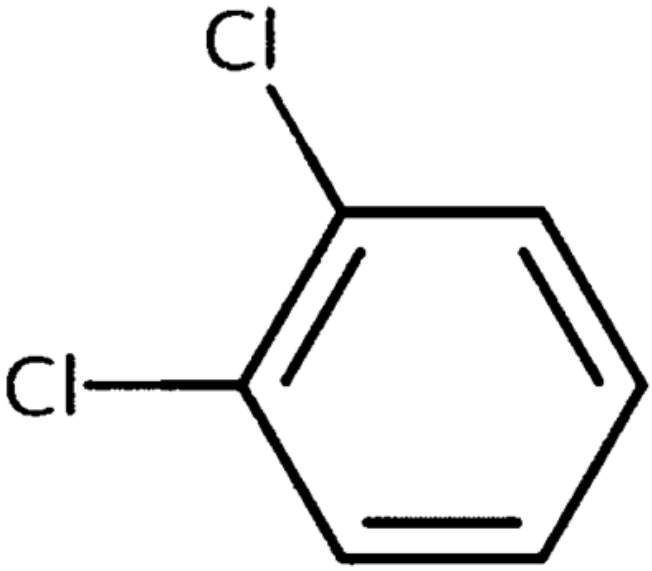
United States
Environmental Protection Agency

April 2026
Office of Chemical Safety and
Pollution Prevention

Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for o-Dichlorobenzene

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 95-50-1



April 2026

This supplemental file contains the data quality evaluation results for epidemiology data sources that met the PECO screening criteria and further filtering criteria for the *Draft Human Health and Environmental Hazard Assessment for o-Dichlorobenzene*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Systematic Review Protocol for o-Dichlorobenzene*.

Table of Contents

Study Citation:	Ehrenstein, Von, O. S., Heck, J. E., Park, A. S., Cockburn, M., Escobedo, L., Ritz, B. (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. Environmental Health Perspectives 124(7):1093-1099.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	5684085

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1:	Participant Selection	High	Cases of childhood brain cancer, including cases of primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, in this case-control study were selected from the California Cancer Registry. Cases were selected before age 6 and diagnosed in 1990-2007. Cases were then matched to California birth certificates from the California Department of Public Health's Office of Vital Records using first and last names as well as birth dates; matching was successful in 89% of cases. Controls without a cancer diagnosis before age 6 were randomly selected from California birth rolls and frequency matched to all childhood cancer cases during the same period at a ratio of 20 controls per case. Subjects were excluded if they had a missing gestational age from birth certificates (n=74 cases and n=12,035 controls), if they did not have at least one air toxics reading for each full month of pregnancy and within the last 30 days of pregnancy, if they did not live within <5 miles from a California Air Resources Board monitor, or if their gestational ages or birth weights were considered non-viable (viable gestational ages were considered to be 146-323 days, viable birth weights were considered to be 500-6,800 g). 719 controls were also excluded due to dying before 6 years of age after matching to California death records. The final sample size included n=183 cases and n=30,569 controls. There is no direct evidence of selection bias as the study attempted to draw cases and controls from the same eligible population, and none of the selection criteria are expected to be disproportionately affected by exposure or outcome.
	Metric 2:	Attrition	Medium	74 cases and 12,035 controls were excluded overall due to missing data on gestational age, while other exclusion criteria included: if they did not have at least one air toxics reading for each full month of pregnancy and within the last 30 days of pregnancy, if they did not live within <5 miles from a California Air Resources Board monitor, or if their gestational ages or birth weights were considered non-viable. It is not clear how many participants had missing air toxics readings; however, there is no evidence to suggest that missing air toxics readings would be associated with the studied outcomes.
	Metric 3:	Comparison Group	High	Cases and control were recruited from the same population during the same time period and were matched by birth year. Demographic information is presented as stratified by case/control status, and those same variables were considered as covariates in statistical analyses.
Domain 2: Exposure Characterization				

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Domain	Metric		Rating	Comments
	Metric 4:	Measurement of Exposure	Low	Exposure to DCBs was assessed based on participants geocoded residential addresses listed on birth certificates. From 1990 to 1997, only a ZIP code was listed on the birth certificate, and the ZIP code centroid were used for exposure measurement. DCBs exposure was measured via air toxics monitors set up by the California Air Resources Board, which collects 24-hour integrated samples of ambient air concentrations every 12 days (n=31 monitors) at locations expected to representative of the area. The distance from each monitor to geocoded addresses was calculated and addresses more than 5 miles away from the nearest monitor were excluded as exposure estimates may be less accurate at greater distances. The exposure assessment methodology is likely reliable given the use of public data, but the potential discrepancy between listed address on birth certificate and actual residence is also a limitation. The study estimated that up to 9% to 30% of families may move during pregnancy, thus there are concerns over non-differential misclassification bias.
	Metric 5:	Exposure Levels	Medium	Statistical analyses characterized exposure linearly and assessed changes in outcomes per IQR increase. IQRs were provide for each pollutant during each trimester, the entire pregnancy and the first year of life. While the IQRs are quite small (0.076 ppbV for o-DCB and 0.039 ppbV for p-DCB), they are potentially large enough to allow for sufficient exposure contrast.
	Metric 6:	Temporality	High	Exposure was characterized as averages for each trimester, the entire pregnancy period, and the first year of life to ensure temporality.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	The International Classification of Disease Oncology (ICD-O) codes were used to characterize PNET (ICD-O code 9473) and medulloblastoma (ICD-O code 9470), while the International Classification of Childhood Cancer was used to characterize astrocytoma (ICC-3 code 032). Cases were pulled from the California Cancer Registry. Controls were stated to be "without a cancer diagnosis", which may have been checked via linkage of birth certificates with the California Cancer Registry, although this is not explicitly stated by the paper. However, there is no evidence of outcome misclassification.
	Metric 8:	Reporting Bias	High	Adjusted ORs are reported with confidence intervals for each cancer type and each toxicant during pregnancy and the first year of life. The IQR increase in exposure and the number of cases and controls was also provided, alongside case/control numbers for each comparison group.
Domain 4: Potential Confounding / Variability Control				

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Domain	Metric		Rating	Comments
	Metric 9:	Covariate Adjustment	Medium	Potential confounders were selected based on previous knowledge and previous examination of demographic and perinatal factors related to cancer status in the data. Included covariates were birth year (matching variable), maternal age and education, race/ethnicity, and place of birth (United States vs. non-United States). Other variables that were also considered but not included in the final models were types of insurance (socio-economic status measure), rural/urban residence, parity, offspring sex, preterm birth.
	Metric 10:	Covariate Characterization	Low	No information was included on the collection of covariate data, for example, whether the information was self-reported by parents or collected through public records.
	Metric 11:	Co-exposure Counfounding	Medium	Exposure to other air toxics was also measured, and correlations across pollutants were presented. No adjustment was made for co-pollutants.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The case-control design is appropriate to assess the incidence of relatively rare childhood cancers.
	Metric 13:	Statistical Power	Medium	The number of cases with exposure measurements was small due to the rarity of the outcome and the small number of monitoring stations. Case sample sizes of n=23, n=32, and n=73 were reported in analyses of prenatal exposure for (PNET), medulloblastoma, and astrocytoma respectively; case sample sizes were n=23, n=14, and n=54 for analyses of first year-of-life exposure. Despite some small case numbers for some sub-groups, the sample sizes overall are likely large enough to detect an effect.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical Analysis	High	Logistic regression was used to estimate odds ratios per interquartile-range increase in pregnancy exposures during each trimester, the entire pregnancy, and the first 12 months of life for each outcome. Numbers of cases/controls are presented for each analysis. Effect estimates are presented with 95% confidence intervals. Sensitivity analyses were performed adding additional potential confounders and restricted to participants with term birth.

Additional Comments: This case-control study on the association between DCBs and childhood brain cancer had an adequate sample size based on public records from 1990-2007, which was a strength due to the rarity of outcome. There is minimal concern over selection bias. The main limitation of the study is the exposure measurement based on air monitor readings. There is concern over misclassification bias due to discrepancies between registered and actual residential address, even though the bias is non-differential between cases and controls. However, a significant positive association was reported for first year-of-life exposure to o-DCB and the odds of developing primitive neuroectodermal tumors in children by six years of age; exposure during pregnancy resulted in a positive but non-significant association.

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Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Heck, J. E., Park, A. S., Qiu, J., Cockburn, M., Ritz, B. (2015). Retinoblastoma and ambient exposure to air toxics in the perinatal period. Journal of Exposure Science & Environmental Epidemiology 25(2):182-186.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Retinoblastoma
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	2369182

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1:	Participant Selection	Medium	The study analyzed retinoblastoma risk among children younger than age 6 in California as a part of the Air Pollution and Childhood Cancer (APCC) study, which is a large case–control investigation of air pollution exposure among California children. Cases were ascertained from California Cancer Registry records of cancer diagnoses between 1990 and 2007 among children younger than age 6. Population-based controls were selected at random from California birth records for the same time period, and frequency matched to all childhood cancer cases by birth year. Controls had no cancer diagnosis listed in the California Cancer Registry before age 6. Authors linked participants to California death records in order to exclude 1550 controls who had died of other causes in early childhood (< age 6). Children with missing information on gestational age (20 cases, 9219 controls) were excluded from analyses. 30,704 children (103 cases, 30,601 controls) were included in analyses because they were living within 5 miles of a monitor and had sufficient values recorded for at least one pollutant. The 131,314 additional children who were excluded from the present study because they were not living within 5 miles of any monitor were much more likely to be residing in a rural county (21% vs 6%). There was no direct evidence of selection bias.The study clearly indicates the recruitment process and inclusion/exclusion criteria. Per using California state records, there is no indication that there was a significant number of eligible subjects who were not considered for inclusion. There is no evidence to suggest that the exposure-outcome distribution would vary between those included in the cancer registry and birth records, and those who were not in those databases for any reason.
	Metric 2:	Attrition	Medium	Children with missing information on gestational age (20 cases, 9219 controls) were excluded from analyses. There is no evidence to suggest that this was an inappropriate way to handle missingness, but there is also no reason provided for missing gestational age data.
	Metric 3:	Comparison Group	Medium	Demographic characteristics (maternal race, paternal age, source of payment for prenatal care, child sex) are presented stratified by case-control status. There is no distribution of demographic characteristics stratified by exposure status. All reported demographic characteristics, and in addition birth year, are adjusted for in statistical analyses.
Domain 2: Exposure Characterization				

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Reported Health Effect(s):	Retinoblastoma
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Domain	Metric		Rating	Comments
	Metric 4:	Measurement of Exposure	Medium	Exposure to DCBs were assessed via linking participant addresses to values reported from the California Air Resources Board (CARB)"s Air Toxics Program. CARB monitors report data beginning in 1990 and measure ambient concentrations of DCBs by collecting "24-h integrated samples every 12 from each monitor." Monitors are located across the state of California, but are most frequently located in high-traffic urban areas, industrial neighborhoods, or agriculturally intense rural regions. The distance from each monitor to a participant home was assessed and participants were assigned DCBs levels corresponding to the measurements from the nearest monitor. The study reported that they also attempted to use kriging to assign values but did not find significant differences from their original analysis (data not provided). While the exposure assessment does not account for meteorologic factors or individual behaviors, these are not expected to differentially affect cases relative to controls; thus there is no evidence of significant bias.
	Metric 5:	Exposure Levels	Low	The overall range of exposures for DCBs is limited, with a mean among controls (SD) of 0.11 (0.04) ppbV for ortho-DCB and 0.15 (0.04) ppbV for para-DCB. Statistical analyses compare outcomes per 1-IQR increase in exposure, which is equivalent to 0.08 for ortho-DCB and 0.04 for para-DCB.
	Metric 6:	Temporality	High	Measurements were averaged across 3 months pre-conception, each trimester, the whole period of pregnancy, and the first year of life in order to account for latency. This clearly presents a timeline where exposure is recorded prior to outcome, and includes the likely relevant etiologically relevant time window (pregnancy and first year of life).
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	The outcome of interest in this study was retinoblastoma. Cases were reported from the California Cancer Registry records. They included cases with International Classification of Childhood Cancer, Third edition (ICCC-3) code 050. However, no validation was performed.
	Metric 8:	Reporting Bias	High	All outcomes outlined in the methods, abstract, and introduction are reported in the results. Case/control numbers are presented for each analysis, and the IQR is presented for each DCB.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Medium	Considered covariates included maternal race/ethnicity and nativity, paternal age, year of birth, and the method of payment for prenatal care (private health insurance vs. Medi-Cal/other government-sponsored health insurance/self=pay) as a proxy for socioeconomic status. These covariates were pulled from birth certificates and were chosen due to the study authors' previous work on retinoblastoma. The study explains that race, Latino ethnicity, and socioeconomic status are related to air pollution exposures. In general, there is no evidence of residual confounding.

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Domain	Metric		Rating	Comments
	Metric 10:	Covariate Characterization	Medium	Covariate information was pulled from birth certificates. While no other validation was performed, there is no evidence that a large number of variables were incorrectly assigned.
	Metric 11:	Co-exposure Counfounding	Medium	Co-exposure to a wide variety of other air toxics reported by CARB were also considered. Separate analyses were performed for each co-exposure
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The case-control study design with logistic regression analysis was an appropriate method to answer the research question.
	Metric 13:	Statistical Power	Medium	The number of participants (n=103 cases, n=30,601) is likely large enough to detect an effect.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical Analysis	High	Analysis methods were appropriate. Descriptive data presented mean pollutant values and interquartile ranges, as well as numbers of cases and controls. Logistic regression analyses were conducted for each pollutant separately, with adjustment for potential confounding variables. Odds ratios and 95% confidence intervals for associations between pollutants and retinoblastoma were presented, per IQR increase in DCBs. Sensitivity analyses were described, including stratified by region, time period, and whether retinoblastoma was bilateral or unilateral.

Additional Comments: This case-control study used data from the Air Pollution and Childhood Cancer study to examine the association between ambient DCBs levels and retinoblastoma incidence among children. There were no significant concerns for bias across the study, although there are potential concerns for exposure misclassification due to the lack of consideration for individual behaviors that may influence exposure. The study reported significantly higher probability of retinoblastoma in participants exposed to higher levels of para-DCBs during pregnancy, but not for exposures averaged during the first year of a child's life. No significant results were reported for orth-DCBs.

Overall Quality Determination Medium

Study Citation:	Rodrigues, E. G., Herrick, R. F., Stewart, J., Palacios, H., Laden, F., Clark, W., Delzell, E. (2020). Case-control study of brain and other central nervous system cancer among workers at semiconductor and storage device manufacturing facilities. Occupational and Environmental Medicine 77(4):238-248.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Brain and other central nervous system cancer
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	10096148

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1:	Participant Selection	High	Participants in this nested case-control study were drawn from a cohort of 126,836 IBM employees. Detailed information on selection of cases and controls is provided, including time periods of eligibility and ICD codes for cases. Deceased cases were identified via the National Death Index or death certificates, and incident cases were identified via state cancer registries. Ten controls were selected for each case using incidence density sampling and were matched based on year of birth, facility where the case had last worked, gender, and race. Details on the parent cohort can be found in another publications (HEROID 3298947), There is no indication that selection into the study was biased.
	Metric 2:	Attrition	High	There was minimal exclusion from the analysis sample and outcome data and exposure were largely complete. Only one identified case was excluded due to comorbid malignant melanoma.
	Metric 3:	Comparison Group	High	Cases and controls were recruited from the same eligible population within the same time frame. Cases and controls were similar with respect to demographics and facility. Cases and controls were matched based on year of birth, facility where the case had last worked, gender, and race.
Domain 2: Exposure Characterization				
	Metric 4:	Measurement of Exposure	Medium	Exposure was estimated using work group–exposure matrices that linked quantitative exposure levels for o-Dichlorobenzene to participants' job histories. Each job was classified into one of 10 primary exposure groups (PEGs) based on tasks, work environment, and production type. Historical monitoring data were used to calculate mean concentrations for o-Dichlorobenzene by PEG and manufacturing era, and these were combined with job durations to estimate cumulative exposure for each subject. However, detailed work history information was only available beginning in 1965; depending on case status and facility, this resulted in an average of 20% to 44% of participant work history being excluded from the assessment (Table 1). Additionally, historical monitoring data were often sparse and were not available for each combination of chemical, facility, PEG, and time period.
	Metric 5:	Exposure Levels	Medium	The range and distribution of exposure is likely sufficiently large to detect an effect, and 4 levels of exposure (reference plus tertiles) to o-Dichlorobenzene are included in the analyses.
	Metric 6:	Temporality	High	The temporality of exposure and outcome is appropriate and considers relevant exposure windows. A sensitivity analysis using a 5-year latency period was conducted.

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Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Brain and other central nervous system cancer
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	10096148

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	Deceased cases between 1965-1999 were identified from the National Death Index or death certificates. Incident cases were determined from state cancer registries. However, there was no registry for Vermont and records were not available for the entire follow-up period in New York and California. Cases and controls from each facility were followed for the same length of time.
	Metric 8:	Reporting Bias	Medium	Most of the study's measured outcomes are reported in detail, including 95% confidence intervals and the number of cases and controls for each analysis. However, results of the 5-year latency analysis were only reported qualitatively ("similar to those of the main analyses").
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	High	Conditional logistic regression models for each facility were generated and controlled for matching variables (year of birth, gender, and race).
	Metric 10:	Covariate Characterization	High	Covariates appear to have been obtained from case ascertainment sources (National Death Index, death certificates, or state cancer registries) or employee records.
	Metric 11:	Co-exposure Counfounding	Low	Co-exposures to numerous other chemicals were present but were not adjusted for in the analyses. Effect estimates are presented for 30 other chemicals measured in the study, but there is no multi-pollutant model that considers all exposures together.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The nested case-control study design and the conditional logistic regression models were appropriate for the research question.
	Metric 13:	Statistical Power	Medium	The number of cases (n=120) and controls (n=1,028) is likely adequate to detect an effect in the population.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient and would be reproducible with access to the data.
	Metric 15:	Statistical Analysis	High	Descriptions of risk estimate calculations for each outcome were provided and the variables used in each analysis were described. Associations were estimated using conditional logistic regression.

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Domain	Metric	Rating	Comments
Additional Comments:	This nested case-control study explored links between occupational exposures from semiconductor and electronic module manufacturing and central nervous system (CNS) cancer. The study compared 120 CNS cancer cases to 1,028 matched controls, assessing job roles across 10 process groups and cumulative exposure to 31 potential carcinogens. Findings indicated positive associations between CNS cancer and module manufacturing operations, as well as high cumulative exposure to certain chemicals, including o-dichlorobenzene. The exposure assessment was limited by sparse monitoring data, incomplete coverage across chemicals, facilities, and time periods, and potential misclassification. However, there were no significant limitations that would decrease the confidence in the findings of the study.		

Overall Quality Determination High

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Health Outcome(s) Assessed:	Ocular & Sensory
Reported Health Effect(s):	Retinoblastoma
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	2369182

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1:	Participant Selection	Medium	The study analyzed retinoblastoma risk among children younger than age 6 in California as a part of the Air Pollution and Childhood Cancer (APCC) study, which is a large case–control investigation of air pollution exposure among California children. Cases were ascertained from California Cancer Registry records of cancer diagnoses between 1990 and 2007 among children younger than age 6. Population-based controls were selected at random from California birth records for the same time period, and frequency matched to all childhood cancer cases by birth year. Controls had no cancer diagnosis listed in the California Cancer Registry before age 6. Authors linked participants to California death records in order to exclude 1550 controls who had died of other causes in early childhood (< age 6). Children with missing information on gestational age (20 cases, 9219 controls) were excluded from analyses. 30,704 children (103 cases, 30,601 controls) were included in analyses because they were living within 5 miles of a monitor and had sufficient values recorded for at least one pollutant. The 131,314 additional children who were excluded from the present study because they were not living within 5 miles of any monitor were much more likely to be residing in a rural county (21% vs 6%). There was no direct evidence of selection bias.The study clearly indicates the recruitment process and inclusion/exclusion criteria. Per using California state records, there is no indication that there was a significant number of eligible subjects who were not considered for inclusion. There is no evidence to suggest that the exposure-outcome distribution would vary between those included in the cancer registry and birth records, and those who were not in those databases for any reason.
	Metric 2:	Attrition	Medium	Children with missing information on gestational age (20 cases, 9219 controls) were excluded from analyses. There is no evidence to suggest that this was an inappropriate way to handle missingness, but there is also no reason provided for missing gestational age data.
	Metric 3:	Comparison Group	Medium	Demographic characteristics (maternal race, paternal age, source of payment for prenatal care, child sex) are presented stratified by case-control status. There is no distribution of demographic characteristics stratified by exposure status. All reported demographic characteristics, and in addition birth year, are adjusted for in statistical analyses.
Domain 2: Exposure Characterization				

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Health Outcome(s) Assessed:	Ocular & Sensory
Reported Health Effect(s):	Retinoblastoma
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Domain	Metric		Rating	Comments
	Metric 4:	Measurement of Exposure	Medium	Exposure to DCBs were assessed via linking participant addresses to values reported from the California Air Resources Board (CARB)"s Air Toxics Program. CARB monitors report data beginning in 1990 and measure ambient concentrations of DCBs by collecting "24-h integrated samples every 12 from each monitor." Monitors are located across the state of California, but are most frequently located in high-traffic urban areas, industrial neighborhoods, or agriculturally intense rural regions. The distance from each monitor to a participant home was assessed and participants were assigned DCBs levels corresponding to the measurements from the nearest monitor. The study reported that they also attempted to use kriging to assign values but did not find significant differences from their original analysis (data not provided). While the exposure assessment does not account for meteorologic factors or individual behaviors, these are not expected to differentially affect cases relative to controls; thus there is no evidence of significant bias.
	Metric 5:	Exposure Levels	Low	The overall range of exposures for DCBs is limited, with a mean among controls (SD) of 0.11 (0.04) ppbV for ortho-DCB and 0.15 (0.04) ppbV for para-DCB. Statistical analyses compare outcomes per 1-IQR increase in exposure, which is equivalent to 0.08 for ortho-DCB and 0.04 for para-DCB.
	Metric 6:	Temporality	High	Measurements were averaged across 3 months pre-conception, each trimester, the whole period of pregnancy, and the first year of life in order to account for latency. This clearly presents a timeline where exposure is recorded prior to outcome, and includes the likely relevant etiologically relevant time window (pregnancy and first year of life).
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	The outcome of interest in this study was retinoblastoma. Cases were reported from the California Cancer Registry records. They included cases with International Classification of Childhood Cancer, Third edition (ICCC-3) code 050. However, no validation was performed.
	Metric 8:	Reporting Bias	High	All outcomes outlined in the methods, abstract, and introduction are reported in the results. Case/control numbers are presented for each analysis, and the IQR is presented for each DCB.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Medium	Considered covariates included maternal race/ethnicity and nativity, paternal age, year of birth, and the method of payment for prenatal care (private health insurance vs. Medi-Cal/other government-sponsored health insurance/self=pay) as a proxy for socioeconomic status. These covariates were pulled from birth certificates and were chosen due to the study authors' previous work on retinoblastoma. The study explains that race, Latino ethnicity, and socioeconomic status are related to air pollution exposures. In general, there is no evidence of residual confounding.

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Health Outcome(s) Assessed:	Ocular & Sensory
Reported Health Effect(s):	Retinoblastoma
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	2369182

Domain	Metric		Rating	Comments
	Metric 10:	Covariate Characterization	Medium	Covariate information was pulled from birth certificates. While no other validation was performed, there is no evidence that a large number of variables were incorrectly assigned.
	Metric 11:	Co-exposure Counfounding	Medium	Co-exposure to a wide variety of other air toxics reported by CARB were also considered. Separate analyses were performed for each co-exposure
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The case-control study design with logistic regression analysis was an appropriate method to answer the research question.
	Metric 13:	Statistical Power	Medium	The number of participants (n=103 cases, n=30,601) is likely large enough to detect an effect.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical Analysis	High	Analysis methods were appropriate. Descriptive data presented mean pollutant values and interquartile ranges, as well as numbers of cases and controls. Logistic regression analyses were conducted for each pollutant separately, with adjustment for potential confounding variables. Odds ratios and 95% confidence intervals for associations between pollutants and retinoblastoma were presented, per IQR increase in DCBs. Sensitivity analyses were described, including stratified by region, time period, and whether retinoblastoma was bilateral or unilateral.

Additional Comments: This case-control study used data from the Air Pollution and Childhood Cancer study to examine the association between ambient DCBs levels and retinoblastoma incidence among children. There were no significant concerns for bias across the study, although there are potential concerns for exposure misclassification due to the lack of consideration for individual behaviors that may influence exposure. The study reported significantly higher probability of retinoblastoma in participants exposed to higher levels of para-DCBs during pregnancy, but not for exposures averaged during the first year of a child's life. No significant results were reported for orth-DCBs.

Overall Quality Determination Medium

Study Citation:	Ehrenstein, Von, O. S., Heck, J. E., Park, A. S., Cockburn, M., Escobedo, L., Ritz, B. (2016). In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case-control study in California, USA. Environmental Health Perspectives 124(7):1093-1099.
Health Outcome(s) Assessed:	Neurological/Behavioral
Reported Health Effect(s):	Primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	5684085

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1:	Participant Selection	High	Cases of childhood brain cancer, including cases of primitive neuroectodermal tumor (PNET), medulloblastoma, astrocytoma, in this case-control study were selected from the California Cancer Registry. Cases were selected before age 6 and diagnosed in 1990-2007. Cases were then matched to California birth certificates from the California Department of Public Health's Office of Vital Records using first and last names as well as birth dates; matching was successful in 89% of cases. Controls without a cancer diagnosis before age 6 were randomly selected from California birth rolls and frequency matched to all childhood cancer cases during the same period at a ratio of 20 controls per case. Subjects were excluded if they had a missing gestational age from birth certificates (n=74 cases and n=12,035 controls), if they did not have at least one air toxics reading for each full month of pregnancy and within the last 30 days of pregnancy, if they did not live within <5 miles from a California Air Resources Board monitor, or if their gestational ages or birth weights were considered non-viable (viable gestational ages were considered to be 146-323 days, viable birth weights were considered to be 500-6,800 g). 719 controls were also excluded due to dying before 6 years of age after matching to California death records. The final sample size included n=183 cases and n=30,569 controls. There is no direct evidence of selection bias as the study attempted to draw cases and controls from the same eligible population, and none of the selection criteria are expected to be disproportionately affected by exposure or outcome.
	Metric 2:	Attrition	Medium	74 cases and 12,035 controls were excluded overall due to missing data on gestational age, while other exclusion criteria included: if they did not have at least one air toxics reading for each full month of pregnancy and within the last 30 days of pregnancy, if they did not live within <5 miles from a California Air Resources Board monitor, or if their gestational ages or birth weights were considered non-viable. It is not clear how many participants had missing air toxics readings; however, there is no evidence to suggest that missing air toxics readings would be associated with the studied outcomes.
	Metric 3:	Comparison Group	High	Cases and control were recruited from the same population during the same time period and were matched by birth year. Demographic information is presented as stratified by case/control status, and those same variables were considered as covariates in statistical analyses.
Domain 2: Exposure Characterization				

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Domain	Metric		Rating	Comments
	Metric 4:	Measurement of Exposure	Low	Exposure to DCBs was assessed based on participants geocoded residential addresses listed on birth certificates. From 1990 to 1997, only a ZIP code was listed on the birth certificate, and the ZIP code centroid were used for exposure measurement. DCBs exposure was measured via air toxics monitors set up by the California Air Resources Board, which collects 24-hour integrated samples of ambient air concentrations every 12 days (n=31 monitors) at locations expected to representative of the area. The distance from each monitor to geocoded addresses was calculated and addresses more than 5 miles away from the nearest monitor were excluded as exposure estimates may be less accurate at greater distances. The exposure assessment methodology is likely reliable given the use of public data, but the potential discrepancy between listed address on birth certificate and actual residence is also a limitation. The study estimated that up to 9% to 30% of families may move during pregnancy, thus there are concerns over non-differential misclassification bias.
	Metric 5:	Exposure Levels	Medium	Statistical analyses characterized exposure linearly and assessed changes in outcomes per IQR increase. IQRs were provide for each pollutant during each trimester, the entire pregnancy and the first year of life. While the IQRs are quite small (0.076 ppbV for o-DCB and 0.039 ppbV for p-DCB), they are potentially large enough to allow for sufficient exposure contrast.
	Metric 6:	Temporality	High	Exposure was characterized as averages for each trimester, the entire pregnancy period, and the first year of life to ensure temporality.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	The International Classification of Disease Oncology (ICD-O) codes were used to characterize PNET (ICD-O code 9473) and medulloblastoma (ICD-O code 9470), while the International Classification of Childhood Cancer was used to characterize astrocytoma (ICC-3 code 032). Cases were pulled from the California Cancer Registry. Controls were stated to be "without a cancer diagnosis", which may have been checked via linkage of birth certificates with the California Cancer Registry, although this is not explicitly stated by the paper. However, there is no evidence of outcome misclassification.
	Metric 8:	Reporting Bias	High	Adjusted ORs are reported with confidence intervals for each cancer type and each toxicant during pregnancy and the first year of life. The IQR increase in exposure and the number of cases and controls was also provided, alongside case/control numbers for each comparison group.
Domain 4: Potential Confounding / Variability Control				

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Domain	Metric		Rating	Comments
	Metric 9:	Covariate Adjustment	Medium	Potential confounders were selected based on previous knowledge and previous examination of demographic and perinatal factors related to cancer status in the data. Included covariates were birth year (matching variable), maternal age and education, race/ethnicity, and place of birth (United States vs. non-United States). Other variables that were also considered but not included in the final models were types of insurance (socio-economic status measure), rural/urban residence, parity, offspring sex, preterm birth.
	Metric 10:	Covariate Characterization	Low	No information was included on the collection of covariate data, for example, whether the information was self-reported by parents or collected through public records.
	Metric 11:	Co-exposure Counfounding	Medium	Exposure to other air toxics was also measured, and correlations across pollutants were presented. No adjustment was made for co-pollutants.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The case-control design is appropriate to assess the incidence of relatively rare childhood cancers.
	Metric 13:	Statistical Power	Medium	The number of cases with exposure measurements was small due to the rarity of the outcome and the small number of monitoring stations. Case sample sizes of n=23, n=32, and n=73 were reported in analyses of prenatal exposure for (PNET), medulloblastoma, and astrocytoma respectively; case sample sizes were n=23, n=14, and n=54 for analyses of first year-of-life exposure. Despite some small case numbers for some sub-groups, the sample sizes overall are likely large enough to detect an effect.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.
	Metric 15:	Statistical Analysis	High	Logistic regression was used to estimate odds ratios per interquartile-range increase in pregnancy exposures during each trimester, the entire pregnancy, and the first 12 months of life for each outcome. Numbers of cases/controls are presented for each analysis. Effect estimates are presented with 95% confidence intervals. Sensitivity analyses were performed adding additional potential confounders and restricted to participants with term birth.

Additional Comments: This case-control study on the association between DCBs and childhood brain cancer had an adequate sample size based on public records from 1990-2007, which was a strength due to the rarity of outcome. There is minimal concern over selection bias. The main limitation of the study is the exposure measurement based on air monitor readings. There is concern over misclassification bias due to discrepancies between registered and actual residential address, even though the bias is non-differential between cases and controls. However, a significant positive association was reported for first year-of-life exposure to o-DCB and the odds of developing primitive neuroectodermal tumors in children by six years of age; exposure during pregnancy resulted in a positive but non-significant association.

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Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	5684085

Domain	Metric	Rating	Comments
Overall Quality Determination		**Medium**	

Study Citation:	Rodrigues, E. G., Herrick, R. F., Stewart, J., Palacios, H., Laden, F., Clark, W., Delzell, E. (2020). Case-control study of brain and other central nervous system cancer among workers at semiconductor and storage device manufacturing facilities. Occupational and Environmental Medicine 77(4):238-248.
Health Outcome(s) Assessed:	Neurological/Behavioral
Reported Health Effect(s):	Brain and other central nervous system cancer
Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	10096148

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1:	Participant Selection	High	Participants in this nested case-control study were drawn from a cohort of 126,836 IBM employees. Detailed information on selection of cases and controls is provided, including time periods of eligibility and ICD codes for cases. Deceased cases were identified via the National Death Index or death certificates, and incident cases were identified via state cancer registries. Ten controls were selected for each case using incidence density sampling and were matched based on year of birth, facility where the case had last worked, gender, and race. Details on the parent cohort can be found in another publications (HEROID 3298947), There is no indication that selection into the study was biased.
	Metric 2:	Attrition	High	There was minimal exclusion from the analysis sample and outcome data and exposure were largely complete. Only one identified case was excluded due to comorbid malignant melanoma.
	Metric 3:	Comparison Group	High	Cases and controls were recruited from the same eligible population within the same time frame. Cases and controls were similar with respect to demographics and facility. Cases and controls were matched based on year of birth, facility where the case had last worked, gender, and race.
Domain 2: Exposure Characterization				
	Metric 4:	Measurement of Exposure	Medium	Exposure was estimated using work group–exposure matrices that linked quantitative exposure levels for o-Dichlorobenzene to participants' job histories. Each job was classified into one of 10 primary exposure groups (PEGs) based on tasks, work environment, and production type. Historical monitoring data were used to calculate mean concentrations for o-Dichlorobenzene by PEG and manufacturing era, and these were combined with job durations to estimate cumulative exposure for each subject. However, detailed work history information was only available beginning in 1965; depending on case status and facility, this resulted in an average of 20% to 44% of participant work history being excluded from the assessment (Table 1). Additionally, historical monitoring data were often sparse and were not available for each combination of chemical, facility, PEG, and time period.
	Metric 5:	Exposure Levels	Medium	The range and distribution of exposure is likely sufficiently large to detect an effect, and 4 levels of exposure (reference plus tertiles) to o-Dichlorobenzene are included in the analyses.
	Metric 6:	Temporality	High	The temporality of exposure and outcome is appropriate and considers relevant exposure windows. A sensitivity analysis using a 5-year latency period was conducted.

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Chemical:	o-Dichlorobenzene- Parent compound
HERO ID:	10096148

Domain	Metric		Rating	Comments
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	Deceased cases between 1965-1999 were identified from the National Death Index or death certificates. Incident cases were determined from state cancer registries. However, there was no registry for Vermont and records were not available for the entire follow-up period in New York and California. Cases and controls from each facility were followed for the same length of time.
	Metric 8:	Reporting Bias	Medium	Most of the study's measured outcomes are reported in detail, including 95% confidence intervals and the number of cases and controls for each analysis. However, results of the 5-year latency analysis were only reported qualitatively ("similar to those of the main analyses").
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	High	Conditional logistic regression models for each facility were generated and controlled for matching variables (year of birth, gender, and race).
	Metric 10:	Covariate Characterization	High	Covariates appear to have been obtained from case ascertainment sources (National Death Index, death certificates, or state cancer registries) or employee records.
	Metric 11:	Co-exposure Counfounding	Low	Co-exposures to numerous other chemicals were present but were not adjusted for in the analyses. Effect estimates are presented for 30 other chemicals measured in the study, but there is no multi-pollutant model that considers all exposures together.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The nested case-control study design and the conditional logistic regression models were appropriate for the research question.
	Metric 13:	Statistical Power	Medium	The number of cases (n=120) and controls (n=1,028) is likely adequate to detect an effect in the population.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient and would be reproducible with access to the data.
	Metric 15:	Statistical Analysis	High	Descriptions of risk estimate calculations for each outcome were provided and the variables used in each analysis were described. Associations were estimated using conditional logistic regression.

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Domain	Metric	Rating	Comments
Additional Comments:	This nested case-control study explored links between occupational exposures from semiconductor and electronic module manufacturing and central nervous system (CNS) cancer. The study compared 120 CNS cancer cases to 1,028 matched controls, assessing job roles across 10 process groups and cumulative exposure to 31 potential carcinogens. Findings indicated positive associations between CNS cancer and module manufacturing operations, as well as high cumulative exposure to certain chemicals, including o-dichlorobenzene. The exposure assessment was limited by sparse monitoring data, incomplete coverage across chemicals, facilities, and time periods, and potential misclassification. However, there were no significant limitations that would decrease the confidence in the findings of the study.		

Overall Quality Determination High