United States
Environmental Protection Agency

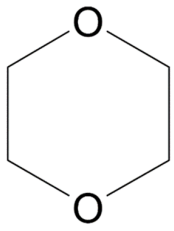
Office of Chemical Safety and
Pollution Prevention

# Final Risk Evaluation for 1,4-Dioxane

## Systematic Review Supplemental File:

## Data Quality Evaluation of Epidemiological Studies

## CASRN: 123-91-1



*December 2020*

# Table Listing



This document presents data quality evaluation results for epidemiological studies evaluated for the Risk Evaluation for 1,4-Dioxane.

EPA's Office of Pollution Prevention and Toxics (OPPT) developed data quality criteria for epidemiological studies. The first version of the criteria was documented in the *Application of Systematic Review in TSCA Risk Evaluations* document (EPA Document #740-P1-8001). The initial criteria were updated as described in the supplemental file *Final Risk Evaluation for 1,4-Dioxane Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies.*

Table 1: **Young 1977: Evaluation of ADME/PBPK Outcomes**

| | |
|---|---|
| Study Citation: | Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE (1977). Pharmacokinetics of 1,4-dioxane in humans Journal of Toxicology and Environmental Health, 3(3,3), 507-520 |
| Data Type: | Dow_volunteers_14D_TK_Half-life_Urine- ADME/PBPK |
| HERO ID: | 62956 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant selection | Medium | × 0.5 | 1 | Some key elements of the study design were not present and a limited number of subjects were selected for the study raises the potential for selection bias. Specifically, the study was conducted on 4 Caucasian male volunteers comprised of healthy scientists and business men ranging in age from 40-49. Due to the low number of participants it is unclear whether the study population is likely to be representative of the exposure-outcome distribution of the population of persons eligible for inclusion. |
| | Metric 2: | Attrition | Medium | × 0.5 | 1 | No attrition. Metabolite used for TK model (HEAA) was not determined in the plasma of 2-3 participants due to poor ability to separate from another chemical. |
| | Metric 3: | Comparison Group | Not Rated | NA | NA | Comparison group not relevant for TK model. Subjects provided history and underwent extensive physical examination, chest x-ray, electrocardiogram, blood chemistry panel, and urine analysis. All tests were repeated 24 hrs and 2 weeks after exposure. Results were not presented, but qualitatively stated to be healthy. |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | High | × 0.4 | 0.4 | Controlled dosage study. Subjects exposed in a controlled airflow chamber with 1,4-dioxane concentration of 48-52 ppm. Concentration in 3 breathing zones confirmed using a Wilks Miram I IR analyzer (8.75 um wavelength, standard curve). Exposure lasted for 6 hrs. Plasma concentrations indicated a dosage of 5.4 +/- 1.1 mg/kg. |
| | Metric 5: | Exposure levels | Medium | × 0.2 | 0.4 | Blood plasma reached a plateau concentration during the study (~4hrs into exposure). Plasma concentrations indicated a dosage of 5.4 +/- 1.1 mg/kg. Multiple levels of exposure not relevant for this study, but exposure sufficiently high to determine TK parameters. |

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Study Citation: Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE (1977). Pharmacokinetics of 1,4-dioxane in humans Journal of Toxicology and Environmental Health, 3(3,3), 507-520
Data Type: Dow_volunteers_14D_TK_Half-life_Urine- ADME/PBPK
HERO ID: 62956

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 6: | Temporality | High | × 0.4 | 0.4 | Plasma collection started 30 minutes after exposure began and continued for another 6 hrs. Urine collection throughout exposure and for the following. Eye irritation and smell sensitization evaluated throughout exposure. |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome measurement or characterization | High | × 0.667 | 0.67 | Venous blood was drawn every hour beginning 30 minutes after initial exposure. Blood samples were collected for 12.5 hrs after initial exposure, yielding 13 time points. Urine was collected for the 6 hrs (during exposure), in 2 hr intervals for the next 10 hrs, then from 16-24, 24-36, and 36-48 hrs. 14D levels in each were determined using GC/MS. |
| | Metric 8: | Reporting Bias | High | × 0.333 | 0.33 | Plasma 14D presented as means/standard deviations, and plasma presented as means alone for HEAA metabolite. Urine concentrations of 14D and HEAA presented for each individual and with mean/standard deviation. All parameters in the TK model and half-lives fully presented. |
| Domain 4: Potential Counfounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Not Rated | NA | NA | No covariates were adjusted for in the TK models, which is appropriate when trying to represent a larger population. Minimal variation in SES expected (based on job titles). All Caucasian males ages 40-49. |
| | Metric 10: | Covariate Characterization | Not Rated | NA | NA | Covariates determined from interviews and physicals. |
| | Metric 11: | Co-exposure Confounding | Medium | × 1 | 2 | No co-exposures expected. Participants experienced identical exposure scenario, but previous history not detailed. As some participants were scientists working at DOW, previous co-exposures are likely. However, not relevant to the current TK analysis. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | Study exposed 4 volunteers to 14D and monitored concentrations of 14D and its primary metabolite in blood plasma and urine over the course of 2 days to create a one-compartment toxicokinetic model for 14D . Study design appropriate for TK models, but not for health outcomes (eye irritation). |
| | Metric 13: | Statistical power | Medium | × 0.2 | 0.4 | Only 4 participants. Statistical power not stated, but able to establish TK parameters with moderate standard deviations. |

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| | |
|---|---|
| Study Citation: | Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE (1977). Pharmacokinetics of 1,4-dioxane in humans Journal of Toxicology and Environmental Health, 3(3,3), 507-520 |
| Data Type: | Dow_volunteers_14D_TK_Half-life_Urine- ADME/PBPK |
| HERO ID: | 62956 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 14: | Reproducibility of analyses | Medium | × 0.2 | 0.4 | Calculations used for the models are clear and fully presented in tables/figures. All data needed to re-created provided. |
| | Metric 15: | Statistical models | Medium | × 0.2 | 0.4 | One-compartment toxicokinetic model developed for 14D using nonlinear parameter estimates. Model parameters obtained per subject, such that standard deviations of individuals would reflect wider population.. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | Low | × 0.167 | 0.5 | 14D and primary metabolite b-hydroxyethoxyacetic acid (HEAA) were determined. HEAA was only determined in 3/4 of the participants (due to interference - not further explained). Study served as a means of determining a quantitative relationship between 14D dose and plasma/urine concentrations. Precision and accuracy of measurement technique not reported. |
| | Metric 17: | Effect biomarker | Not Rated | NA | NA | |
| | Metric 18: | Method Sensitivity | Medium | × 0.167 | 0.33 | 14D detected in all samples. HEAA had some interferences for plasma. LOD 0.1-0.2 ug/ml for 14D in plasma and urine. LOD for HEAA 1 ug/ml in urine and 2-10 ug/ml in plasma. |
| | Metric 19: | Biomarker stability | Low | × 0.167 | 0.5 | Storage history and stability not stated. |
| | Metric 20: | Sample contamination | Low | × 0.167 | 0.5 | Contamination not discussed, but not anticipated. |
| | Metric 21: | Method requirements | High | × 0.167 | 0.17 | Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (GC-MS). |
| | Metric 22: | Matrix adjustment | Low | × 0.167 | 0.5 | Creatinine levels determined in blood plasma and urine, but not clear if adjustments were made. Study only provides results using one method. |
| Overall Quality Determination‡ | | | Medium | | 1.8 | |
| Extracted | | | Yes | | | |

⋆ MWF = Metric Weighting Factor

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

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

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

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

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

Table 2: **Young 1977: Evaluation of Irritation Outcomes**

| | |
|---|---|
| Study Citation: | Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE (1977). Pharmacokinetics of 1,4-dioxane in humans Journal of Toxicology and Environmental Health, 3(3,3), 507-520 |
| Data Type: | Dow_volunteers_14D_EyeIrritation_SmellSensitization-Irritation |
| HERO ID: | 62956 |

| Domain | Metric | | Rating[†] | MWF[⋆] | Score | Comments[††] |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant selection | Medium | × 0.4 | 0.8 | Some key elements of the study design were not present and a limited number of subjects were selected for the study raises the potential for selection bias. Specifically, the study was conducted on 4 Caucasian male volunteers comprised of healthy scientists and business men ranging in age from 40-49. Due to the low number of participants it is unclear whether the study population is likely to be representative of the exposure-outcome distribution of the population of persons eligible for inclusion. |
| | Metric 2: | Attrition | High | × 0.4 | 0.4 | No attrition. |
| | Metric 3: | Comparison Group | High | × 0.2 | 0.2 | Table 1 indicates characteristics of the 4 subjects were generally similar, although there were variations in urine flow rate (range: 1.14 - 2.74 ml/min) and weight (range: 74.5 - 100.75 kg) |
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | High | × 0.4 | 0.4 | Controlled dosage study. Subjects exposed in a controlled airflow chamber with 1,4-dioxane concentration of 48-52 ppm. Concentration in 3 breathing zones confirmed using a Wilks Miram I IR analyzer (8.75 um wavelength, standard curve). Exposure lasted for 6 hrs. Plasma concentrations indicated a dosage of 5.4 +/- 1.1 mg/kg. |
| | Metric 5: | Exposure levels | Low | × 0.2 | 0.6 | Same individuals served as unexposed and exposed group (physical before/after exposure). |
| | Metric 6: | Temporality | High | × 0.4 | 0.4 | Plasma collection started 30 minutes after exposure began and continued for another 6 hrs. Urine collection throughout exposure and for the following. Eye irritation and smell sensitization evaluated throughout exposure. |
| Domain 3: Outcome Assessment | | | | | | |
| | Metric 7: | Outcome measurement or characterization | Low | × 0.667 | 2 | The outcome assessment method is an insensitive measure: eye irritation and the loss of sensitivity to the smell of dioxane were self-reported. |

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|---|---|
| Study Citation: | Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE (1977). Pharmacokinetics of 1,4-dioxane in humans Journal of Toxicology and Environmental Health, 3(3,3), 507-520 |
| Data Type: | Dow_volunteers_14D_EyeIrritation_SmellSensitization-Irritation |
| HERO ID: | 62956 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 8: | Reporting Bias | Medium | × 0.333 | 0.67 | No specific result (e.g., frequency) presented on eye irritation other than the comment 'Eye irritation was a frequent complaint throughout exposure'. |
| Domain 4: Potential Counfounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Medium | × 0.5 | 1 | Participants served as own controls for the eye irritation. Minimal variation in SES expected (based on job titles). All Caucasian males ages 40-49. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Covariates determined from interviews and physicals with no method validation against well-established methods. |
| | Metric 11: | Co-exposure Confounding | Medium | × 0.25 | 0.5 | No co-exposures expected. Participants experienced identical exposure scenario, but previous history not detailed. As some participants were scientists working at DOW, previous co-exposures are likely. However, not relevant to the current TK analysis. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.5 | 1 | Study exposed 4 volunteers to 14D in an controlled experiment. Monitored irritations and smell sensitization during the experiment. Conducted full physicals before and after. Smell sensitization results were descriptive. |
| | Metric 13: | Statistical power | Unacceptable | × 0.25 | 0.06 | Only 4 participants. |
| | Metric 14: | Reproducibility of analyses | Medium | × 0.25 | 0.5 | The study did not use a statistical model. |
| | Metric 15: | Statistical models | Not Rated | NA | NA | No statistical models were used in the study. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | Low | × 0.167 | 0.5 | 14D and primary metabolite b-hydroxyethoxyacetic acid (HEAA) were determined. HEAA was only determined in 3/4 of the participants (due to interference - not further explained). Study served as a means of determining a quantitative relationship between 14D dose and plasma/urine concentrations. Precision and accuracy of measurement technique not reported. |
| | Metric 17: | Effect biomarker | Not Rated | NA | NA | |
| | Metric 18: | Method Sensitivity | Medium | × 0.167 | 0.33 | 14D detected in all samples. HEAA had some interferences for plasma. LOD 0.1-0.2 ug/ml for 14D in plasma and urine. LOD for HEAA 1 ug/ml in urine and 2-10 ug/ml in plasma. |
| | Metric 19: | Biomarker stability | Low | × 0.167 | 0.5 | Storage history and stability not stated. |
| | Metric 20: | Sample contamination | Low | × 0.167 | 0.5 | Contamination not discussed, but not anticipated. |

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| | |
|---|---|
| Study Citation: | Young, JD; Braun, WH; Rampy, LW; Chenoweth, MB; Blau, GE (1977). Pharmacokinetics of 1,4-dioxane in humans Journal of Toxicology and Environmental Health, 3(3,3), 507-520 |
| Data Type: | Dow_volunteers_14D_EyeIrritation_SmellSensitization-Irritation |
| HERO ID: | 62956 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 21: | Method requirements | High | × 0.167 | 0.17 | Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (GC-MS). |
| | Metric 22: | Matrix adjustment | Low | × 0.167 | 0.5 | Creatinine levels determined in blood plasma and urine, but not clear if adjustments were made. Study only provides results using one method. |
| Overall Quality Determination‡ | | | Unacceptable⋆⋆ | | 1.9 | |
| Extracted | | | No | | | |

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

⋆ MWF = Metric Weighting Factor

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

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

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

where High $=\geq 1$ to $< 1.7$; Medium $=\geq 1.7$ to $< 2.3$; Low $=\geq 2.3$ to $\leq 3.0$. 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: **Union Carbide 1989: Evaluation of Cancer Outcomes**

| | |
|---|---|
| Study Citation: | Union Carbide (1989). Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment with attached tables and cover letter dated 02/21/89 |
| Data Type: | occupational 1,4-D, lymphatic & hematopoietic cancer-Cancer |
| HERO ID: | 597727 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| Domain 1: Study Participation | | | | | | |
| | Metric 1: | Participant selection | High | × 0.4 | 0.4 | Subjects were part of a large cohort mortality study in two Union Carbide Corporation chemical manufacturing facilities and a research and development center. This case-control study selected cases of four distinct subcategories of lymphatic and hematopoietic tissue cancers. Study was restricted to men because only 4 cases were identified in women. Controls were selected from the total employee cohort. Participation rates are not a concern because all information was obtained via records. Controls were randomly selected and all cases (follow-up was available for 96%) were included indicating that selection into or out of the study was not likely to be biased. |
| | Metric 2: | Attrition | Low | × 0.4 | 1.2 | Vital status at follow-up was complete for 96% of the 29,139 men in the cohort. It was noted that 5 controls were selected per case. Based on the 129 cases identified this would suggest 645 controls selected. However, the study report does not indicate how many controls were included in the study nor does it report the numbers of controls in the different work areas or chemical exposures. There is insufficient information provided on the control numbers during important stages of the study to determine if there was any attrition. |
| | Metric 3: | Comparison Group | Low | × 0.2 | 0.6 | It is unclear that the controls were free of the outcomes. The study authors did not provide baseline characteristics for the subjects to determine if the cases and controls were similar. Analysis only addressed age (and only males were used), but no other potential differences were addressed. Controls were selected from the total employee cohort according to an unmatched incidence density sampling design. It was noted that there were 5 controls selected per case, but other than that the number of controls was not mentioned. Time of hire to death for cases was categorized into five year increments of survival. Controls were selected such that they were first employed in the same decade and survived to the same five year survival period as the case. |

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| | |
|---|---|
| Study Citation: | Union Carbide (1989). Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment with attached tables and cover letter dated 02/21/89 |
| Data Type: | occupational 1,4-D, lymphatic & hematopoietic cancer-Cancer |
| HERO ID: | 597727 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| Domain 2: Exposure Characterization | | | | | | |
| | Metric 4: | Measurement of Exposure | Medium | × 0.4 | 0.8 | Exposure was based on job assignment and potential exposure, and classified on an ever/never basis. Ever exposure was based on working 1 or more days with the chemical. Details were stated to be available in Ott et al., 1989 (HERO ID 104202), which provides more details on the definition of work areas and environmental agents. All workplace exposures were subdivided into six major categories. Using departmental and job assignment records and historical information regarding process dates and descriptions from 1925-1978, all work activities were further subdivided into 111 distinct and mutually exclusive work areas. Exposure to each work area or activity was based on the work history information for each subject. 1,020 substances were identified as having been used or produce in one or more of the production units over the 54 years. Potential employee contact was based on assignment to a departmental unit, which implied potential exposure to any chemical in use during the time period of the employee's assignment to that unit. 21 substances were selected for analysis. Because 1,4-dioxane did not have more than 4 cases, it was not evaluated by duration of exposure. |
| | Metric 5: | Exposure levels | Low | × 0.2 | 0.6 | Exposure was ever/never |
| | 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. In the event that exposures which occurred close to the time of death were unrelated to outcome, the data were also analyzed with a lagged dose. Crude odds ratios were recalculated excluding exposures that occurred 5 years or less from the beginning of the case survival interval. The lag period was an average of 7 years. Because mortality was evaluated and not incidence it cannot be specifically determined if exposure occurred prior to development of the disease, just that it occurred prior to death. Nor can it be determined if 7 years is a sufficient window to be considered a critical window for the mortality from these cancers. |
| Domain 3: Outcome Assessment | | | | | | |

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| | |
|---|---|
| Study Citation: | Union Carbide (1989). Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment with attached tables and cover letter dated 02/21/89 |
| Data Type: | occupational 1,4-D, lymphatic & hematopoietic cancer-Cancer |
| HERO ID: | 597727 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 7: | Outcome measurement or characterization | Medium | × 0.667 | 1.33 | Cases were identified from a review of both underlying and contributory causes of death among male decedents (1940-1978) from the cohort. Based in information provided in HERO ID 1010430, this information was obtained from death certificate diagnosis. This misses cases that survived and cases where there may have been another cause of death. The study authors acknowledge that there may be some misclassification of disease status, they also note that there was agreement between death certificates and tumor registry diagnoses for these tumors. |
| | Metric 8: | Reporting Bias | Medium | × 0.333 | 0.67 | All outcomes were reported. Confidence intervals for risk estimates are provided in the text, but not in tables. Number of cases were reported, but number of controls was not. |
| Domain 4: Potential Counfounding/Variable Control | | | | | | |
| | Metric 9: | Covariate Adjustment | Low | × 0.5 | 1.5 | Only age-adjusted stratified analyses were also conducted. No other confounder was considered. |
| | Metric 10: | Covariate Characterization | Medium | × 0.25 | 0.5 | Work records were presumably the source of the information, but it was not specifically identified. Age and gender were the only covariates considered and work records are likely a reliable source. For cases, this information was also likely available on the death records. |
| | Metric 11: | Co-exposure Confounding | Low | × 0.25 | 0.75 | Co-exposures were considered when discussing the cases and their exposures. However, for dioxane this information was not available nor was indicated if this exposure occurred in a single work area or over several areas where co-exposures would have varied. Controls might have been subject to different co-exposures than cases. |
| Domain 5: Analysis | | | | | | |
| | Metric 12: | Study Design and Methods | Medium | × 0.4 | 0.8 | The case-control design and calculation of odds ratios were appropriate for determining the association between exposure to 1-4D and lymphatic and hematopoietic tissue cancers. |

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| | |
|---|---|
| Study Citation: | Union Carbide (1989). Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment with attached tables and cover letter dated 02/21/89 |
| Data Type: | occupational 1,4-D, lymphatic & hematopoietic cancer-Cancer |
| HERO ID: | 597727 |

| Domain | Metric | | Rating† | MWF⋆ | Score | Comments†† |
|---|---|---|---|---|---|---|
| | Metric 13: | Statistical power | Unacceptable | × 0.2 | 0.04 | The number of cases exposed to dioxane was too low to detect an effect of exposure. The number of controls was not reported. There were only 4 cases total exposed to dioxane and the 4 outcomes were evaluated separately so there was 1 case with non-Hodgkins lymphoma and 3 cases of non-lymphatic leukemia. This was likely insufficient to determine the effects of exposure. |
| | Metric 14: | Reproducibility of analyses | Low | × 0.2 | 0.6 | The description of the analysis is insufficient to understand precisely what has been done and to be reproducible. |
| | Metric 15: | Statistical models | Low | × 0.2 | 0.6 | No description of the model was provided. |
| Domain 6: Other Considerations for Biomarker Selection and Measurement | | | | | | |
| | Metric 16: | Use of Biomarker of Exposure | | NA | NA | |
| | Metric 17: | Effect biomarker | | NA | NA | |
| | Metric 18: | Method Sensitivity | | NA | NA | |
| | Metric 19: | Biomarker stability | | NA | NA | |
| | Metric 20: | Sample contamination | | NA | NA | |
| | Metric 21: | Method requirements | | NA | NA | |
| | Metric 22: | Matrix adjustment | | NA | NA | |
| Overall Quality Determination‡ | | | Unacceptable⋆⋆ | | 2.4 | |
| Extracted | | | No | | | |

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

⋆ MWF = Metric Weighting Factor

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

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

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

where High $=\geq 1$ to $< 1.7$; Medium $=\geq 1.7$ to $< 2.3$; Low $=\geq 2.3$ to $\leq 3.0$. 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: **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_1,4-D_CTS_BreastCancer_Q1-Cancer |
| HERO ID: | 3014082 |

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

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| Study Citation: | Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study Environmental Health: A Global Access Science Source, 14(1), 14 |
| Data Type: | Cohort_1,4-D_CTS_BreastCancer_Q1-Cancer |
| HERO ID: | 3014082 |

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

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

⋆ MWF = Metric Weighting Factor

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

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

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

where High $=\geq 1$ to $< 1.7$; Medium $=\geq 1.7$ to $< 2.3$; Low $=\geq 2.3$ to $\leq 3.0$. 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