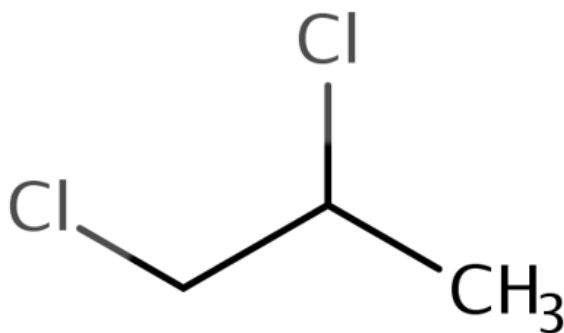

**Draft Data Quality Evaluation Information for
Human Health Hazard Epidemiology for
1,2-Dichloropropane**

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 78-87-5



May 2026

This supplemental file contains the data quality evaluation results for epidemiology data sources that met the PECO screening criteria for the *Draft Risk Evaluation for 1,2-Dichloropropane* and were used to characterize human health hazard. 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* (referred to hereafter as the '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 1,2-Dichloropropane*.

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HERO ID	Reference	Page
1,2-Dichloropropane		
Cancer/Carcinogenesis		
3014082	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. <i>Environmental Health</i> 14(1):14.	4
4821835	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. <i>Environmental Health</i> 17(1):28.	7
1936441	Kumagai, S., Kurumatani, N., Arimoto, A., Ichihara, G. (2013). Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. <i>Occupational and Environmental Medicine</i> 70(7):508-510.	10
3419929	Kumagai, S., Sobue, T., Makiuchi, T., Kubo, S., Uehara, S., Hayashi, T., Sato, K. K., Endo, G. (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers. <i>Occupational and Environmental Medicine</i> 73(8):545-552.	12
5440630	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. <i>Environment International</i> 130:104897.	14
3064884	Sobue, T., Utada, M., Makiuchi, T., Ohno, Y., Uehara, S., Hayashi, T., Sato, K. K., Endo, G. (2015). Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane. <i>Journal of Occupational Health</i> 57(3):230-236.	17
Reproductive/Developmental		
2799700	Brender, J. D., Shinde, M. U., Zhan, F. B., Gong, X., Langlois, P. H. (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. <i>Environmental Health</i> 13(1):96.	19
3014082	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. <i>Environmental Health</i> 14(1):14.	21
4821835	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. <i>Environmental Health</i> 17(1):28.	24

Study Citation:	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. Environmental Health 14(1):14.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	breast cancer in females		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	3014082		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	A total of 112,378 women were included in this study out of 133,479 eligible female participants from the California Teacher Study cohort. A full description of the cohort is provided in Bernstein et al. 2002 (HERO ID 808446). Reasons for exclusion were provided. The reported information indicates that participant selection in or out of the study and participation was not likely to be biased.
Metric 2:	Attrition	High	112,378/133,479 participants were included in the study. Exclusions were for the purpose of the study and analysis. Exclusion criteria were documented. Included participants had completed questionnaires. The California Cancer Registry is estimated to be 99% complete.
Metric 3:	Comparison Group	Medium	There is only indirect evidence that groups are similar. Participants were recruited from the same eligible population with the same method of ascertainment. Comparisons were provided for participants with and without breast cancer. Characteristics between these two groups were generally similar. 5 Quintiles of exposure were used, and Q2-5 were compared with Q1.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	The Assessment System for Population Exposure Nationwide and the Human Exposure Model are used as part of the National-Scale Air Toxics Assessment produced by the EPA and was used to estimate ambient HAP concentrations for geographic locations. Methods are described online through the US EPA Assessment Methods.
Metric 5:	Exposure Levels	Medium	The distribution of the NATA annual ambient concentration for each compound was plotted in Figure 1 using a box plot, and 5 Quintiles were used in the analyses.
Metric 6:	Temporality	Medium	The follow-up period was from 1995-2011, and the NATA estimates were made in 2002 because it was approximately half way between the start and end of the follow-up period. However, it is unclear whether exposures fall within relevant exposure windows for the outcome of interest.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Annual linkage between the CTS cohort and the California Cancer Registry (CCR) was used to identify cases of invasive breast cancer. The CCR is estimated to be 99% complete. The case of invasive breast cancer was defined by ICD codes.
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Study Citation:	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. Environmental Health 14(1):14.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	breast cancer in females			
Chemical:	1,2-Dichloropropane- Parent compound			
HERO ID:	3014082			
Domain	Metric	Rating	Comments	
	Metric 8: Reporting Bias	Medium	A description of measured outcome is reported for adjustments by age and race, and effect estimates are reported with a 95% confidence interval. The measured outcomes using multiple comparisons were generally described in the text, but non-significant results were excluded from Table 3.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Medium	The models were stratified by age and race. Additionally, adjustments were made for multiple comparisons among subsets of the participants (significant results reported in Table 3). Socioeconomic status (SES) of each participant was not evaluated, however, cohort SES characteristics were thought to be similar by study authors.	
	Metric 10: Covariate Characterization	Medium	Information about baseline characteristics for each participant was collected through a questionnaire. It is unknown if the questionnaire was validated.	
	Metric 11: Co-exposure Counfounding	Medium	A total of 37 compounds were identified as mammary gland carcinogens, but 13 were not included in this analysis. Thirteen compounds were excluded from the analysis due to insufficient variability (nine because they had the same value for all census tracts in the state of California; and four because they had less than 25% non-zero values). Propylene dichloride (1,2-dichloropropane) was among the 24 compounds evaluated in this assessment, and evaluations for breast cancer were conducted for each of these 24 individual compounds.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	High	The study design chosen (prospective cohort) was appropriate for the research question (incidence of breast cancer). Cox proportional hazard models and SAS 9.3 were used in this assessment. Data analysis was described.	
	Metric 13: Statistical Power	Medium	Statistical power calculations were not provided. No significant effects were observed with propylene dichloride (1,2-dichloropropane), however, this study utilized a large cohort, approximately 112,000 individuals. Distributions of chemicals of interest suggest there were sufficient numbers of participants in exposure subgroups.	
	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	The statistical models that were used were identified and described. "No apparent violation of the underlying assumption of proportional hazards was detected".	
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Study Citation:	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. Environmental Health 14(1):14.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	breast cancer in females
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	3014082

Domain	Metric	Rating	Comments
Additional Comments:	A group of 112,378 female participants from the California Teacher Study cohort were assessed for their estimated exposure to ambient air pollutants, including propylene dichloride (1,2-dichloropropane), and the incidence of invasive breast cancer. Air contaminant concentrations were estimated using the US EPA NATA and the ASPEN and HEM models. The approximate median concentration of 1,2-dichloropropane is between 1E-5 and 1E-3 (estimated from Figure 1). Exposures were categorized into 5 Quintiles, and compared against Quintile 1. No significant increase in the estimated hazard rate ratio for invasive breast cancer was observed with Quintile 2-5 exposure estimates for 1,2-dichloropropane, adjusted for age and race, when compared against Quintile 1, or when further adjusted using multiple comparisons.		

Overall Quality Determination

High

Study Citation:	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environmental Health 17(1):28.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	Invasive incident breast cancer		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	4821835		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	Medium	Participants were drawn from the Nurses' Health Study II, a prospective cohort of 116,430 female nurses established in 1989. Female nurses (ages 15-42 years) completed a baseline questionnaire at enrollment across 14 US states. Study authors note that biennial follow-up questionnaires had response rates of over 90%. Women were excluded from the current analysis if they had been diagnosed with cancer before they returned the baseline questionnaire, if they lived outside of the contiguous US, or if they lived in a census tract with no information on exposure. Participants were censored if they were diagnosed with a cancer other than breast or non-melanoma skin cancer. The final sample size consisted of 109,239 women. Details of the initial participation rate were not reported, but concern is mitigated by the prospective study design (and high follow up response rate) and limits the concern that inclusion was selective with regard to exposure or outcome.
	Metric 2: Attrition	High	After applying exclusion criteria, there were a total of 109,239 women included in the study. Authors note that biennial follow up response rates are over 90%. No other details were provided, and loss to follow up is considered minimal.
	Metric 3: Comparison Group	High	Participants were all nurses from the United States and recruited during the same using the same eligibility criteria.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Low	Exposure to hazardous air pollutants, including 1,1-dichloroethane, was determined using residential addresses obtained from questionnaires and modeled data from EPA's National Air Toxics Assessment (NATA). Participant residential addresses were available for each participant from 1989 forward, and addresses were geocoded to census tract for exposure assignment. Data on air pollutants was developed from dispersion modeling of exposure data obtained from outdoor monitoring sources. The method was not specifically described as validated, but was based on EPA exposure assessment methods and detailed information on exposure modeling is provided in the cited references. However, there are concerns for exposure misclassification due to the use of census-tract level data, especially since the methods cannot account for variation in an individual's daily activities that could lead to increased or decreased levels of exposure.
	Metric 5: Exposure Levels	Medium	The risk of incident breast cancer was modeled by quartiles of exposure. Exposure distribution data is provided in supplemental Table 1, and ranges appear to be wide enough to allow for sufficient exposure contrast.
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Study Citation:	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environmental Health 17(1):28.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Invasive incident breast cancer
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	4821835

Domain	Metric	Rating	Comments
	Metric 6: Temporality	Low	Participants were followed from 1989 through 2011, while exposure estimates were drawn from modeled 2002 NATA data. Study authors note analyses were also conducted using 1996 NATA data, and results were similar. However, data from both timepoints does not capture the entire follow-up period, and the impact of earlier exposure to HAPs (i.e., pre-1996) is unclear. The study also does not account for lagged exposure, which is relevant for cancers as the etiologically relevant time window is typically years prior to the first appearance of the outcome.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	High	Incident breast cancer cases were self-reported during biennial questionnaires, and deaths were ascertained from family members, the US Postal Service, and annual searches of the National Death Index. Study authors note that medical record review confirmed 99% of self-reported breast cancer diagnoses. ER status was determined from tissue microarray, immunohistochemical analysis, or medical record.
	Metric 8: Reporting Bias	High	All outcomes outlined in the abstract, introduction, and methods were reported in sufficient detail. Results were provided as Hazard Ratios, 95% confidence intervals, and the number of incident cases.
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	Information on demographics, lifestyle characteristics, and potential risk factors were obtained from the biennial follow-up questionnaires. A wide range of potential confounders associated with invasive breast cancer were identified a priori. Each potential confounder was added to models "to determine its impact on the effect estimates," but further detail on how this was determined was not provided. Results stratified by smoking also reported in the supplement. Final models adjusted for age, calendar period, race, family history of breast cancer, history of aspiration or biopsy confirmed benign breast disease, age at menarche, parity and age at first birth, menopausal status and post-menopausal hormone use, oral contraception use, recent mammogram, height, BMI at age 18, difference between current BMI and BMI at age 18, smoking status, physical activity, overall diet quality (including alcohol consumption), alcohol consumption at age 15 and age 18, individual-level SES (marital status, living arrangements, household income), shift work, area-level SES (Census tract median home value and median income), and Census region of residence.
	Metric 10: Covariate Characterization	Medium	Information on demographics, lifestyle characteristics, and potential risk factors were obtained from the biennial follow-up questionnaires. The questionnaire was not noted to be validated, but there was no direct evidence the method had poor validity.

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Study Citation:	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environmental Health 17(1):28.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Invasive incident breast cancer
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	4821835

Domain	Metric	Rating	Comments
	Metric 11: Co-exposure Counfounding	Medium	Other hazardous air pollutants were measured and analyzed in the study, but there was no direct evidence to suggest an unbalanced provision of additional co-exposures across study groups.

Domain 5: Analysis	Metric 12: Study Design and Methods	High	The association between exposure to hazardous air pollutants was analyzed in a large prospective cohort using modeled air pollution concentrations with a long follow-up period. Study design was appropriate for the research question.
	Metric 13: Statistical Power	Medium	No concerns regarding statistical power. The study included 109,239 women with 2,203,192 person-years of follow-up.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was sufficient to understand the process and reproduce given original data.
	Metric 15: Statistical Analysis	High	The method for calculating hazard ratios was transparent. While there is no discussion of testing for the proportional hazards assumption, there is also no evidence to suggest that the assumption was violated. Details on inclusion of potential confounders was limited but was not of concern.

Additional Comments:	This study analyzed the association between air pollution exposures (modeled using EPA NATA and linked via residential address) and incident breast cancer in a large prospective cohort. Strengths of the study included a large sample size, long follow-up period, high rate of follow-up, and robust assessment. There are concerns regarding exposure misclassification due to the use of census-tract level exposure data for individuals, and potential concerns for temporality due to no assessment of lagged exposures. While air pollution concentrations from 2002 were used to analyze the whole study period (1989-2011), no other major concerns noted.
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Overall Quality Determination	High
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Study Citation:	Kumagai, S., Kurumatani, N., Arimoto, A., Ichihara, G. (2013). Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occupational and Environmental Medicine 70(7):508-510.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	mortality from cholangiocarcinoma		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	1936441		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	All employees working in the identified facility between 1991 and 2006 for at least one year were eligible to participate. 62 men and 11 women were identified, however, the women were excluded from SMR analysis due to a lack of cholangiocarcinoma in the female workers. The study setting was adequately described.
Metric 2:	Attrition	Low	Eleven proof-printing workers and three front room workers could not be traced and were assumed alive at the end of 2011. This represents moderate attrition from the over-all analysis sample (n=62).
Metric 3:	Comparison Group	High	"Sex, age, calendar year, and cause-specific mortality rates among the Japanese population" were used as the comparator, indicating groups were similar.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	The Japanese National Institute of Occupational Safety and Health measured exposure concentrations during an experiment that reproduced working conditions of proof-printing workers. Interviews were conducted with 12 proof-printing workers and 4 front room workers to identify chemicals that were used. It is not clear how estimates of front room worker exposure were derived, and it is not clear if job histories were documented.
Metric 5:	Exposure Levels	Medium	Exposure estimates were provided for both proof-printing and front room workers. The general population of Japan was used as a comparator group.
Metric 6:	Temporality	Medium	It is not certain if at least 1 year of occupational exposure to 1,2-dichloromethane is appropriate to examine mortality from cholangiocarcinoma. Latency periods were reported for each case of cholangiocarcinoma.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Medical records were collected and interviews were conducted for the 11 participants diagnosed with cholangiocarcinoma. Out of the whole population, 14 untraceable participants were assumed to be alive at the end of 2011 - it was not specified if any of these participants were included in the 11 cases of cholangiocarcinoma.
Metric 8:	Reporting Bias	High	A description of measured outcomes is reported and effect estimates are reported with a 95% confidence interval.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	High	Only men were included in the assessment. SMRs were stratified by job duty and calculated using sex, age, calendar year, and cause-specific mortality rates using the Japanese population.

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Study Citation:	Kumagai, S., Kurumatani, N., Arimoto, A., Ichihara, G. (2013). Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occupational and Environmental Medicine 70(7):508-510.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	mortality from cholangiocarcinoma			
Chemical:	1,2-Dichloropropane- Parent compound			
HERO ID:	1936441			
Domain	Metric		Rating	Comments
	Metric 10:	Covariate Characterization	Medium	Medical records or interviews were used to collect information about the patients.
	Metric 11:	Co-exposure Counfounding	Medium	Exposure duration for dichloromethane was reported and indirectly adjusted for.
Domain 5: Analysis	Metric 12:	Study Design and Methods	High	Study authors utilized a retrospective cohort to calculate cause-specific SMRs in a group of workers highly exposed to 1,2-DCP and DCM.
	Metric 13:	Statistical Power	Low	11/62 men were diagnosed with cholangiocarcinoma, and 6 deaths occurred among the 11 diagnoses. Statistical power calculations were not provided.
	Metric 14:	Reproducibility of Analyses	Medium	The method to calculate SMRs was adequately described.
	Metric 15:	Statistical Analysis	High	SMRs were adequately described and there were no concerns regarding model assumptions.
Additional Comments:	Out of a group of 62 male workers that worked at a printing company between 1991 and 2006, 11 cases of cholangiocarcinoma were identified. The study took place in Osaka, Japan and examined standardized mortality ratios for the 11 cases of cholangiocarcinoma. Average estimated exposures to 1,2-dichloropropane ranged from 190-310 ppm for proof-printing workers and from 70-110 ppm for front room workers. The SMRs for cholangiocarcinoma were 5000 (expected deaths (E): 0.00100, 95% CI 1,600-12,000) for proof-printing workers, 960 (E: 0.00104, 95% CI 24-5,400) for front room workers, and 2,900 (E: 0.00204, 95% CI 1,100-6,400) for all. This study reported limited details, did not describe the statistical analysis, and the stated research question/objective (assessing if occupational exposure to solvents is associated with cholangiocarcinoma) did not directly align with the outcome (SMR) that was presented.			

Overall Quality Determination

Low

Study Citation:	Kumagai, S., Sobue, T., Makiuchi, T., Kubo, S., Uehara, S., Hayashi, T., Sato, K. K., Endo, G. (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers. Occupational and Environmental Medicine 73(8):545-552.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	Cholangiocarcinoma (bile duct cancer)		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	3419929		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	Participants identified from company lists of workers and records of the Ministry of Health, Labour, and Welfare, Japanese government.
Metric 2:	Attrition	Medium	Eight participants were excluded from the study because they lacked vital info or retirement info, which could be linked to disease status. They also excluded 11 workers because they had not been exposed to 1,2-DCP.
Metric 3:	Comparison Group	High	SIR analysis adjusted for age, sex, and calendar year of exposure. and was pulled from the same general population (Japan).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	A lab replicated work conditions to estimate concentration in air for one plant, and study used those calculations to estimate exposure concentration. For the other three plants without experiment to reproduce the conditions, two mathematical models, a near-field and far-field model and a well-mixed model, were used to estimate exposure concentrations.
Metric 5:	Exposure Levels	Medium	Sufficiently wide range of exposure. Four levels of exposure based on cumulative exposure were used in the analysis.
Metric 6:	Temporality	High	Documented estimated exposure history is from 1987-2006, and documented dates of diagnosis for cholangiocarcinoma are from 1987-2012.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	The study used the International Classification of Disease Ninth Edition (ICD-9) and ICD-10 to identify cholangiocarcinoma. Japanese Ministry of Health provided diagnosis information in 2013, which was checked against medical records for confirmation in a prior study of this population by the Ministry (not available in HERO)
Metric 8:	Reporting Bias	High	Number of cases are reported, as well as standardized incidence ratios and relative risks with confidence intervals (95% CIs).
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	High	Adjustments for age, sex, and calendar year (1987-1994, 1995-2004, 2005-2012) are described and taken into account in statistical modeling.
Metric 10:	Covariate Characterization	High	Used occupational and governmental data to characterize potential confounders such as age and sex.
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Study Citation:	Kumagai, S., Sobue, T., Makiuchi, T., Kubo, S., Uehara, S., Hayashi, T., Sato, K. K., Endo, G. (2016). Relationship between cumulative exposure to 1,2-dichloropropane and incidence risk of cholangiocarcinoma among offset printing workers. Occupational and Environmental Medicine 73(8):545-552.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Cholangiocarcinoma (bile duct cancer)
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	3419929

Domain	Metric	Rating	Comments
	Metric 11: Co-exposure Counfounding	Medium	Study considered exposure to dichloromethane as a potential co-exposure and adjusted for it in statistical models.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The cohort study assessed cancer incidence over time, calculated standardized incidence ratio (SIR), and used Poisson regression to estimate incidence rate ratios (RRs) with 95% CI.
	Metric 13: Statistical Power	Low	Case numbers were relatively high (n=17), however, the overall cohort sample size was limited (n=95). Models without lag time and with a 5-year lag time were able to obtain statistically significant results (<0.001).
	Metric 14: Reproducibility of Analyses	Medium	This study has clearly documented methods.
	Metric 15: Statistical Analysis	High	Statistical modeling is transparent. Akaike's information criterion was calculated to verify goodness-of-fit of the model.

Additional Comments: The study used an occupational cohort of printer workers to understand their exposure of 1,2-dichloropropane and evaluate if there is an association with cholangiocarcinoma. Exposure was estimated by reproducing the condition of use (printing) in a laboratory, determining the ratio between chemical used and airborne concentration, and extrapolating those results to the amount of chemical historically used in several printing plants as reported by industry and government officials. For the other three plants without experiment to reproduce the conditions, two mathematical models, a near-field and far-field model and a well-mixed model, were used to estimate exposure concentrations. Cumulative exposures were then calculated for each worker. Cholangiocarcinoma data assessed by industry and government data. The standardized incidence ratio for male workers was 1203 (CI: 701, 1927) and 0 (CI: 0, 9426) for female workers. The adjusted relative risks for the high exposure group compared to the low-exposure group were 17.1 (CI: 3.8, 76.2) for no lag time and 32.4 (CI: 6.4, 163.9) for 5-year lag time.

Overall Quality Determination

High

Study Citation:	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. Environment International 130:104897.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	Breast cancer diagnosis (overall), tumor characteristics, and estrogen receptor positive (ER+) invasive breast cancer		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	5440630		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	Data from the Sister Study were used. The Sister Study is "a prospective cohort of 50,884 women from across the US who were ages 35–74 at enrollment (Sandler et al., 2017). Participants were recruited from 2003 to 2009 using a national advertising campaign in English and Spanish. Women were eligible for the Sister Study if they had a sister who had been diagnosed with breast cancer, but no prior breast cancer themselves."Exclusions from the study occurred for the following reasons:-breast cancer diagnosed before enrollment was complete, or did not have follow-up information (n = 163)-Residential address couldn't be geocoded (n = 1003, < 2%) - This is a small percentage, but all of those who were excluded for this reason were from Puerto Rico, West Virginia, Missouri, or Oklahoma.Key elements of the study design are reported. There is some potential for selection bias, but based on the small percentage of those eligible who were excluded, participation was not likely to be substantially biased.
Metric 2:	Attrition	High	Response rates in the overall Sister study remained over 91% over follow-up. Reasons for non-response were not reported, and characteristics of those lost to follow up were not reported or compared with those included, but 9% loss to follow-up is minimal.
Metric 3:	Comparison Group	High	Differences in baseline characteristics of groups were considered as potential confounding variables.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	The EPA NATA database of census-tract level modeled air toxics data was used. The study authors note the potential for exposure misclassification: "Concentrations at the census tract level do not fully account for variation in an individual's daily activities that could lead to higher or lower exposure, and all women within a census tract are assigned the same concentration."
Metric 5:	Exposure Levels	Medium	There were five quintiles of exposure, so there was a sufficient range and distribution of exposure.
Metric 6:	Temporality	Medium	This is a prospective cohort study.Exposure data from 2005 were chosen because they represented the middle of the enrollment period (2003-2009).The study reported that "94% of women enrolled in 2005 or later, and thus the exposure assessment primarily predated enrollment for the majority of Sister Study participants."The six percent of women who had the potential to have the outcome before exposure was measured in 2005 are a concern. But sensitivity analyses were used to assess whether the associations changed when restricted to those who enrolled in 2005 or later.The authors note that the study is making assumptions about the relevant exposure windows - therefore the exposure window is not certain.

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Study Citation:	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. Environment International 130:104897.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	Breast cancer diagnosis (overall), tumor characteristics, and estrogen receptor positive (ER+) invasive breast cancer		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	5440630		
Domain	Metric	Rating	Comments
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Women who reported a breast cancer diagnosis on the annual health updates or follow-up questionnaires were asked to provide additional diagnosis information, and to grant permission for the study to obtain medical records and pathology reports. Medical records were obtained for 81% of breast cancer diagnoses. Agreement between self-reported breast cancers and medical records was high (positive predictive value > 99%) (Sandler et al., 2017), so self-report was used when medical records were not available. Tumor characteristics (stage; histology; and estrogen receptor (ER) status) were abstracted from medical records, or self-reported.
Metric 8:	Reporting Bias	High	A description of measured outcomes is reported. Effect estimates are reported with confidence intervals.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	High	Covariates considered included age, race, BMI, residence type, education, and smoking status. Potential confounders were identified using DAGs and literature review. Appropriate considerations were made for potential confounders.
Metric 10:	Covariate Characterization	Medium	"Most covariates were assessed by self-report at the baseline interview." "At baseline, women completed a computer-assisted telephone interview and written questionnaires." Previous publications might describe whether the questionnaires were validated, but validation was not specified in this publication.
Metric 11:	Co-exposure Counfounding	Medium	Co-exposures to other air pollutants were assessed, but at the census tract level. Multipollutant classification trees were used, which might provide useful qualitative information.
Domain 5: Analysis			
Metric 12:	Study Design and Methods	High	The study design (large prospective cohort) and analysis method (Cox proportional hazard single and multi-pollutant models accounting for potential confounders) were appropriate to assess the association between exposure and disease.
Metric 13:	Statistical Power	Medium	The study had an adequate sample size (1975 cancer cases) and follow-up time (mean=8.4 years).
Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient to be conceptually reproducible.
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Study Citation:	Niehoff, N. M., Gammon, M. D., Keil, A. P., Nichols, H. B., Engel, L. S., Sandler, D. P., White, A. J. (2019). Airborne mammary carcinogens and breast cancer risk in the Sister Study. Environment International 130:104897.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Breast cancer diagnosis (overall), tumor characteristics, and estrogen receptor positive (ER+) invasive breast cancer
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	5440630

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	High	Hazard ratios and 95% confidence intervals (CIs) are reported "comparing index categories of exposure to exposures below the first quintile using Cox proportional hazards regression, with age as the time scale." The method of calculating the hazard ratios is transparent. The authors reported that "the proportional hazards assumption was evaluated by conducting a Wald test for an interaction between the continuous form of the air toxic measure and time." Censoring times and times at-risk are described.

Additional Comments: This was a well-conducted study of a large prospective cohort, but the measurement of exposure at the census-tract rather than the individual level is a limitation.

Overall Quality Determination

Medium

Study Citation:	Sobue, T., Utada, M., Makiuchi, T., Ohno, Y., Uehara, S., Hayashi, T., Sato, K. K., Endo, G. (2015). Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Journal of Occupational Health 57(3):230-236.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	cholangiocarcinoma of the bile duct		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	3064884		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	High	A total of 106 workers (86 men, 20 women) were included in this study. Key elements of the study design and participant selection were described.
	Metric 2: Attrition	Medium	106/116 workers were included in the study. The 10 excluded workers either had missing information or an unknown vital status. It is not clear if the characteristics of excluded participants were similar to included participants. Reasons for exclusion were documented.
	Metric 3: Comparison Group	High	Age and sex stratification is described and choice of reference population is reported. Participants were selected from the same cohort of workers and were compared with the general population of Japan.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Medium	"Cumulative exposure years were calculated for each chemical on an individual basis". Information for each participant was not provided.
	Metric 5: Exposure Levels	Low	Reports 2 levels of exposure (exposed/unexposed).
	Metric 6: Temporality	High	"Cumulative exposure durations were calculated using a range of different lag times (0, 3, and 5 years)", and 17 cases of cholangiocarcinoma were reported between 1985-2012.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	Medium	Incidences of cholangiocarcinoma "were based on claims of Industrial Accident Compensation Insurance submitted to the Labour Standards Inspection Office, Japan" or from information collected from mailed in questionnaires for participants to account for cases of cholangiocarcinoma not reported to the insurance company.
	Metric 8: Reporting Bias	High	A description of the measured outcomes is reported and effect estimates (SIRs) are reported with a 95% confidence interval. Number of exposed and person-years was reported in both tables.
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	Medium	Person-years of presumed exposure to each 1,2-dichloropropane and dichloromethane were estimated for each individual and results in Table 1 are stratified by sex. Table 2 is not stratified by sex, but examined years of cumulative exposure for the whole cohort.
	Metric 10: Covariate Characterization	Medium	Copies of medical records, health check-ups, or mailed questionnaires were used to collect information about the participants. We do not know if the questionnaires were validated.
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Study Citation:	Sobue, T., Utada, M., Makiuchi, T., Ohno, Y., Uehara, S., Hayashi, T., Sato, K. K., Endo, G. (2015). Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Journal of Occupational Health 57(3):230-236.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	cholangiocarcinoma of the bile duct			
Chemical:	1,2-Dichloropropane- Parent compound			
HERO ID:	3064884			
Domain	Metric	Rating	Comments	
	Metric 11: Co-exposure Counfounding	Medium	Co-exposure to dichloromethane was appropriately adjusted for each individual based on person-years of occupational exposure.	
Domain 5: Analysis	Metric 12: Study Design and Methods	High	The study design (retrospective cohort) was appropriate to assess the outcome of interest (SIR of cholangiocarcinoma). SIR with 95% CI was used to compare incidence rates of cholangiocarcinoma.	
	Metric 13: Statistical Power	Medium	The number of participants are adequate to detect an effect in the exposed population (17 incidents of cholangiocarcinoma), but statistical power calculations were not provided.	
	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	Assumptions of lag time and incidence rates between 2008-2011 were described and used in the analyses.	
Additional Comments:	A group of 106 current and former workers in the printing department of a printing company in Osaka, Japan exposed to 1,2-dichloropropane and/or dichloromethane were examined for the incidence of cholangiocarcinoma (bile duct cancer), compared incidence rates among the general population of Japan. Person-years of exposure were calculated for each chemical for each participant. Increased SIRs were observed with increased exposure to 1,2-dichloropropane using a 5-year lag time. SIRs were also increased for participants employed between the years of 1996-1999.			
Overall Quality Determination		Medium		

Study Citation:	Brender, J. D., Shinde, M. U., Zhan, F. B., Gong, X., Langlois, P. H. (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environmental Health 13(1):96.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	birth defects (neural tube defects, limbs deficiencies, oral cleft defects, heart defects, spina bifida, anencephaly)		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	2799700		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	Participants were drawn from the Texas Birth Defects Registry (TBDR) for years 1996-2008. Controls were frequency matched from the same registry. Study authors state that neural tube cases were more likely to not be successfully geocoded which may introduce selection bias, however, the authors note that both cases and controls with addresses that could not be geocoded were similar. In spite of that, the inclusion criteria, methods of participant selection, and frequency match were reported.
Metric 2:	Attrition	Medium	13.3% case mother addresses and 12.8% control mother addresses were unable to be geocoded, however this most likely only lowered the precision of the study and most likely does not vary based on exposure level.
Metric 3:	Comparison Group	Medium	Controls were matched to cases and pulled from the same eligible population by year of delivery and public health service region. Other demographic factors, e.g., race was not matched in population selection. However, statistical analyses were adjusted for year of delivery, maternal age, race/ethnicity, education, and public health region of residence.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Used Emission Weighted Proximity Model to estimate exposure at a given address based on proximity to emission sources and the specific amount or type of pollutant emitted. There may be some exposure misclassification due to mothers moving away from geocoded addresses. Previous studies indicate ~67% of mothers do not move between conception and delivery.
Metric 5:	Exposure Levels	Medium	Reports exposure as "exposure risk value" and groups the risk values into quartiles, with exposure risk values < 0 being the referent group
Metric 6:	Temporality	Medium	The study authors estimated exposure based on residence during pregnancy and evaluated birth outcomes. Temporality is established. Previous studies indicate ~67% mothers don't move between trimester and delivery. For mothers who moved during the pregnancy, the temporality is unknown.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Outcomes determined by Texas Birth Defect Registry, checking for birth defect diagnosis. Birth certificates came from Center for Health Statistics at Texas Department of State Health Services
Metric 8:	Reporting Bias	High	Outcome data measured and reported clearly, stratified by specific type of birth defect
Domain 4: Potential Confounding / Variability Control			
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Study Citation:	Brender, J. D., Shinde, M. U., Zhan, F. B., Gong, X., Langlois, P. H. (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environmental Health 13(1):96.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	birth defects (neural tube defects, limbs deficiencies, oral cleft defects, heart defects, spina bifida, anencephaly)			
Chemical:	1,2-Dichloropropane- Parent compound			
HERO ID:	2799700			
Domain	Metric	Rating	Comments	
	Metric 9: Covariate Adjustment	Medium	Cases were frequency matched by year of delivery and public health service region. Final models were adjusted for year of delivery, public health region, maternal age (<20, 20-24, 25-29, 30-34, 35-39, >39 years), education (<12 years, 12 years, >12 years), and race/ethnicity (Whit non-Hispanic, Black non-Hispanic, Hispanic, other non-Hispanic).	
	Metric 10: Covariate Characterization	High	Used birth and death certificates for demographic information	
	Metric 11: Co-exposure Counfounding	Medium	other co-exposures were not described	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	High	study used logistic regression to measure association between exposure and birth defects	
	Metric 13: Statistical Power	Medium	Overall adequate number of cases and controls - some effects have low cell counts, but at least one health effect has sufficient statistical power.	
	Metric 14: Reproducibility of Analyses	Medium	Methods sufficiently detailed for reproducibility	
	Metric 15: Statistical Analysis	High	No logistic regression model assumption violations were identified.	
Additional Comments:	This study examined the association between proximity to several point sources of chlorinated solvents and birth defects. Exposure was assessed using EPA's Toxic Release Inventory, and birth defects were assessed using Texas birth registries. The geocoded address of mothers on day of delivery and the amount of solvent was plugged into the Emission Weighted Probability model to assign each mother an exposure risk value. Limitations include limited evidence of temporality. Additionally, elective terminations lacked a vital record, which meant only 69% of mothers with neural tube defects were geocoded. Mothers highly exposed to 1,2-dichloropropane were 1.77 times more likely to have the cleft palate than the controls.			

Overall Quality Determination**High**

Study Citation:	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. Environmental Health 14(1):14.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	breast cancer in females		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	3014082		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	A total of 112,378 women were included in this study out of 133,479 eligible female participants from the California Teacher Study cohort. A full description of the cohort is provided in Bernstein et al. 2002 (HERO ID 808446). Reasons for exclusion were provided. The reported information indicates that participant selection in or out of the study and participation was not likely to be biased.
Metric 2:	Attrition	High	112,378/133,479 participants were included in the study. Exclusions were for the purpose of the study and analysis. Exclusion criteria were documented. Included participants had completed questionnaires. The California Cancer Registry is estimated to be 99% complete.
Metric 3:	Comparison Group	Medium	There is only indirect evidence that groups are similar. Participants were recruited from the same eligible population with the same method of ascertainment. Comparisons were provided for participants with and without breast cancer. Characteristics between these two groups were generally similar. 5 Quintiles of exposure were used, and Q2-5 were compared with Q1.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	The Assessment System for Population Exposure Nationwide and the Human Exposure Model are used as part of the National-Scale Air Toxics Assessment produced by the EPA and was used to estimate ambient HAP concentrations for geographic locations. Methods are described online through the US EPA Assessment Methods.
Metric 5:	Exposure Levels	Medium	The distribution of the NATA annual ambient concentration for each compound was plotted in Figure 1 using a box plot, and 5 Quintiles were used in the analyses.
Metric 6:	Temporality	Medium	The follow-up period was from 1995-2011, and the NATA estimates were made in 2002 because it was approximately half way between the start and end of the follow-up period. However, it is unclear whether exposures fall within relevant exposure windows for the outcome of interest.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Annual linkage between the CTS cohort and the California Cancer Registry (CCR) was used to identify cases of invasive breast cancer. The CCR is estimated to be 99% complete. The case of invasive breast cancer was defined by ICD codes.

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Study Citation:	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. Environmental Health 14(1):14.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	breast cancer in females			
Chemical:	1,2-Dichloropropane- Parent compound			
HERO ID:	3014082			
Domain	Metric	Rating	Comments	
	Metric 8: Reporting Bias	Medium	A description of measured outcome is reported for adjustments by age and race, and effect estimates are reported with a 95% confidence interval. The measured outcomes using multiple comparisons were generally described in the text, but non-significant results were excluded from Table 3.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Medium	The models were stratified by age and race. Additionally, adjustments were made for multiple comparisons among subsets of the participants (significant results reported in Table 3). Socioeconomic status (SES) of each participant was not evaluated, however, cohort SES characteristics were thought to be similar by study authors.	
	Metric 10: Covariate Characterization	Medium	Information about baseline characteristics for each participant was collected through a questionnaire. It is unknown if the questionnaire was validated.	
	Metric 11: Co-exposure Counfounding	Medium	A total of 37 compounds were identified as mammary gland carcinogens, but 13 were not included in this analysis. Thirteen compounds were excluded from the analysis due to insufficient variability (nine because they had the same value for all census tracts in the state of California; and four because they had less than 25% non-zero values). Propylene dichloride (1,2-dichloropropane) was among the 24 compounds evaluated in this assessment, and evaluations for breast cancer were conducted for each of these 24 individual compounds.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	High	The study design chosen (prospective cohort) was appropriate for the research question (incidence of breast cancer). Cox proportional hazard models and SAS 9.3 were used in this assessment. Data analysis was described.	
	Metric 13: Statistical Power	Medium	Statistical power calculations were not provided. No significant effects were observed with propylene dichloride (1,2-dichloropropane), however, this study utilized a large cohort, approximately 112,000 individuals. Distributions of chemicals of interest suggest there were sufficient numbers of participants in exposure subgroups.	
	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	The statistical models that were used were identified and described. "No apparent violation of the underlying assumption of proportional hazards was detected".	
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Study Citation:	Garcia, E., Hurley, S., Nelson, D. O., Hertz, A., Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: A cohort study. Environmental Health 14(1):14.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	breast cancer in females
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	3014082

Domain	Metric	Rating	Comments
Additional Comments:	A group of 112,378 female participants from the California Teacher Study cohort were assessed for their estimated exposure to ambient air pollutants, including propylene dichloride (1,2-dichloropropane), and the incidence of invasive breast cancer. Air contaminant concentrations were estimated using the US EPA NATA and the ASPEN and HEM models. The approximate median concentration of 1,2-dichloropropane is between 1E-4 and 1E-2 (estimated from Figure 1). Exposures were categorized into 5 Quintiles, and compared against Quintile 1. No significant increase in the estimated hazard rate ratio for invasive breast cancer was observed with Quintile 2-5 exposure estimates for 1,2-dichloropropane, adjusted for age and race, when compared against Quintile 1, or when further adjusted using multiple comparisons.		

Overall Quality Determination

High

Study Citation:	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environmental Health 17(1):28.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Invasive incident breast cancer		
Chemical:	1,2-Dichloropropane- Parent compound		
HERO ID:	4821835		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	Participants were drawn from the Nurses' Health Study II, a prospective cohort of 116,430 female nurses established in 1989. Female nurses (ages 15-42 years) completed a baseline questionnaire at enrollment across 14 US states. Study authors note that biennial follow-up questionnaires had response rates of over 90%. Women were excluded from the current analysis if they had been diagnosed with cancer before they returned the baseline questionnaire, if they lived outside of the contiguous US, or if they lived in a census tract with no information on exposure. Participants were censored if they were diagnosed with a cancer other than breast or non-melanoma skin cancer. The final sample size consisted of 109,239 women. Details of the initial participation rate were not reported, but concern is mitigated by the prospective study design (and high follow up response rate) and limits the concern that inclusion was selective with regard to exposure or outcome.
Metric 2:	Attrition	High	After applying exclusion criteria, there were a total of 109,239 women included in the study. Authors note that biennial follow up response rates are over 90%. No other details were provided, and loss to follow up is considered minimal.
Metric 3:	Comparison Group	High	Participants were all nurses from the United States and recruited during the same using the same eligibility criteria.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure to hazardous air pollutants, including 1,1-dichloroethane, was determined using residential addresses obtained from questionnaires and modeled data from EPA's National Air Toxics Assessment (NATA). Participant residential addresses were available for each participant from 1989 forward, and addresses were geocoded to census tract for exposure assignment. Data on air pollutants was developed from dispersion modeling of exposure data obtained from outdoor monitoring sources. The method was not specifically described as validated, but was based on EPA exposure assessment methods and detailed information on exposure modeling is provided in the cited references. However, there are concerns for exposure misclassification due to the use of census-tract level data, especially since the methods cannot account for variation in an individual's daily activities that could lead to increased or decreased levels of exposure.
Metric 5:	Exposure Levels	Medium	The risk of incident breast cancer was modeled by quartiles of exposure. Exposure distribution data is provided in supplemental Table 1, and ranges appear to be wide enough to allow for sufficient exposure contrast.
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Study Citation:	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environmental Health 17(1):28.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Invasive incident breast cancer			
Chemical:	1,2-Dichloropropane- Parent compound			
HERO ID:	4821835			
Domain	Metric	Rating	Comments	
	Metric 6: Temporality	Low	Participants were followed from 1989 through 2011, while exposure estimates were drawn from modeled 2002 NATA data. Study authors note analyses were also conducted using 1996 NATA data, and results were similar. However, data from both timepoints does not capture the entire follow-up period, and the impact of earlier exposure to HAPs (i.e., pre-1996) is unclear. The study also does not account for lagged exposure, which is relevant for cancers as the etiologically relevant time window is typically years prior to the first appearance of the outcome.	
Domain 3: Outcome Assessment				
	Metric 7: Outcome Measurement or Characterization	High	Incident breast cancer cases were self-reported during biennial questionnaires, and deaths were ascertained from family members, the US Postal Service, and annual searches of the National Death Index. Study authors note that medical record review confirmed 99% of self-reported breast cancer diagnoses. ER status was determined from tissue microarray, immunohistochemical analysis, or medical record.	
	Metric 8: Reporting Bias	High	All outcomes outlined in the abstract, introduction, and methods were reported in sufficient detail. Results were provided as Hazard Ratios, 95% confidence intervals, and the number of incident cases.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	High	Information on demographics, lifestyle characteristics, and potential risk factors were obtained from the biennial follow-up questionnaires. A wide range of potential confounders associated with invasive breast cancer were identified a priori. Each potential confounder was added to models "to determine its impact on the effect estimates," but further detail on how this was determined was not provided. Results stratified by smoking also reported in the supplement. Final models adjusted for age, calendar period, race, family history of breast cancer, history of aspiration or biopsy confirmed benign breast disease, age at menarche, parity and age at first birth, menopausal status and post-menopausal hormone use, oral contraception use, recent mammogram, height, BMI at age 18, difference between current BMI and BMI at age 18, smoking status, physical activity, overall diet quality (including alcohol consumption), alcohol consumption at age 15 and age 18, individual-level SES (marital status, living arrangements, household income), shift work, area-level SES (Census tract median home value and median income), and Census region of residence.	
	Metric 10: Covariate Characterization	Medium	Information on demographics, lifestyle characteristics, and potential risk factors were obtained from the biennial follow-up questionnaires. The questionnaire was not noted to be validated, but there was no direct evidence the method had poor validity.	

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Study Citation:	Hart, J. E., Bertrand, K. A., Dupre, N., James, P., Vieira, V. M., Vopham, T., Mittleman, M. R., Tamimi, R. M., Laden, F. (2018). Exposure to hazardous air pollutants and risk of incident breast cancer in the nurses' health study II. Environmental Health 17(1):28.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	Invasive incident breast cancer
Chemical:	1,2-Dichloropropane- Parent compound
HERO ID:	4821835

Domain	Metric	Rating	Comments
	Metric 11: Co-exposure Counfounding	Medium	Other hazardous air pollutants were measured and analyzed in the study, but there was no direct evidence to suggest an unbalanced provision of additional co-exposures across study groups.

Domain 5: Analysis	Metric 12: Study Design and Methods	High	The association between exposure to hazardous air pollutants was analyzed in a large prospective cohort using modeled air pollution concentrations with a long follow-up period. Study design was appropriate for the research question.
	Metric 13: Statistical Power	Medium	No concerns regarding statistical power. The study included 109,239 women with 2,203,192 person-years of follow-up.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was sufficient to understand the process and reproduce given original data.
	Metric 15: Statistical Analysis	High	The method for calculating hazard ratios was transparent. While there is no discussion of testing for the proportional hazards assumption, there is also no evidence to suggest that the assumption was violated. Details on inclusion of potential confounders was limited but was not of concern.

Additional Comments:	This study analyzed the association between air pollution exposures (modeled using EPA NATA and linked via residential address) and incident breast cancer in a large prospective cohort. Strengths of the study included a large sample size, long follow-up period, high rate of follow-up, and robust assessment. There are concerns regarding exposure misclassification due to the use of census-tract level exposure data for individuals, and potential concerns for temporality due to no assessment of lagged exposures. While air pollution concentrations from 2002 were used to analyze the whole study period (1989-2011), no other major concerns noted.
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Overall Quality Determination	High
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