adjustment | High | × 0.5 | 0.5 | For each association between occupational exposure and cancer type, adjustments included age, height, place of birth, and race. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Confounders based on literature and questionnaire data. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | Adjustments for other occupational exposure types, smoking, and alcohol intake were made. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | This is a case-control study that collected cancer type and lifetime occupational history from cancer patients to determine if occupational history effected cancer risk. |
| | Metric 13: | Statistical Power | Medium | × 0.2 | 0.4 | Table 1 (PDF page 61, in text page 142) results, selected for associations where power was adequate (# participants and at least 2% exposure). DCM was included in Table 2 which shows elevated ORs only (irrespective of power to detect excess risk). |
| | Metric 14: | Reproducibility of Analyses | Medium | × 0.2 | 0.4 | Analysis was fully described and a Mantel-Haenszel analysis was performed to analyze odds ratios for the data. |
| | Metric 15: | Statistical Models | Medium | × 0.2 | 0.4 | Method was transparent. A Mantel-Haenszel analysis was performed to analyze odds ratios for the data. P-values were computed by the Mantel-Haenszel chi-square test. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect Biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker Stability | | NA | NA | |
| | Metric 20: | Sample Contamination | | NA | NA | |
| | Metric 21: | Method Requirements | | NA | NA | |
| | Metric 22: | Matrix Adjustment | | NA | NA | |
| Overall Quality Determination‡ | | | Medium | | 1.7 | |
| Extracted | | | Yes | | | |

⋆ MWF = Metric Weighting Factor

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

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

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

where High: $\geq 1$ to $< 1.7$; Medium: $\geq 1.7$ to $< 2.3$; Low: $\geq 2.3$ to $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Heineman et al., 1994: Evaluation of Cancer Outcomes**

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

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

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 | | | | | | |
| | 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 Confounding/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. |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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. |
| | 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Seidler et al., 2007: Evaluation of Cancer Outcomes**

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

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

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

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

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

| Domain | Metric | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|
| 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Dosemeci et al., 1999: Evaluation of Cancer Outcomes**

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant Selection | High | × 0.4 | 0.4 | Selection was provided in detail and indicates that selection into or out of the study is not likely biased. |
| | Metric 2: | Attrition | Medium | × 0.4 | 0.8 | There was an overall 86% response rate that did not differ between cases and controls. For the occupational analysis, 438 of the 690 cases and 687 of the 690 controls with complete personal interviews were included. There does not appear to be any missing data for the included 438 cases and 687 controls. However, all cases who died (35%) were excluded from the analysis to avoid using next-of-kin interviews. |
| | Metric 3: | Comparison Group | Medium | × 0.2 | 0.4 | For subjects age 20-64 years, an age- and gender-stratified random sample of white controls was obtained with random digit dialing. For subjects age 65-85 years, an age-and gender-stratified systematic sample of white controls was obtained from the listing of the Health Care Financing Administration. This is a population-based case control study in Minnesota. No information on characteristics were provided for comparing the cases and controls, but they were similar in terms of age, sex, and ethnicity (all were noted to be white). |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Medium | × 0.4 | 0.8 | Occupational history was obtained via interview. Duration of employment in 13 specific occupations/industries and seven jobs with specific exposures were o btained. 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). 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 | | | | | | |
| | 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 Confounding/Variable Control | | | | | | |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 | | | |

⋆ MWF = Metric Weighting Factor

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

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

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

where High: $\geq 1$ to $< 1.7$; Medium: $\geq 1.7$ to $< 2.3$; Low: $\geq 2.3$ to $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out 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: **Wang et al., 2009: Evaluation of Cancer Outcomes**

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

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

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

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 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 Confounding/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 |
| | 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. |

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

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| | Metric 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 | |
| | 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 $\leq 3.0$. If the reviewer determines that the overall rating needs adjustment, the original rating is crossed out and an arrow points to the new rating.

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