
**Draft Data Quality Evaluation Information for
Human Health Hazard Epidemiology for
Ethylene Dibromide**

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 106-93-4



June 2026

This supplemental file contains the data quality evaluation results for epidemiology data sources that met the PECO (Population, Exposure, Comparator or Scenario, and Outcomes) screening criteria for the *Draft Systematic Review Protocol for Ethylene Dibromide*. 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 *the Draft Systematic Review Protocol for Ethylene Dibromide*.

HERO ID	Reference	Page
Ethylene Dibromide		
Mortality		
5591185	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.	5
1357737	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Chemosphere 16(8-9):2095-2099.	8
62587	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.	11
54256	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.	13
Cardiovascular		
5591185	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.	21
62587	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.	24
54256	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.	26
Reproductive/Developmental		
12935803	Equitable Environmental Health Inc, (1977). A retrospective study of inferred fertility of married men occupationally exposed to ethylene dibromide (EDB).	30
11187123	Gong, X., Zhan, F. B. (2022). A method for identifying critical time windows of maternal air pollution exposures associated with low birth weight in offspring using massive geographic data. Environmental Science and Pollution Research 29(22):33345-33360.	33
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. Environmental Health 17(1):28.	37
2857973	Larsen, S. B., Joffe, M., Bonde, J. P. (1998). Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. Occupational and Environmental Medicine 55(4):278-283.	40
62566	Ratcliffe, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., Hornung, R. W. (1987). Semen quality in papaya workers with long term exposure to ethylene dibromide. Occupational and Environmental Medicine 44(5):317-326.	43
62572	Schrader, S. M., Turner, T. W., Ratcliffe, J. M. (1988). The effects of ethylene dibromide on semen quality: a comparison of short-term and chronic exposure. Reproductive Toxicology 2(3-4):191-198.	47
62588	Takahashi, W., Wong, L., Rogers, B. J., Hale, R. W. (1981). Depression of sperm counts among agricultural workers exposed to dibromochloropropane and ethylene dibromide. Bulletin of Environmental Contamination and Toxicology 27(4):551-558.	51
54256	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.	54

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94772	Wong, O., Utidjian, D., H.M., Karten, V. S. (1979). Retrospective evaluation of reproductive performance of workers exposed to ethylene dibromide (EDB). <i>Journal of Occupational and Environmental Medicine</i> 21(2):98-102.	56
Cancer/Carcinogenesis		
5591185	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.	58
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.	61
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.	64
1357737	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. <i>Chemosphere</i> 16(8-9):2095-2099.	67
62587	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. <i>Archives of Environmental Health</i> 41(1):23-28.	70
54256	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. <i>Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology</i> 30:621-626.	72
Lung/Respiratory		
5591185	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.	74
5556064	Hoppin, J. A., Umbach, D. M., London, S. J., Henneberger, P. K., Kullman, G. J., Coble, J., Alavanja, M. C., Freeman, Beane, L. E., Sandler, D. P. (2009). Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. <i>European Respiratory Journal</i> 34(6):1296-1303.	77
62587	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. <i>Archives of Environmental Health</i> 41(1):23-28.	79
Neurological/Behavioral		
5554770	Beard, J. D., Umbach, D. M., Hoppin, J. A., Richards, M., Alavanja, M. C., Blair, A., Sandler, D. P., Kamel, F. (2014). Pesticide exposure and depression among male private pesticide applicators in the agricultural health study. <i>Environmental Health Perspectives</i> 122(9):984-991..	81
62587	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. <i>Archives of Environmental Health</i> 41(1):23-28.	83
Immune/Hematological		
5591185	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.	85
5621630	Lebailly, P., Vigreux, C., Lechevrel, C., Ledemeny, D., Godard, T., Sichel, F., Letalae, J. Y., Henry-Amar, M., Gauduchon, P. (1998). DNA damage in mononuclear leukocytes of farmers measured using the alkaline comet assay: Discussion of critical parameters and evaluation of seasonal variations in relation to pesticide exposure. <i>Cancer Epidemiology Biomarkers and Prevention</i> 7(10):917-927.	88
Nutrition & Metabolic		
12791626	Wang, Z., Chen, D., Peng, L., Wang, X., Ding, Q., Li, L., Xu, T. (2024). Exposure to volatile organic compounds is a risk factor for diabetes retinopathy: A cross-sectional study. <i>Frontiers in Public Health</i> 12:1347671.	91

Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.		
Health Outcome(s) Assessed:	Mortality		
Reported Health Effect(s):	All cause mortality, all external causes mortality, all other cause mortality, respiratory system cancer mortality, digestive system cancer mortality, all other site cancer mortality, emphysema mortality, chronic bronchitis mortality, asthma mortality, influenza mortality, pneumonia mortality, diseases of the cardiovascular system mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	In this retrospective occupational cohort study, employees were identified from two facilities (Michigan and Texas). Each facility was described in detail. Job descriptions of those included in the study were provided. The study authors indicate they selected all employees from four specific job types that were likely to have had contact with EDB. Some details regarding the participation rate are unclear, however, there was no direct evidence to suggest selection bias. A total number of 261 subjects were reported.
Metric 2:	Attrition	Medium	Only one individual was reported to be untraced and three individuals did not have obtainable death certificates. Some employees were excluded from the analysis due to leaving the company prior to 1940, citing traceability issues. The number of participants excluded for this reason is unclear.
Metric 3:	Comparison Group	Low	Employees were compared to the US general population of white males, calculated in five year age groups. While all employees were reported to be male, other demographic characteristics such as race were not discussed, resulting in minor uncertainty about whether the reference group is wholly appropriate.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was determined by employment at one of the two facilities. The study authors note that detailed employment records exist for the two facilities, and that there was periodic environmental surveillance data for the 62 Michigan employees. The 99 Texas employees did not have routine environmental surveillance data, but job process documentation implies "significant EDB exposure might have occurred." for the selected jobs. For the 62 Michigan employees, the authors describe personal and area sampling (1950, 1952, 1971-1972) and ranges for each job type. Due to the incomplete surveillance data, only employment length for highest concern job types was used in the analysis. Overall, despite a disparity in levels of detail between the two population types, there is reasonable confidence that all employees were exposed to some level of EDB.
Metric 5:	Exposure Levels	Low	Number of observed and expected cases were calculated both by employment status (exposed/unexposed), and by employment length (three levels) as well as stratifying by interval since first exposure (three levels). Since none of these provide quantitative concentrations of EDB in a form useful for a dose-response assessment, this metric is rated Low.
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Health Outcome(s) Assessed:	Mortality			
Reported Health Effect(s):	All cause mortality, all external causes mortality, all other cause mortality, respiratory system cancer mortality, digestive system cancer mortality, all other site cancer mortality, emphysema mortality, chronic bronchitis mortality, asthma mortality, influenza mortality, pneumonia mortality, diseases of the cardiovascular system mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306			
Domain		Metric	Rating	Comments
	Metric 6:	Temporality	Medium	Employees were recruited if they had been employed after 1940 and were followed until 1976. Some individuals were still currently employed which may not allow for enough latency time for the outcome of interest, mortality. The healthy worker effect may also be of concern due to the use of an occupational cohort.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	Former employees were followed using Social Security checks. The evaluation and coding of death certificates was not detailed. ICD codes used to identify relevant mortalities were not provided. The source of US general population mortality rates was not detailed.
	Metric 8:	Reporting Bias	Medium	The number of observed cases and expected cases were provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Low	Only males were included in the study. The authors calculate age-stratified SMRs. Demographic characteristics of the participants was not provided, and only white male mortality data was utilized in the SMR calculation. It is not clear if race would be an applicable stratification factor in this population. Potentially relevant behaviors such as smoking and alcohol use are not discussed.
	Metric 10:	Covariate Characterization	Medium	Collection of potential confounders (sex, age) was not described but presumably based on employment records.
	Metric 11:	Co-exposure Counfounding	Low	Other co-exposures were described and included lead, bromine, ethylene, hydrogen, iodine, ammonia, silica, copper, nickel acetate, vinyl bromide, and numerous other chlorinated and/or brominated hydrocarbons. These exposures varied by job type. Five individuals suspected to be exposed to arsenic were evaluated separately. Adjustments or other considerations for co-exposures were not made.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	This study utilized a retrospective occupational cohort of men to evaluate the relationship between chronic EDB exposure and various cause-specific mortalities. No concerns about study design.
	Metric 13:	Statistical Power	Low	The sample size was somewhat small (n=161) with limited number of cases per cause of death and a total of only 35 reported deaths. Stratification by employment length and interval since first exposure may result in very small comparison groups and should be interpreted with caution.
	Metric 14:	Reproducibility of Analyses	Medium	Data was provided on employment length and interval since first exposure by facility. Other descriptions were sufficient to reproduce the main analysis and analyses stratified by employment duration/exposure interval.

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Health Outcome(s) Assessed:	Mortality
Reported Health Effect(s):	All cause mortality, all external causes mortality, all other cause mortality, respiratory system cancer mortality, digestive system cancer mortality, all other site cancer mortality, emphysema mortality, chronic bronchitis mortality, asthma mortality, influenza mortality, pneumonia mortality, diseases of the cardiovascular system mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
Metric 15:	Statistical Analysis	Low	Expected deaths were calculated, however, standardized mortality ratios were not calculated.

Additional Comments: This study utilized a retrospective occupational cohort on 161 men to evaluate the relationship between EDB exposure and cause-specific mortality. Some concerns about this study include lack of information on participation rates, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants and cases. Additionally, there was a lack of information on the study population characteristics, and expected cases were calculated without a measure of variance. Urine bromine was measured, however, this was not used for the analysis and study authors indicate this would be non-specific for EDB exposure.

Overall Quality Determination	Low
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Study Citation:	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Chemosphere 16(8-9):2095-2099.		
Health Outcome(s) Assessed:	Mortality		
Reported Health Effect(s):	soft-tissue sarcoma deaths		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	1357737		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	Low	The paper reported that the target population was 37,000 individuals who worked for at least one year at a chemical production facility in Midland, Michigan. From this population, all death certificates that had an underlying or contributing cause of death that mentioned cancer were reviewed to determine whether the cancer type was soft-tissue sarcoma. A concern is that the authors did not specify how many of the study subjects had died, how many of those had death certificates available, or how many of the death certificates mentioned cancer. From the death certificates that mentioned cancer, 10 probable and 12 questionable cases of soft-tissue sarcoma were identified. Death certificates, medical records, and histology reports for these 22 individuals were reviewed and 15 were determined to meet the case definition. Referents were matched 9 to 1 to cases. Inclusion and exclusion criteria for the referents were specified but randomization in selection of referents was not mentioned.
	Metric 2: Attrition	Medium	Of the 15 cases identified, no matching controls were found for one case. Therefore, this case was excluded from the analyses.
	Metric 3: Comparison Group	Medium	Cases and controls were obtained from the same eligible population. The target population was described as having worked at the chemical production facility for at least one year between January 1, 1940 and December 31, 1979 but it is unclear whether that was a requirement for inclusion for cases. Referents had to have worked at the facility for at least one year and had to have been employed "during or after 1940 but before 1978". It is unclear why potential controls who worked at the facility in 1979 were excluded. The referents were matched with cases on sex and race, and "with a few exceptions," year of birth and year of hire. The exceptions were not explained further.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Low	Work histories for cases and referents were coded and reviewed by an industrial hygienist to determine potential exposure to the chemical of interest. The industrial hygienist was blinded to case/control status. The paper noted that the use of employee exposure and work histories enabled the study "to avoid the potential problem" of recall bias. However, measured concentrations of the chemicals were not reported and the exposure assessment was based on "presumptive chemical exposures".
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Study Citation:	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Chemosphere 16(8-9):2095-2099.			
Health Outcome(s) Assessed:	Mortality			
Reported Health Effect(s):	soft-tissue sarcoma deaths			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	1357737			
Domain	Metric	Rating	Comments	
	Metric 5:	Exposure Levels	Low	Exposure was considered as a dichotomous variable with categories of ever exposed vs never exposed. No quantitative information was reported on exposure levels or range of exposures, other than duration of exposure. Latency periods and duration of exposure were not adequately addressed in the analyses. The authors reported that "the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his 6 referents ranged from 66 days to 9.4 years."
	Metric 6:	Temporality	Low	Temporality of exposure and outcome is established. It is unclear if the interval between exposure and outcome is sufficient for soft tissue sarcoma outcomes. Duration of exposure was not adequately addressed in the analyses. The authors reported that "the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his 6 referents ranged from 66 days to 9.4 years."
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	To identify soft-tissue sarcoma deaths, all death certificates that had "an underlying or contributing case of death which mentioned cancer" were reviewed. These included ICD codes 140 to 239. From the death certificates that mentioned cancer, 10 probable and 12 questionable cases of soft-tissue sarcoma were identified. The probable cases had a "cause of death listed as a malignant soft-tissue sarcoma according to the classification of Morton and Eilber". The questionable cases were listed as "sarcoma-undefined site" or "lymphoma". For these 22 potential cases, the authors reported that "attempts were made to obtain copies of medical records, pathology reports, and tissue specimens" and the final determination was based on the "best available medical information: death certificates, medical records, or histopathology report". The proportion of cases determined by each of these methods was not reported.The referents "must not have died from ill-defined cancers possibly of soft-tissue origin". The referents "must have survived at least as long as the case". Therefore, the outcome was assessed well in the referents, except for the potential that the referents might have had cancer but might not have died from it.
	Metric 8:	Reporting Bias	High	Numbers of cases and controls were reported in Table 3. Maximum likelihood estimate odds ratios with 95% confidence intervals were reported for ethylene dibromide and other chemicals.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Medium	The referents were matched with cases on sex and race, and "with a few exceptions," year of birth and year of hire. The exceptions were not explained further. The authors also reported that the medical records of cases and referents were reviewed for information on "various heritable syndromes, family history of cancer, history of lymphedema, steroids, throrotrast, foreign body implants, chronic extensive scarring, radiation therapy, and immunologic defects". However, it is unclear how that information was used.

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Health Outcome(s) Assessed:	Mortality
Reported Health Effect(s):	soft-tissue sarcoma deaths
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	1357737

Domain	Metric	Rating	Comments
	Metric 10: Covariate Characterization	High	Potential covariates were assessed using medical and work records.
	Metric 11: Co-exposure Counfounding	Low	In addition to ethylene dibromide, the study identified 12 other chemicals used at the same facility that were determined by the National Toxicology Program to be associated with soft-tissue sarcoma. The authors noted that some individuals were exposed to multiple chemicals during their employment history and therefore were counted multiple times in the results table (Table 3). Co-exposures do not appear to have been adjusted for in the analyses.

Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	Soft tissue sarcoma is a group of rare cancers, so a case-control study design is appropriate. Odds ratios are appropriate for assessing case-control studies.
	Metric 13: Statistical Power	Low	The study included a small sample size of 14 cases and 126 matched controls. One case and 6 controls were identified as having ethylene dibromide exposure. No statistically significant associations were found for any of the 13 chemicals that had been associated with soft-tissue sarcomas by the National Toxicology Program. Therefore, the statistical power might not have been sufficient to detect an association.
	Metric 14: Reproducibility of Analyses	Low	The study calculated odd ratios and 95% confidence intervals. The analyses appear to have accounted for the matching of cases and controls, but those details are not adequately described.
	Metric 15: Statistical Analysis	Low	Full details of the analyses and assumptions were not reported. The analyses appear to have accounted for the matching of cases and controls, but those details are not adequately described.

Additional Comments:	This case-control study assessed soft-tissue sarcoma deaths in workers at a facility that used 13 chemicals potentially associated with soft-tissue sarcomas including ethylene dibromide. Some of the reporting of methods lacked sufficient details. The study included a small sample size of 14 cases and 126 matched controls. No statistically significant associations were found for any of the 13 chemicals that had been associated with soft-tissue sarcomas by the National Toxicology Program. Therefore, the statistical power might not have been sufficient to detect an association. One case and 6 controls were identified as having ethylene dibromide exposure. Duration of exposure and latency periods were not adequately addressed in this study. The exposure was assessed as dichotomous ever exposed vs never exposed. However, the authors reported that "the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his 6 referents ranged from 66 days to 9.4 years."
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Overall Quality Determination	Low
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Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.		
Health Outcome(s) Assessed:	Mortality		
Reported Health Effect(s):	all cause mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62587		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cohort was identified using several record sources. Females were excluded. All males who worked at the plant for at least one day from 1952 - 1977 were included. Computer tapes identified employees from 1960-1976 but other record sources were used for 1952-1959 and 1977, so there might have been some inconsistency in selection into the study. There is no information provided on the accuracy of the sources, but it is considered likely that identifying the subjects who worked in the plant would not omit subjects based on exposure or outcome.
Metric 2:	Attrition	High	There was only 1% loss to follow-up.
Metric 3:	Comparison Group	Medium	Standardized mortality ratios (SMRs) were calculated using race-specific person years at risk for 5-year categories of age with the expected numbers for males in the United States, stratified by race, 5-year age group, and 5-year calendar time period. Mortality for workers was compared to mortality for the general population so there is the potential for healthy worker effect.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	The study does not include assessment of industrial hygiene sampling for EDB, nor any personal monitoring for EDB, nor use of biomarkers for EDB, nor use of job matrices that would indicate EDB exposure, nor any other way to distinguish exposure to EDB from exposures to the other chemicals at the plant including tetraethyl lead (TEL), etc. The only measurements of exposure are work at the plant (SMRs: cause-specific mortality rates for males who worked at the plant vs cause-specific mortality rates of males in the U.S.) and duration of exposure measured by length of exposure. These are not adequate measures to quantify exposure specific to EDB.
Metric 5:	Exposure Levels	Low	Exposed workers were compared to the general population, so there were only two levels of exposure.
Metric 6:	Temporality	Medium	Since mortality is the endpoint, exposure would have to precede the outcome. It is unclear whether the exposures fall within the relevant exposure window.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Vital status was determined using company records, Social Security, IRS, and the Texas Bureau of Safety and Vital Statistics. The cause of death was coded by a nosologist using the ICD codes in effect at the time of death.
Metric 8:	Reporting Bias	High	SMRs were appropriately reported.
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Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.
Health Outcome(s) Assessed:	Mortality
Reported Health Effect(s):	all cause mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62587

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	SMRs were adjusted for race, age, and sex.
	Metric 10: Covariate Characterization	Low	Information was obtained from work records. Study subjects "whose race was white or unknown, and individuals with Hispanic surnames, were classified as white." All others were classified as non-white. Thus, there was potential misclassification of race. Only a small proportion of the workers were female. Females "were excluded from the study because historically they held nonproduction positions."
	Metric 11: Co-exposure Counfounding	Low	In addition to EDB, exposure was noted to include tetraethyl lead, ethylene dichloride, inorganic lead, and vinyl chloride monomer. It was noted that work histories lacked sufficient data to identify specific jobs in processing and manufacturing areas. Therefore, results cannot be separated by chemical nor can it be known if there was exposure to more than one of these chemicals for any specific job.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The analyses were appropriate and well described.
	Metric 13: Statistical Power	Medium	There were 2493 subjects included with 156 deaths.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was appropriate.
	Metric 15: Statistical Analysis	High	The method for calculating Standardized Mortality Ratios (SMR) is transparent.
Additional Comments:	The main limitations of this study are the lack of EDB-specific quantitative exposure data, the inability to separate out the exposure of interest from other co-exposures, and the potential for healthy worker effect.		

Overall Quality Determination

Medium

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Mortality		
Reported Health Effect(s):	Total mortality, cancer mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory (A and B) for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
Metric 2:	Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
Metric 3:	Comparison Group	Low	The unexposed comparison group was drawn from the general local population, but no information was reported to determine if the local population and exposed population were similar.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
Metric 5:	Exposure Levels	Low	The only 2 reported levels of exposure for total mortality and cancer mortality are exposed (factory population) and unexposed (local population). Although years of employment are available elsewhere in the article and could serve to help distinguish levels of exposure, this is not accounted for in measures of mortality outcomes.
Metric 6:	Temporality	Medium	Temporality appears to be established, but some individuals may not have been followed for a sufficient period of time given the latency period of cancer and other outcomes.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Low	The outcome (mortality and cause of death) measurement appears to differ slightly for exposed vs. unexposed populations: The factory population reports death rate per 1000 person-years, but the comparison group from the local population instead reports annual death rates for only select years.
Metric 8:	Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			
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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.
Health Outcome(s) Assessed:	Mortality
Reported Health Effect(s):	Total mortality, cancer mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	54256

Domain	Metric	Rating	Comments
	Metric 9: Covariate Adjustment	Medium	Results are stratified by age and only men are included in the study population so confounding by sex is not a concern. No other adjustments for potential confounders are made.
	Metric 10: Covariate Characterization	N/A	There was no information reported on covariates assessment or adjustment.
	Metric 11: Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, potential co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	Low	Overall, there were no statistical analyses utilized. Cancer mortality and total mortality rates were reported for exposed and unexposed groups, but there was no statistical comparison between them.
	Metric 13: Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14: Reproducibility of Analyses	Low	There were no statistical analyses utilized. Additionally, there are minimal details on how mortality rates were calculated, particularly for the local population.
	Metric 15: Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for other potential confounders.
Additional Comments:	This occupational study reports mortality rates for factory workers and the general local population. However, no statistical analyses were conducted to determine differences between the two populations. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.		

Overall Quality Determination

Low

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.
Health Outcome(s) Assessed:	Mortality
Reported Health Effect(s):	Total mortality, cancer mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	54256

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory (A and B) for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
	Metric 2: Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
	Metric 3: Comparison Group	Low	The unexposed comparison group was drawn from the general local population, but no information was reported to determine if the local population and exposed population were similar.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
	Metric 5: Exposure Levels	Low	The only 2 reported levels of exposure for total mortality and cancer mortality are exposed (factory population) and unexposed (local population). Although years of employment are available elsewhere in the article and could serve to help distinguish levels of exposure, this is not accounted for in measures of mortality outcomes.
	Metric 6: Temporality	Medium	Temporality appears to be established, but some individuals may not have been followed for a sufficient period of time given the latency period of cancer and other outcomes.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	Low	The outcome (mortality and cause of death) measurement appears to differ slightly for exposed vs. unexposed populations: The factory population reports death rate per 1000 person-years, but the comparison group from the local population instead reports annual death rates for only select years.
	Metric 8: Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			

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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.
Health Outcome(s) Assessed:	Mortality
Reported Health Effect(s):	Total mortality, cancer mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	54256

Domain	Metric	Rating	Comments
	Metric 9: Covariate Adjustment	Medium	Results are stratified by age and only men are included in the study population so confounding by sex is not a concern. No other adjustments for potential confounders are made.
	Metric 10: Covariate Characterization	N/A	There was no information reported on covariates assessment or adjustment.
	Metric 11: Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, potential co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	Low	Overall, there were no statistical analyses utilized. Cancer mortality and total mortality rates were reported for exposed and unexposed groups, but there was no statistical comparison between them.
	Metric 13: Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14: Reproducibility of Analyses	Low	There were no statistical analyses utilized. Additionally, there are minimal details on how mortality rates were calculated, particularly for the local population.
	Metric 15: Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for other potential confounders.
Additional Comments:	This occupational study reports mortality rates for factory workers and the general local population. However, no statistical analyses were conducted to determine differences between the two populations. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.		

Overall Quality Determination

Low

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Mortality		
Reported Health Effect(s):	cardiovascular disease mortality, cerebrovascular disease mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
Metric 2:	Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
Metric 3:	Comparison Group	Uninformative	No unexposed group is reported for cardiovascular or cerebrovascular specific mortality. (Local population is used as a comparator for cancer mortality and total mortality, but not for other causes).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
Metric 5:	Exposure Levels	Uninformative	Number of years worked is reported for both cardiovascular disease and cerebrovascular disease mortality as an indicator of exposure level, but there is no comparator group.
Metric 6:	Temporality	Medium	Temporality is established, but some individuals may not have been followed for a sufficient period given the latency period of the reported diseases.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Uninformative	The article does not report how mortality and cause of death were ascertained. Additionally, the outcome measurement is reported only as a count of deaths with no statistical analysis.
Metric 8:	Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	Uninformative	Average age is reported but there is no adjustment or stratification by age. No other adjustments are made.
Metric 10:	Covariate Characterization	N/A	There was no information reported on covariates assessment or adjustment.
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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.			
Health Outcome(s) Assessed:	Mortality			
Reported Health Effect(s):	cardiovascular disease mortality, cerebrovascular disease mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	54256			
Domain	Metric		Rating	Comments
	Metric 11:	Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, potential co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis	Metric 12:	Study Design and Methods	Low	No statistical analyses were utilized. For cardiovascular and cerebrovascular mortality, only a count of deaths for factory workers is reported and there is no comparison to the local population.
	Metric 13:	Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14:	Reproducibility of Analyses	Low	No statistical analyses were utilized.
	Metric 15:	Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for potential confounders.
Additional Comments:	This occupational study reports mortality due to cardiovascular and cerebrovascular disease among factory workers in an ethylene dibromide plant. However, no statistical analyses were conducted, and no comparator group is provided for these outcomes. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.			

Overall Quality Determination

Uninformative

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Mortality		
Reported Health Effect(s):	cardiovascular disease mortality, cerebrovascular disease mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
Metric 2:	Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
Metric 3:	Comparison Group	Uninformative	No unexposed group is reported for cardiovascular or cerebrovascular specific mortality. (Local population is used as a comparator for cancer mortality and total mortality, but not for other causes).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
Metric 5:	Exposure Levels	Uninformative	Number of years worked is reported for both cardiovascular disease and cerebrovascular disease mortality as an indicator of exposure level, but there is no comparator group.
Metric 6:	Temporality	Medium	Temporality is established, but some individuals may not have been followed for a sufficient period given the latency period of the reported diseases.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Uninformative	The article does not report how mortality and cause of death were ascertained. Additionally, the outcome measurement is reported only as a count of deaths with no statistical analysis.
Metric 8:	Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	Uninformative	Average age is reported but there is no adjustment or stratification by age. No other adjustments are made.
Metric 10:	Covariate Characterization	N/A	There was no information reported on covariates assessment or adjustment.
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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.			
Health Outcome(s) Assessed:	Mortality			
Reported Health Effect(s):	cardiovascular disease mortality, cerebrovascular disease mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	54256			
Domain	Metric		Rating	Comments
	Metric 11:	Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, potential co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis	Metric 12:	Study Design and Methods	Low	No statistical analyses were utilized. For cardiovascular and cerebrovascular mortality, only a count of deaths for factory workers is reported and there is no comparison to the local population.
	Metric 13:	Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14:	Reproducibility of Analyses	Low	No statistical analyses were utilized.
	Metric 15:	Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for potential confounders.
Additional Comments:	This occupational study reports mortality due to cardiovascular and cerebrovascular disease among factory workers in an ethylene dibromide plant. However, no statistical analyses were conducted, and no comparator group is provided for these outcomes. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.			

Overall Quality Determination

Uninformative

Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Cardiovascular
Reported Health Effect(s):	diseases of the cardiovascular system mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	In this retrospective occupational cohort study, employees were identified from two facilities (Michigan and Texas). Each facility was described in detail. Job descriptions of those included in the study were provided. The study authors indicate they selected all employees from four specific job types that were likely to have had contact with EDB. Some details regarding the participation rate are unclear, however, there was no direct evidence to suggest selection bias. A total number of 261 subjects were reported.
Metric 2:	Attrition	Medium	Only one individual was reported to be untraced and three individuals did not have obtainable death certificates. Some employees were excluded from the analysis due to leaving the company prior to 1940, citing traceability issues. The number of participants excluded for this reason is unclear.
Metric 3:	Comparison Group	Low	Employees were compared to the US general population of white males, calculated in five year age groups. While all employees were reported to be male, other demographic characteristics such as race were not discussed, resulting in minor uncertainty about whether the reference group is wholly appropriate.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was determined by employment at one of the two facilities. The study authors note that detailed employment records exist for the two facilities, and that there was periodic environmental surveillance data for the 62 Michigan employees. The 99 Texas employees did not have routine environmental surveillance data, but job process documentation implies "significant EDB exposure might have occurred." for the selected jobs. For the 62 Michigan employees, the authors describe personal and area sampling (1950, 1952, 1971-1972) and ranges for each job type. Due to the incomplete surveillance data, only employment length for highest concern job types was used in the analysis. Overall, despite a disparity in levels of detail between the two population types, there is reasonable confidence that all employees were exposed to some level of EDB.
Metric 5:	Exposure Levels	Low	Number of observed and expected cases were calculated both by employment status (exposed/unexposed), and by employment length (three levels) as well as stratifying by interval since first exposure (three levels). Since none of these provide quantitative concentrations of EDB in a form useful for a dose-response assessment, this metric is rated Low

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.			
Health Outcome(s) Assessed:	Cardiovascular			
Reported Health Effect(s):	diseases of the cardiovascular system mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306			
Domain	Metric	Rating	Comments	
	Metric 6:	Temporality	Medium	Employees were recruited if they had been employed after 1940 and were followed until 1976. Some individuals were still currently employed which may not allow for enough latency time for the outcome of interest, mortality. The healthy worker effect may also be of concern due to the use of an occupational cohort.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	Former employees were followed using Social Security checks. The evaluation and coding of death certificates was not detailed. ICD codes used to identify relevant mortalities were not provided. The source of US general population mortality rates was not detailed.
	Metric 8:	Reporting Bias	Medium	The number of observed cases and expected cases were provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Low	Only males were included in the study. The authors calculate age-stratified SMRs. Demographic characteristics of the participants was not provided, and only white male mortality data was utilized in the SMR calculation. It is not clear if race would be an applicable stratification factor in this population. Potentially relevant behaviors such as smoking and alcohol use are not discussed.
	Metric 10:	Covariate Characterization	Medium	Collection of potential confounders (sex, age) was not described but presumably based on employment records.
	Metric 11:	Co-exposure Counfounding	Low	Other co-exposures were described and included lead, bromine, ethylene, hydrogen, iodine, ammonia, silica, copper, nickel acetate, vinyl bromide, and numerous other chlorinated and/or brominated hydrocarbons. These exposures varied by job type. Five individuals suspected to be exposed to arsenic were evaluated separately. Adjustments or other considerations for co-exposures were not made.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	This study utilized a retrospective occupational cohort of men to evaluate the relationship between chronic EDB exposure and various cause-specific mortalities. No concerns about study design.
	Metric 13:	Statistical Power	Low	The sample size was somewhat small (n=161) with limited number of cases per cause of death and a total of only 35 reported deaths. Stratification by employment length and interval since first exposure may result in very small comparison groups and should be interpreted with caution.
	Metric 14:	Reproducibility of Analyses	Medium	Data was provided on employment length and interval since first exposure by facility. Other descriptions were sufficient to reproduce the main analysis and analyses stratified by employment duration/exposure interval.
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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Cardiovascular
Reported Health Effect(s):	diseases of the cardiovascular system mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	Low	Expected deaths were calculated, however, standardized mortality ratios were not calculated.

Additional Comments: This study utilized a retrospective occupational cohort on 161 men to evaluate the relationship between EDB exposure and cause-specific mortality. Some concerns about this study include lack of information on participation rates, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants and cases. Additionally, there was a lack of information on the study population characteristics, and expected cases were calculated without a measure of variance. Urine bromine was measured, however, this was not used for the analysis and study authors indicate this would be non-specific for EDB exposure.

Overall Quality Determination

Low

Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.		
Health Outcome(s) Assessed:	Cardiovascular		
Reported Health Effect(s):	stroke, cardiovascular diseases		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62587		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cohort was identified using several record sources. Females were excluded. All males who worked at the plant for at least one day from 1952 - 1977 were included. Computer tapes identified employees from 1960-1976 but other record sources were used for 1952-1959 and 1977, so there might have been some inconsistency in selection into the study. There is no information provided on the accuracy of the sources, but it is considered likely that identifying the subjects who worked in the plant would not omit subjects based on exposure or outcome.
Metric 2:	Attrition	High	There was only 1% loss to follow-up.
Metric 3:	Comparison Group	Medium	Standardized mortality ratios (SMRs) were calculated using race-specific person years at risk for 5-year categories of age with the expected numbers for males in the United States, stratified by race, 5-year age group, and 5-year calendar time period. Mortality for workers was compared to mortality for the general population so there is the potential for healthy worker effect.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	The study does not include assessment of industrial hygiene sampling for EDB, nor any personal monitoring for EDB, nor use of biomarkers for EDB, nor use of job matrices that would indicate EDB exposure, nor any other way to distinguish exposure to EDB from exposures to the other chemicals at the plant including tetraethyl lead (TEL), etc. The only measurements of exposure are work at the plant (SMRs: cause-specific mortality rates for males who worked at the plant vs cause-specific mortality rates of males in the U.S.) and duration of exposure measured by length of exposure. These are not adequate measures to quantify exposure specific to EDB.
Metric 5:	Exposure Levels	Low	Exposed workers were compared to the general population, so there were only two levels of exposure.
Metric 6:	Temporality	Medium	Since mortality is the endpoint, exposure would have to precede the outcome. It is unclear whether the exposures fall within the relevant exposure window.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Vital status was determined using company records, Social Security, IRS, and the Texas Bureau of Safety and Vital Statistics. The cause of death was coded by a nosologist using the ICD codes in effect at the time of death.
Metric 8:	Reporting Bias	High	SMRs were appropriately reported.
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Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.
Health Outcome(s) Assessed:	Cardiovascular
Reported Health Effect(s):	stroke, cardiovascular diseases
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62587

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	SMRs were adjusted for race, age, and sex.
	Metric 10: Covariate Characterization	Low	Information was obtained from work records. Study subjects "whose race was white or unknown, and individuals with Hispanic surnames, were classified as white." All others were classified as non-white. Thus, there was potential misclassification of race. Only a small proportion of the workers were female. Females "were excluded from the study because historically they held nonproduction positions."
	Metric 11: Co-exposure Counfounding	Low	In addition to EDB, exposure was noted to include tetraethyl lead, ethylene dichloride, inorganic lead, and vinyl chloride monomer. It was noted that work histories lacked sufficient data to identify specific jobs in processing and manufacturing areas. Therefore, results cannot be separated by chemical nor can it be known if there was exposure to more than one of these chemicals for any specific job.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The analyses were appropriate and well described.
	Metric 13: Statistical Power	Medium	There were 2493 subjects included with 156 deaths.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was appropriate.
	Metric 15: Statistical Analysis	High	The method for calculating Standardized Mortality Ratios (SMR) is transparent.
Additional Comments:	The main limitations of this study are the lack of EDB-specific quantitative exposure data, the inability to separate out the exposure of interest from other co-exposures, and the potential for healthy worker effect.		

Overall Quality Determination

Medium

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Cardiovascular		
Reported Health Effect(s):	Cardiovascular disease mortality, cerebrovascular disease mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
Metric 2:	Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
Metric 3:	Comparison Group	Uninformative	No unexposed group is reported for cardiovascular or cerebrovascular specific mortality. (Local population is used as a comparator for cancer mortality and total mortality, but not for other causes).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
Metric 5:	Exposure Levels	Uninformative	Number of years worked is reported for both cardiovascular disease and cerebrovascular disease mortality as an indicator of exposure level, but there is no comparator group.
Metric 6:	Temporality	Medium	Temporality is established, but some individuals may not have been followed for a sufficient period given the latency period of the reported diseases.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Uninformative	The paper does not report how mortality and cause of death were ascertained. Additionally, the outcome measurement is reported only as a count of deaths with no statistical analysis.
Metric 8:	Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	Uninformative	Average age is reported but there is no adjustment or stratification by age. No other adjustments for potential confounders are made.
Metric 10:	Covariate Characterization	N/A	There was no information reported on covariates assessment and adjustment.

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Health Outcome(s) Assessed:	Cardiovascular			
Reported Health Effect(s):	Cardiovascular disease mortality, cerebrovascular disease mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	54256			
Domain	Metric		Rating	Comments
	Metric 11:	Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis	Metric 12:	Study Design and Methods	Low	No statistical analyses were utilized. For cardiovascular and cerebrovascular mortality, only a count of deaths for factory workers is reported and there is no comparison to the local population.
	Metric 13:	Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14:	Reproducibility of Analyses	Low	The description of the analysis is insufficient to understand what has been done. For example, no statistical analyses were utilized.
	Metric 15:	Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for potential confounders.
Additional Comments:	This occupational study reports mortality due to cardiovascular and cerebrovascular disease among factory workers in an ethylene dibromide plant. However, no statistical analyses were conducted, and no comparator group is provided for these outcomes. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.			

Overall Quality Determination

Uninformative

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Cardiovascular		
Reported Health Effect(s):	Cardiovascular disease mortality, cerebrovascular disease mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
Metric 2:	Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
Metric 3:	Comparison Group	Uninformative	No unexposed group is reported for cardiovascular or cerebrovascular specific mortality. (Local population is used as a comparator for cancer mortality and total mortality, but not for other causes).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
Metric 5:	Exposure Levels	Uninformative	Number of years worked is reported for both cardiovascular disease and cerebrovascular disease mortality as an indicator of exposure level, but there is no comparator group.
Metric 6:	Temporality	Medium	Temporality is established, but some individuals may not have been followed for a sufficient period given the latency period of the reported diseases.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Uninformative	The paper does not report how mortality and cause of death were ascertained. Additionally, the outcome measurement is reported only as a count of deaths with no statistical analysis.
Metric 8:	Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	Uninformative	Average age is reported but there is no adjustment or stratification by age. No other adjustments for potential confounders are made.
Metric 10:	Covariate Characterization	N/A	There was no information reported on covariates assessment and adjustment.
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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.			
Health Outcome(s) Assessed:	Cardiovascular			
Reported Health Effect(s):	Cardiovascular disease mortality, cerebrovascular disease mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	54256			
Domain	Metric		Rating	Comments
	Metric 11:	Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis	Metric 12:	Study Design and Methods	Low	No statistical analyses were utilized. For cardiovascular and cerebrovascular mortality, only a count of deaths for factory workers is reported and there is no comparison to the local population.
	Metric 13:	Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14:	Reproducibility of Analyses	Low	The description of the analysis is insufficient to understand what has been done. For example, no statistical analyses were utilized.
	Metric 15:	Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for potential confounders.
Additional Comments:	This occupational study reports mortality due to cardiovascular and cerebrovascular disease among factory workers in an ethylene dibromide plant. However, no statistical analyses were conducted, and no comparator group is provided for these outcomes. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.			

Overall Quality Determination

Uninformative

Study Citation:	Equitable Environmental Health Inc, (1977). A retrospective study of inferred fertility of married men occupationally exposed to ethylene dibromide (EDB).		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Male fertility as measured by live births		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	12935803 Linked HERO ID(s): 94772, 4822833, 12935803		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This retrospective occupational cohort examined the relationships between EDB exposure and inferred fertility among male workers from 4 US plants and 1 UK plant. Numbers of included participants are provided, but limited information is provided on the participation rate or the recruitment strategy. It is unclear how this specific set of workers was recruited. Exclusion criteria are specified, with a marital status of "single" being a major contributor to exclusion. A total of 297 participants were included from the 4 US plants (Wong et al. 1979 HERO ID: 94777) and 82 participants were included from UK plant (Turner and Barry 1979, HERO ID: 54256).
Metric 2:	Attrition	Medium	Among married workers that were eligible, no overall attrition was reported. Some case "births" were removed if children were adopted. In one of the US plants, there was a high proportion of self-reported sterilization due to vasectomies, mumps, hysterectomies, x-ray treatment in childhood, or low sperm count since age 22 (prior to EDB exposure). Analyses on this plant are conducted separately with and without the sterilized participants. Small numbers of exclusions were made for participants where date of births of wives were not included (n=3 from Plant D out of a total of 70) or because their exposure dates were after the most recent available US standardized fertility data (n=12 from Plant C out of a total of 56).
Metric 3:	Comparison Group	Medium	All analyses are adjusted for maternal age, parity, race, and calendar year of birth. Participant fertility rates are compared to "expected births" per successive US birth cohorts published by the National Center for Health Statistics. This is an appropriate comparison group since birth probabilities were age-parity-year-race specific, and probabilities were compared by calendar year.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	For the US data: while the authors performed exposure measurements, the methodologies used well not well-described. For example, exposures ranged from <0.5 to 5 ppm. For the UK data: exposure groups were based on type of job role and were categorized based on frequency of exposure, but not directly quantified.
Metric 5:	Exposure Levels	Medium	All participants in the 4 US plants were reported to be exposed, and were compared to a US reference population expected to be unexposed. Two separate levels of exposure are reported for the white population (<0.5 ppm or 0.5-5.0 ppm), who comprise the majority of the sample (78-95%). Participants from the UK plant were divided into 4 groups of unexposed, occasional exposure, regular exposure, and irregular exposure.
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Study Citation:	Equitable Environmental Health Inc, (1977). A retrospective study of inferred fertility of married men occupationally exposed to ethylene dibromide (EDB).			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Male fertility as measured by live births			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	12935803 Linked HERO ID(s): 94772, 4822833, 12935803			
Domain	Metric	Rating	Comments	
	Metric 6:	Temporality	Medium	For the purposes of this analysis, births were only considered to have been "exposed" to EDB if the father was exposed to EDB at least 9 months prior to birth. Thus, a relevant time order is established. However, the study does not provide any specific evidence on the etiologically relevant time window for sperm effects and EDB exposure.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	The primary outcome was male fertility, as measured by the successful "live birth" from workers' wives. Information on birth was self-reported by participants. The study assumed that the workers in the study were the sole sexual partner for their wives. There is confidence in the assessment of whether or not live births occurred, and the study specifies that miscarriages/abortions were excluded and that pregnancies that were underway at the time of data collection were not counted as live births. However, fertility/birth rate was used a surrogate measure of male fertility, which is no a sensitive measure of the outcome.
	Metric 8:	Reporting Bias	Medium	All outcomes indicated in the methods are reported in the results. For each plant and exposure group most relevant details are reported (sample size, observed vs. expected births, ratio of observed/expected and statistical significance) but no confidence intervals are calculated and no specific p-values are provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Medium	Live births from workers' wives were measured as an indicator of male fertility. The relationship between exposure to EDB and male fertility may be mediated by the effect of EDB exposure on semen parameters, which are not measured in this study. The female contribution to live births may also be responsible for a lack of fertility, but some maternal characteristics (maternal age at birth, parity, maternal race) were controlled for in statistical analyses.
	Metric 10:	Covariate Characterization	Low	All information on covariates was self-reported, which may be susceptible to recall bias. The race of wives was assumed to be the same race as their husbands, which may not be an accurate assumption. The assumption that all workers were the exclusive sexual partner of their wives is difficult to verify, and may be a key confounder in the relationship between fertility measured by males in this study and their wives.
	Metric 11:	Co-exposure Counfounding	Medium	Any co-exposures to pollutants other than EDB that would likely bias the results are not likely to be present per the study's description.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The study design chosen (assessing the impact of exposure to EDB on fertility via an occupational cohort using standardized fertility ratios) is appropriate.

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Study Citation:	Equitable Environmental Health Inc, (1977). A retrospective study of inferred fertility of married men occupationally exposed to ethylene dibromide (EDB).
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	Male fertility as measured by live births
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	12935803 Linked HERO ID(s): 94772, 4822833, 12935803

Domain	Metric	Rating	Comments
	Metric 13: Statistical Power	Medium	The overall sample size (n=297 participants from the 4 US plants and n=82 participants from the UK plant) is likely large enough to detect an effect. Some comparison groups may be smaller and have lower statistical power, most notably for non-white participants where the largest sample size (from all 4 US plants) is n=34; however, the majority of analyses are likely able to detect an effect.
	Metric 14: Reproducibility of Analyses	Medium	The description of their analytic methods is detailed enough that it could be reproduced if given access to the data.
	Metric 15: Statistical Analysis	High	The study calculates standardized fertility ratios and adequately explains the procedures they used. Statistical tests were based on the Poisson distribution to assess statistical significance.

Additional Comments: This occupational cohort study examined male workers from 4 US plants and 1 UK plant to assess the relationship between exposure to EDB and male fertility, as measured by live births. The largest concern for bias in this study is the lack of detail on exposure assessment. There are no details on how exactly exposure to EDB was measured, despite the study reporting specific exposure concentrations of EDB, making it difficult to rely on the findings of this study. There are further concerns for participant selection, as there is no description of the recruitment process for the study. The findings of the study may also be limited by outcome data only being reported as live births from the wives of workers, which may not fully account for the wives' contributions to fertility and only accounts for male exposure. However, some maternal characteristics are adjusted for such as maternal age and parity. No significant findings are reported from this study.

Overall Quality Determination

Low

Study Citation:	Gong, X., Zhan, F. B. (2022). A method for identifying critical time windows of maternal air pollution exposures associated with low birth weight in offspring using massive geographic data. Environmental Science and Pollution Research 29(22):33345-33360.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Low birth weight		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	11187123		
Domain	Metric	Rating	Comments
Domain 1: Study Participation	Metric 1: Participant Selection	Medium	In this case-control study, participants were selected from birth certificate data for all registered births in Texas from 1996-2008. Data were gathered from the Centre for Health Statistics in the Texas Department of State Health Services (DSHS). The use and analysis of the birth certificate data were reviewed and approved by the IRB at the Texas DSHS and Texas State University. Births were excluded if they had incomplete location information or invalid data on the mother's last menstrual period (10.9% of all eligible births), if they had birth weights of more than 5,500 g or less than 1,000 g (0.1%), if the gestational age was more than 44 weeks or less than 37 weeks (17.8%), if there were plural deliveries (2.7%), or if mothers were not Texas residents or if births occurred outside of Texas (0.2%). From the remaining births in the data set, all cases of low birth weight (less than 2,500 g) were selected as cases alongside four controls for each case in the same year of birth, selected via an unspecified random process. The final sample included 94,106 cases and 376,424 controls. While the randomization process to select controls is not extensively detailed, there is no evidence to suggest methods were inappropriate. There is also no description of exposure or outcome characteristics among those excluded compared to those included, but there is no evidence to suggest that the two groups would have different exposure-outcome distributions.
	Metric 2: Attrition	Medium	Some number of participants were excluded due to missing exposure data, but specific numbers are not specified. This study utilized a spatial-temporal exposure assessment that relied on air quality monitoring. If cases or controls were outside of a 1.0 km radius from any of the 331 monitoring sites, they were excluded from the analysis. If participants had multiple monitoring sites within a 1.0 km radius, the average ambient concentration value for each chemical was used in analysis; however, if more than one-fourth of those values were missing during any studied time window, that combination of participant-chemical-time window was removed from further analysis. Exact numbers of participants excluded are not specified in the study. The reasons for exclusion given are reasonable, and there is no evidence to suggest that their missingness would be related to exposure or outcome status.
	Metric 3: Comparison Group	High	In this study, cases and controls were specified to have been pulled from the same eligible population of Texas births. Cases and controls were pulled from the same dataset and matched 1:4 on their year of birth to ensure adequate study power. A table of demographic characteristics, split by case and control status, is provided. The study explains that the group of case mothers were on average younger, less educated, and more likely to be non-Hispanic blacks relative to the control group. All of those factors were adjusted for in statistical analyses.

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Study Citation:	Gong, X., Zhan, F. B. (2022). A method for identifying critical time windows of maternal air pollution exposures associated with low birth weight in offspring using massive geographic data. Environmental Science and Pollution Research 29(22):33345-33360.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Low birth weight			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	11187123			
Domain	Metric	Rating	Comments	
Domain 2: Exposure Characterization				
	Metric 4: Measurement of Exposure	Medium	Exposure was assessed via air quality monitoring data collected by the Texas Commission on Environmental Quality, which collects air quality data from 331 ambient monitoring sites which are primarily concentrated in urban areas. All included participants were within 1.0 km of at least one air quality monitor. If participants were within 1.0 km of more than one monitor, the average concentration was used for each chemical. Concentrations of chemicals were analyzed within specific 90-day time windows, beginning 366 before the estimated date of conception and following through delivery. Time windows were examined in moving 6-day increments, each one exactly 90 days long. The exposure measurement is consistent for all included participants, and there is no evidence that the Texas Commission on Environmental Quality used inappropriate air sampling methods. There is some potential for exposure misclassification given that the address at delivery was used to represent the whole exposure period, including more than a year prior to conception. However, there is no evidence that any misclassification, if it occurred, would be related to outcome status.	
	Metric 5: Exposure Levels	Low	Only two levels of exposure are used in statistical analyses, and this corresponds to exposed vs. unexposed status. There are no summary statistics presented for the distribution of ethylene dibromide, so it is not possible to assess whether the range of exposure is large.	
	Metric 6: Temporality	High	This study utilizes a wide variety of exposure window, where 90-day exposure windows from a year before conception to delivery are assessed in 6-day increments. Since the outcome of interest is measured at delivery, there is high confidence that the interval between exposure and the outcome is appropriately large to identify a critical time window for developmental outcomes.	
Domain 3: Outcome Assessment				
	Metric 7: Outcome Measurement or Characterization	High	The outcome of interest was low birth weight, which was classified as birth weights lower than 2,500 g. Data on birth weight was collected directly from birth certificates that were registered in Texas with the Center for Health Statistics in the Texas Department of State Health Services. While no specific methodology for assessing birth weight was described, the use of birth certificates is a well-established method.	
	Metric 8: Reporting Bias	Medium	All outcomes that are mentioned in the methods are reported in the results. Among several significant associations that were observed and reported, only one was presented in a format suitable for data extraction (e.g. as an effect estimate with a 95% confidence interval alongside numbers of cases and controls in the analysis). The decision to only present some effect estimates is reasonable given the large amount of results available for each combination of chemical and 90-day exposure window in 6 day increments. Effect estimates that are not presented suitably for data extraction are shown graphically.	

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Study Citation:	Gong, X., Zhan, F. B. (2022). A method for identifying critical time windows of maternal air pollution exposures associated with low birth weight in offspring using massive geographic data. Environmental Science and Pollution Research 29(22):33345-33360.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Low birth weight		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	11187123		
Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	Medium	Considered covariates included child's sex, gestational weeks, maternal age, race/ethnicity, and education. Cases and controls were also matched on year of birth. Covariates were reported to have been chosen based on a review of the literature. Potentially key covariates, such as maternal age and education, are considered.
	Metric 10: Covariate Characterization	High	Information on covariates was collected via birth certificate data for births that were registered in Texas with the Center for Health Statistics within the Texas Department of State Health Services. The use of a state-run database implies that covariates were assessed using valid and reliable methodology.
	Metric 11: Co-exposure Counfounding	Medium	The study measured 367 non-criteria air pollutant exposures. However, the study only reported results for ten chemicals that had exposure windows with statistically significant adjusted odds ratios, which also had more than twenty participants who were low-exposed cases, low-exposed controls, high-exposed cases, and high-exposed controls each. Chemicals that met that criteria with the highest statistically significant adjusted odds ratios were presented graphically in single-exposure models. These chemicals included the chemical of interest (ethylene dibromide) alongside benzaldehyde, n-Undecane, m-Tolualdehyde, valeraldehyde, propionaldehyde, 4-methyl-1-pentene, zirconium PM2.5, the unadjusted organic carbon fraction (OC2) in PM2.5, and the sum of the Photochemical Assessment Monitoring station (PAMS) target compounds. Results for each chemical are presented separately in single-pollutant models.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The use of a retrospective birth cohort design is sufficient to assess the relationship between 90-day exposure to air pollutants and low birth weight. The use of binary logistic regression models is appropriate.
	Metric 13: Statistical Power	Medium	The overall sample size is likely large enough to detect an effect. The number of participants (both cases and controls) in each exposure group is larger than 20.
	Metric 14: Reproducibility of Analyses	Medium	The results of the study are reproducible if given access to the analytic data.
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Study Citation:	Gong, X., Zhan, F. B. (2022). A method for identifying critical time windows of maternal air pollution exposures associated with low birth weight in offspring using massive geographic data. Environmental Science and Pollution Research 29(22):33345-33360.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	Low birth weight
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	11187123

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	High	Exposure ranges were stratified into "low" and "high" exposure groups such that controls were equally represented among the two groups. Binary logistic regression was used to estimate the association between ethylene dibromide and low birth weight, with the low exposure group as the reference category. Covariates were included per a review of the literature. Sensitivity analyses examining all 30-day time windows for 90-day time windows for which significant results were found and adjusting the required minimum distance from a monitoring site to 0.5 km and 1.5 km. The study specifies that adjustment for multiple comparisons (ex: Bonferonni's correction) were not used, as the large amount of comparisons studied would result in an overly-conservative estimation of statistical significance. The study acknowledges that this may produce Type 1 errors in the results.

Additional Comments: This retrospective cohort study compared low birth weight data from a Texas registry to exposure to 367 different air pollutants, using a spatial-temporal exposure assessment where associations were calculated for discrete 90-day time windows. The 90-day time windows advanced in increments of 6 days from 366 days prior to conception through to delivery. There are overall minimal study quality concerns in this study, with high confidence in the selection process, outcome ascertainment, and their analysis method. The study's approach to exposure assessment also increases confidence that exposures were measured within the relevant etiological time window. Notable concerns include the possibility of Type 1 errors due to the large amount of comparisons tested, and the nature of only having an exposed vs. unexposed analysis. The study observed a positive, statistically significant association between low birth weight and ambient ethylene dibromide exposure in the time window of less than 294 days to 204 days prior to conception.

Overall Quality Determination

Medium

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:	Ethylene Dibromide- 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 ethylene dibromide, 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:	Ethylene Dibromide- 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:	Ethylene Dibromide- 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:	Larsen, S. B., Joffe, M., Bonde, J. P. (1998). Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. Occupational and Environmental Medicine 55(4):278-283.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	fecundability, time to pregnancy for female partners		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	2857973		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	Eligible participants were identified through the Danish Ministry of Agriculture lists of traditional and organic farmers. All organic farmers and a random sample of traditional farmers were invited to participate via letter. Participation and inclusion rates are reported for each stage of recruitment (80.2% of eligible traditional farmers and 90.5% of eligible organic farmers agreed to participate and met inclusion criteria). Men who were never married, men with no children or whose wife was less than six months pregnant, men where the pregnancy was due to failure of birth control, and men without an occupation in agriculture before the youngest child was born were excluded from analyses. Reasons for exclusion of these subjects from analyses were adequately addressed.
Metric 2:	Attrition	High	Two subjects were missing age information and 36 subjects were missing number of children information. Methods for handling missing data were not mentioned. No subjects voluntarily withdrew from the study.
Metric 3:	Comparison Group	High	This study had multiple appropriate comparison groups, including organic farmers, traditional farmers who did not spray pesticides themselves, and men who were not in the farming trade during the exposure period of interest (the year prior to conception of their youngest child). All participants were drawn from the Danish Ministry of Agriculture lists of traditional and organic farmers during the same time frame (October 1995-May 1996).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Uninformative	The exposure of interest was use of pesticides that may contain EDB. EDB-specific exposure is not directly assessed. Farmers reporting pesticides were asked about the number of hectares they sprayed themselves, type of spraying and protective equipment used, and type of crops. Farmers were given a list of the most used pesticides during the past 10 years and asked to check off the ones they had used. Exact pesticides used by each farmer and whether those contained EDB were not reported. EDB was banned in the EU 10 years before this study took place.
Metric 5:	Exposure Levels	Low	Traditional farmers using pesticides were assigned an exposure index of 1-3 based on the number of hectares sprayed, type of crop, and sprayer equipment used. Traditional farmers not using pesticides, organic farmers, and men not farming during the year prior to their youngest child's conception were considered unexposed. However, exposure is only defined as exposure to pesticides - it is unclear which pesticides participants were exposed to and unlikely that any of the groups were exposed to EDB since it was banned 10 years before the study took place.

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Study Citation:	Larsen, S. B., Joffe, M., Bonde, J. P. (1998). Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. Occupational and Environmental Medicine 55(4):278-283.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	fecundability, time to pregnancy for female partners			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	2857973			
Domain		Metric	Rating	Comments
	Metric 6:	Temporality	High	The exposure period of interest was the year leading up to conception of each farmer's youngest child, allowing temporality to be established. Exposure was assessed retroactively via questionnaire. Subject ages and child birth years are reported.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	The outcome of interest was fecundability measured by time to pregnancy for male subjects' female partners. Outcome information was collected via interview ("How many months did it take your wife to get pregnant?"). Outcome information was not validated by medical record or other method. Recall bias is possible as the study relied on participants to report time to pregnancy. Outcome was self-reported.
	Metric 8:	Reporting Bias	Medium	Results for both outcome measures are reported in the results section. Fecundability (probability of conception within one menstrual cycle) ratios are reported with 95% CIs. Time to pregnancy information is reported in figure format (not ideal for data extraction). No concern regarding reporting bias.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Medium	Statistical models were adjusted for male and female smoking, female age, recent oral contraceptive use, and parity. Alcohol use is a potential key confounder that was not considered. The study population only included men. Distributions of covariates across exposure groups are reported.
	Metric 10:	Covariate Characterization	Medium	Covariate information was collected via phone interview. Interviews were not reported to be validated, but authors indicate that questions were structured. No specific concerns.
	Metric 11:	Co-exposure Counfounding	Low	The outcome of interest was general pesticide use, not EDB specifically. Farmers were shown a list of the most commonly used pesticides and asked to check off the ones they used personally, but this information did not impact outcome classification. Co-exposure to other toxic pesticides in varying proportions is highly likely.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	The study aimed to assess the relationship between pesticide use in the year leading up to conception and fecundability/time to pregnancy. Appropriately, the study assessed pesticide use in the year before conception. Statistical methods were appropriate for comparing fecundability across exposure groups.
	Metric 13:	Statistical Power	Medium	Study groups were adequately sized to detect present associations.
	Metric 14:	Reproducibility of Analyses	Medium	Analytical methods were described adequately such that they could be repeated if provided with the original study data.

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Study Citation:	Larsen, S. B., Joffe, M., Bonde, J. P. (1998). Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. Occupational and Environmental Medicine 55(4):278-283.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	fecundability, time to pregnancy for female partners		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	2857973		

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	High	Method for calculating risk estimates (fecundability ratios) is transparent and model assumptions are met. Adequate rationale is provided for inclusion of specific adjustment factors.

Additional Comments:	This study assessed effects of pesticide use by male farmers on time to pregnancy for their female partners. Farmers were asked about pesticide use during the year prior to conception of their youngest child and the number of months it took their partner to become pregnant when trying to conceive. The primary deficiency of the study was lack of specificity for EDB exposure. The exposure of interest was general pesticide use, which could have included EDB in varying proportions or not included EDB at all, especially given that EDB was banned in the EU 10 years before this study took place. This likely resulted in serious exposure misclassification.		
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Overall Quality Determination	Uninformative
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Study Citation:	Ratcliffe, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., Hornung, R. W. (1987). Semen quality in papaya workers with long term exposure to ethylene dibromide. Occupational and Environmental Medicine 44(5):317-326.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	semen characteristics: semen volume, sperm concentration, sperm count, sperm viability, sperm motility, sperm morphology		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62566 Linked HERO ID(s): 62566, 62571, 62572		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	Key elements of the study design were reported. The reported information indicates a difference in the timing of recruitment for the first five vs the sixth plant in the exposed group, resulting in lower participation from the sixth plant. Recruitment for the exposed group consisted of letters and interviews to all male workers, and all who agreed to participate were included. Recruitment for the control group consisted of letters, and the first 50 workers who volunteered to participate were included. The control group volunteered for payment (specified in linked reference Schrader et al. 1987, HERO ID 62571 page 964), but there was no mention of payment for the exposed group. Thus, there was some difference in recruitment methods between groups and some potential for selection bias. However, the authors note that there "were no clear differences between participants and non-participants with respect to demographic characteristics, and reasons given for non-participation were generally unrelated to factors which may potentially affect semen quality."
Metric 2:	Attrition	Medium	Semen samples were received from 96% of the exposed and 86% of the unexposed participants. Four individuals from the exposed group were identified as azoospermatic or employed for less than two months and subsequently excluded from the analysis.
Metric 3:	Comparison Group	Medium	Workers from a nearby sugar processing plant were generally a good choice of control group because several characteristics of the exposed and unexposed workers were generally similar, and both groups consisted of workers. However, the exposed and unexposed groups differed in age, race, and use of marijuana. Although the choice of control group eliminates concerns about healthy worker effect, co-exposures to other chemicals might have differed between fumigation plant workers and the control group of sugar processing plant workers.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	Exposure was assessed using relatively consistent methods for the papaya workers: "workers were sampled for a full eight hour shift unless their duty cycle indicated a shorter sample period". In addition to 82 full-shift samples, 19 short-term samples were assessed. Exposure was assessed using well-established methods: industrial hygiene surveys including worker samples analyzed according to NIOSH methods. Exposure wasn't measured in the control group, but it is unlikely that workers were exposed to EDB at the sugar refinery.

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Study Citation:	Ratliffe, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., Hornung, R. W. (1987). Semen quality in papaya workers with long term exposure to ethylene dibromide. Occupational and Environmental Medicine 44(5):317-326.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	semen characteristics: semen volume, sperm concentration, sperm count, sperm viability, sperm motility, sperm morphology			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	62566 Linked HERO ID(s): 62566, 62571, 62572			
Domain	Metric	Rating	Comments	
	Metric 5: Exposure Levels	Low	Despite more detailed measurement of exposure levels, the main comparisons of outcomes were between only two exposure levels: exposed (papaya plant workers) vs unexposed (sugar plant workers). Some analyses were performed by job and duration of exposure (Ratliffe et al. 1987, HERO ID 62566, page 323), which partially addressed the variety of exposure levels within the papaya plant workers, particularly differences between forklift drivers and fumigators who frequently enter the fumigation area and other workers such as packers and sorters who rarely enter the fumigation area. However, these analyses by job type were potentially limited by small sample sizes, and were not reported in sufficient detail for data extraction.	
	Metric 6: Temporality	Medium	In this cross-sectional study, workers in the exposed group were only included if they had been working for at least two months. The relevant exposure window is not clear.	
Domain 3: Outcome Assessment				
	Metric 7: Outcome Measurement or Characterization	High	The field methods and mobile laboratory used were new at the time of the study such that the authors produced a publication about these methods (linked reference Schrader et al. 1987, HERO ID 62571), but the outcome was assessed using established methods for semen analysis, which were described in detail.	
	Metric 8: Reporting Bias	High	A description of measured outcomes was reported. Effect estimates were reported with standard deviations and p-values. The number of exposed and unexposed participants were reported for each analysis.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	High	The authors reported that "The following potentially confounding variables and effect modifiers were considered a priori for inclusion in the regression models: tobacco smoking (current, ex-, and non-smokers), marijuana use (times a week), alcohol consumption (drinks a week), caffeine consumption (cups of coffee or tea or both a day), history of urogenital disorders and prescription medication use in the preceding year, history of fever in the preceding three months, abstinence time, sample age, and subject's age and ethnic background."	
	Metric 10: Covariate Characterization	Medium	A detailed questionnaire was administrated by personal interview, but it is unknown whether the questionnaire was validated.	
	Metric 11: Co-exposure Counfounding	Low	This was an occupational study population with potential co-exposures that might have differed by exposure group because workers came from different plants. The use of other chemicals that might effect semen characteristics was not mentioned, though there is some possibility that other pesticides were used. Potential differences in exposures to other pesticides were not assessed.	
Domain 5: Analysis				
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Study Citation:	Ratcliffe, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., Hornung, R. W. (1987). Semen quality in papaya workers with long term exposure to ethylene dibromide. Occupational and Environmental Medicine 44(5):317-326.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	semen characteristics: semen volume, sperm concentration, sperm count, sperm viability, sperm motility, sperm morphology			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	62566 Linked HERO ID(s): 62566, 62571, 62572			
Domain	Metric	Rating	Comments	
	Metric 12: Study Design and Methods	High	The cross-sectional study design and t-tests and regression models were appropriate for assessing the association between exposure to EDB and semen characteristics.	
	Metric 13: Statistical Power	Medium	Power was explicitly discussed in the study in terms of the approximate percent changes in specific semen characteristics that could be detected. The authors also note that much smaller sample sizes are required for sufficient power for analyses of semen characteristics compared to analyses of live births.	
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was sufficient to be conceptually reproducible.	
	Metric 15: Statistical Analysis	High	Data for each semen characteristic were tested for normality. The data were analyzed using two-sided t-tests and least squares linear regression, "except for abnormal sperm classifications, which were analyzed using the FUNCAT procedure for multinomial data." Variables were considered for inclusion in the models using a forward and backward stepwise technique with exposure forced into the model. Assessment for effect modification was performed using two factor interaction terms.	
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16: Use of Biomarker of Exposure	N/A	No biomarkers of exposure were assessed.	
	Metric 17: Effect Biomarker	High	Alterations in semen characteristics are a key event in an adverse outcome pathway (AOP) to impaired fertility. Additionally, Schrader et al. 1987 (linked HERO ID 62571) note "there are several lines of evidence from animal and clinical studies which link alterations in sperm count, viability, motility, and morphology with impaired fertility." Furthermore, the section of the Ratcliffe et al. 1987 paper (HERO ID 62566) titled "Biological Significance of Changes in Semen Quality" (page 325) provides detailed information and citations supporting the association between several semen characteristics and impaired fertility.	
	Metric 18: Method Sensitivity	Low	The limit of detection wasn't explicitly reported, but was low enough to detect differences in semen characteristics.	
	Metric 19: Biomarker Stability	Medium	Participants collected the sample at home and were instructed to bring it to the mobile laboratory in a provided thermos within one hour of collection. Each participant was instructed to record the time of collection and any spillage issues. Time from collection to analysis was provided in the results and did not appear to differ between exposed and unexposed groups.	
	Metric 20: Sample Contamination	Medium	Sample contamination was not discussed but is not likely. Samples were reported to be collected in sterile glass jars.	
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Study Citation:	Ratcliffe, J. M., Schrader, S. M., Steenland, K., Clapp, D. E., Turner, T., Hornung, R. W. (1987). Semen quality in papaya workers with long term exposure to ethylene dibromide. Occupational and Environmental Medicine 44(5):317-326.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	semen characteristics: semen volume, sperm concentration, sperm count, sperm viability, sperm motility, sperm morphology			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	62566 Linked HERO ID(s): 62566, 62571, 62572			
Domain	Metric		Rating	Comments
	Metric 21:	Method Requirements	Medium	The instrumentation provided unambiguous identification and quantification of all biomarkers with the exception of YFF bodies, and the authors note that the results of that particular assay "should be interpreted with extreme caution." Based on the authors' description of the analysis of YFF bodies, the results in Table 7 should be interpreted with more caution than the other results. The main biomarkers assessed were assessed using appropriate instrumentation.
	Metric 22:	Matrix Adjustment	N/A	Matrix adjustment was not required.
Additional Comments:	This study analyzed differences in semen characteristics between workers in papaya fumigation plants who were exposed to EDB and a group of sugar workers. Most of the analyses used dichotomous comparisons of exposed vs unexposed and therefore are not informative for dose-response. However, in an analysis by years of exposure, "longer duration of exposure was associated with poorer sperm viability and motility" based on vital stain ($p < 0.02$), hypo-osmotic swelling ($p < 0.01$), and percentage motility ($p < 0.03$). Although p-values were provided for these analyses, further details such as risk estimates were not provided.			

Overall Quality Determination

Medium

Study Citation:	Schrader, S. M., Turner, T. W., Ratcliffe, J. M. (1988). The effects of ethylene dibromide on semen quality: a comparison of short-term and chronic exposure. Reproductive Toxicology 2(3-4):191-198.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Semen and Sperm Parameters: semen pH, semen volume, sperm count, sperm velocity, sperm motility, sperm viability, sperm concentration, sperm morphology, and sperm head morphometry including sperm head area, perimeter, length, width, width/length ratio, and Pi factor		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62572 Linked HERO ID(s): 62566, 62571, 62572		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	For the forestry study: Selection methods for study participants are not presented or described. It appears to have been an opportunistic sampling. The study measured exposure for 15 forestry workers who "were engaged in the task of applying EDB insecticide to felled pine trees" and reports that ejaculates were collected from 12 men. The paper didn't specify why the 3 other workers were excluded. The exposed workers were compared to a control group of 6 forestry workers whose duties "did not allow contact with the EDB fumigation operations". Participation rates for controls were not presented. Age ranges of exposed and unexposed are presented.
Metric 2:	Attrition	Medium	For the forestry study: Exposure was measured for 15 exposed workers and ejaculates were collected for 12 of them. Two men from the exposed group were excluded from the analyses due to missing data on abstinence. There was no loss to follow-up in the control group of 6 men. Therefore, 10 exposed and 6 control men were included in the analyses.
Metric 3:	Comparison Group	Medium	For the forestry study: The comparison group of male forestry workers in Colorado whose "duties did not allow contact with the EDB fumigation operations" was an appropriate control group for male forestry workers exposed to EDB in Colorado. The age range and mean age were similar between groups, although measures of statistical significance weren't provided for this comparison. Although the paper mentioned that a detailed questionnaire including demographic data was administered by personal interview, other characteristics of the exposed and unexposed were only briefly discussed and statistical comparisons were not reported for these other characteristics.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	For the forestry study: The work processes, including EDB application, and the provision and use (or lack of use) of PPE were described. EDB airborne concentrations were determined for exposed workers using high-rate pumps for samples ranging from 15 minutes to 1 hour in duration, and low-rate pumps for 8 hour samples. Breathing zone samples were collected by attaching the sample tube to workers' collars, with the sampling pump worn on the workers' belts. The charcoal sample tubes were assessed for EDB using gas chromatography and an electron capture detector. EDB concentrations were reported for specific job tasks: filling truck tanks, spraying log piles, and pouring an EDB emulsion on log piles. Additionally, the use of dermal dosimeters was attempted and dermal exposure was noted by observation. Exposure sampling was not reported for the control group.
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Study Citation:	Schrader, S. M., Turner, T. W., Ratcliffe, J. M. (1988). The effects of ethylene dibromide on semen quality: a comparison of short-term and chronic exposure. Reproductive Toxicology 2(3-4):191-198.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Semen and Sperm Parameters: semen pH, semen volume, sperm count, sperm velocity, sperm motility, sperm viability, sperm concentration, sperm morphology, and sperm head morphometry including sperm head area, perimeter, length, width, width/length ratio, and Pi factor			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	62572 Linked HERO ID(s): 62566, 62571, 62572			
Domain	Metric	Rating	Comments	
	Metric 5: Exposure Levels	Low	For the forestry study: Despite the measurement of personal breathing zone exposures for all of the exposed individuals and the reporting of exposures for different job tasks, in the quantitative analyses exposure status was only considered as two levels of exposure: unexposed and exposed. The exposed group had a time-weighted average of 60 ppb and a peak of 2165 ppb for airborne exposure and "extensive skin exposure" was noted.	
	Metric 6: Temporality	Medium	For the forestry study: Outcome samples were collected 1 to 2 weeks before exposure and during the last week of exposure.	
Domain 3: Outcome Assessment				
	Metric 7: Outcome Measurement or Characterization	High	The field methods and mobile laboratory used were new at the time of the study such that the authors produced a publication about these methods (linked reference Schrader et al. 1987, HERO ID 62571), but the outcome was assessed using established methods for semen analysis, which were described in detail. Analyses were performed at a NIOSH laboratory. Replicates, controls, and blinding were used where appropriate.	
	Metric 8: Reporting Bias	Medium	For the forestry study: Data for some of the potential confounders included in the questionnaire were not reported. All of the semen and sperm outcomes that were outlined in the abstract, introduction, or methods section of the paper were reported, but some results were only presented qualitatively in the text with p-values but without effect estimates.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Medium	For the forestry study: Wilcoxon comparisons were performed without accounting for potential confounders. However, there is no direct or indirect evidence that there were differences between workers. All workers were male and within a similar age range. Although demographic data, medical history, and smoking and drinking habits were included in the questionnaire, data for these other potential confounders were not compared using statistical tests and were not adjusted for in analyses. Abstinence time was assessed but was not found to have a significant correlation with change in volume. Age of the semen sample differed between groups but was not significantly associated with sperm velocity.	
	Metric 10: Covariate Characterization	Medium	For the forestry study: Data on personal and demographic data, medical history, smoking and drinking habits, work history, and current and previous exposures to chemical and physical hazards were obtained from "detailed questionnaires" that were "administered by personal interview". It is unknown whether the questionnaire was validated. The data on several potential confounding variables were not reported, but the reported data did not indicate differences between groups.	

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Study Citation:	Schrader, S. M., Turner, T. W., Ratcliffe, J. M. (1988). The effects of ethylene dibromide on semen quality: a comparison of short-term and chronic exposure. Reproductive Toxicology 2(3-4):191-198.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Semen and Sperm Parameters: semen pH, semen volume, sperm count, sperm velocity, sperm motility, sperm viability, sperm concentration, sperm morphology, and sperm head morphometry including sperm head area, perimeter, length, width, width/length ratio, and Pi factor			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	62572 Linked HERO ID(s): 62566, 62571, 62572			
Domain	Metric	Rating	Comments	
	Metric 11: Co-exposure Counfounding	Medium	For the forestry study: Although the questionnaire asked about "current and previous exposures to known or suspected chemical or physical hazards", there is no indication that these potential co-exposures were accounted for in the analyses. The control and exposed groups consisted of forestry workers so co-exposures might not have been substantially different between groups.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	High	For the forestry study: The longitudinal study design was appropriate for the research question. Although few details of the statistical analyses were provided, the Wilcoxon rank test is an appropriate method.	
	Metric 13: Statistical Power	Low	For the forestry study: The relatively small sample size (10 exposed and 6 unexposed) might have limited the power to observe effects.	
	Metric 14: Reproducibility of Analyses	Low	For the forestry study: Some details of the analyses and results were insufficiently reported.	
	Metric 15: Statistical Analysis	High	For the forestry study: Although few details were provided, the Wilcoxon rank sum test is non-parametric so there aren't concerns about assumptions.	
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16: Use of Biomarker of Exposure	N/A	The study did not assess biomarkers of exposure.	
	Metric 17: Effect Biomarker	High	Alterations in semen characteristics are a key event in an adverse outcome pathway (AOP) to impaired fertility. Additionally, Schrader et al. 1987 (linked HERO ID 62571) note "there are several lines of evidence from animal and clinical studies which link alterations in sperm count, viability, motility, and morphology with impaired fertility." Furthermore, the section of the Ratcliffe et al. 1987 paper (HERO ID 62566) titled "Biological Significance of Changes in Semen Quality" (page 325) provides detailed information and citations supporting the association between several semen characteristics and impaired fertility.	
	Metric 18: Method Sensitivity	Low	The number of cells used to evaluate each semen parameter was reported. Azoospermic men were not included in the analysis. However, the LOD was not explicitly stated.	
	Metric 19: Biomarker Stability	Medium	Participants provided the sample at home and were instructed to bring it to the laboratory in a provided thermos within an hour of collection. Each participant was instructed to record the time of collection and any spillage issues. Time from collection to analysis was provided in the results and did not appear to differ between exposed and unexposed groups.	
	Metric 20: Sample Contamination	Medium	Sample contamination was not discussed but is not likely. Samples were reported to be collected in sterile glass jars.	
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Study Citation:	Schrader, S. M., Turner, T. W., Ratcliffe, J. M. (1988). The effects of ethylene dibromide on semen quality: a comparison of short-term and chronic exposure. Reproductive Toxicology 2(3-4):191-198.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	Semen and Sperm Parameters: semen pH, semen volume, sperm count, sperm velocity, sperm motility, sperm viability, sperm concentration, sperm morphology, and sperm head morphometry including sperm head area, perimeter, length, width, width/length ratio, and Pi factor
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62572 Linked HERO ID(s): 62566, 62571, 62572

Domain	Metric	Rating	Comments
	Metric 21: Method Requirements	High	Morphology analyses were conducted at NIOSH laboratories. Sperm velocity and motility were assessed using video recordings and automated software. Sperm pH was determined using a pH meter. Viability was assessed using differential interference contrast microscopy.
	Metric 22: Matrix Adjustment	N/A	Matrix adjustment wasn't required for most of the biomarkers assessed. Study authors provided sperm concentration with and without adjustment for semen volume (million/ejaculate and million/ml, respectively).

Additional Comments: This paper reported the results of two studies – a study of papaya workers and a study of forestry workers. The study of papaya workers was reported on in two additional papers. The data quality evaluation for that papaya study is reported for HERO ID 62566. The present data quality evaluation focuses on the study of forestry workers. The forestry worker study was a longitudinal study of acute or short term effects of EDB exposure on semen and sperm characteristics. The small sample size might have limited the ability to detect effects, but decreases in semen volume and sperm distance velocity were found.

Overall Quality Determination

Medium

Study Citation:	Takahashi, W., Wong, L., Rogers, B. J., Hale, R. W. (1981). Depression of sperm counts among agricultural workers exposed to dibromochloropropane and ethylene dibromide. Bulletin of Environmental Contamination and Toxicology 27(4):551-558.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Semen Characteristics (sperm counts, morphology, and motility)		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62588		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Low	This was a pilot study. Volunteers were solicited from three groups of non-vasectomized men: agricultural workers, allegedly infertile men seen at a clinic, and men from the general population of Molokai, Hawaii. Further information on recruitment methods and inclusion and exclusion criteria were not provided.
Metric 2:	Attrition	Low	Numbers of eligible participants were not reported. Semen analyses were performed on 13 pineapple field workers and a reference group of 19 men including one infertile male. However, information was not provided on what the proportion of participants with semen analyzed was in relation to total eligible participants.
Metric 3:	Comparison Group	Low	The location and age of the pineapple workers and the reference group were similar. Ten men in the reference group smoked marijuana, but only one pineapple worker smoked marijuana. The reference group included "unemployed, clerical, skilled and unskilled, technical, and kindred workers." Participants were asked to complete a medical history questionnaire. However, there was not much other information provided on characteristics of the two groups. Results were also compared to those of a fertile Honolulu population from a previous study.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Drip irrigators applied EDB for 6 days and field research workers used EDB for 5 days. Thus, those in the exposed group were known to have used EDB. However, exposure to EDB was not directly measured. There was no industrial hygiene sampling, no personal sampling, and no measurement of biomarkers of exposure. The only measurement of EDB was water sampling, which produced negative results.
Metric 5:	Exposure Levels	Low	Only two exposure levels were compared. Exposed pineapple workers were compared to unexposed groups.
Metric 6:	Temporality	Medium	The pineapple fields were fumigated from May through December 1979. Drip irrigators applied EDB from May - July 1979. The field research workers used EDB in August 1979. Semen samples were collected from October 1979 - January 1980. Therefore, exposure occurred before the outcome was assessed, with the possible exception of some fumigators. However, the relevant exposure window is unclear.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	The outcome was assessed using semen analyses, which is a well-established method. General details on semen collection and analysis were reported. It was not reported whether examiners were blinded. Additionally, details on scoring criteria for morphology were not described.

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Study Citation:	Takahashi, W., Wong, L., Rogers, B. J., Hale, R. W. (1981). Depression of sperm counts among agricultural workers exposed to dibromochloropropane and ethylene dibromide. Bulletin of Environmental Contamination and Toxicology 27(4):551-558.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Semen Characteristics (sperm counts, morphology, and motility)			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	62588			
Domain	Metric	Rating	Comments	
	Metric 8: Reporting Bias	Medium	A description of measured outcomes is reported in the Methods section. Effect estimates were reported with p-values. Ranges were reported, but confidence intervals and standard errors were not reported.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Low	The analyses were stratified by marijuana use, but adjustment or stratification for other potential confounders was not performed.	
	Metric 10: Covariate Characterization	Low	Volunteers completed a medical history questionnaire. It is unknown whether the questionnaire was validated.	
	Metric 11: Co-exposure Counfounding	Low	The exposed workers used both DBCP and EDB. The authors note that both DBCP and EDB are known to affect spermatogenesis. Potential co-exposure confounding is a substantial concern for this study because there is no way to separate exposure to EDB from exposure to DBCP in this study.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	High	This study was a pilot study and a cross-sectional study, which is appropriate for the research question. Groups were compared using chi-square and Dunn’s multiple comparison tests.	
	Metric 13: Statistical Power	Low	Although the sample size was small, some statistically significant results were observed.	
	Metric 14: Reproducibility of Analyses	Medium	The analysis is conceptually reproducible.	
	Metric 15: Statistical Analysis	High	Non-parametric techniques using chi-square tests and Dunn’s multiple comparison test were performed. These methods were transparent and appropriate for a pilot study.	
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16: Use of Biomarker of Exposure	N/A	Biomarkers of exposure weren’t assessed in this study.	
	Metric 17: Effect Biomarker	High	Semen characteristics are an indicator of a key event in an adverse outcome pathway to impaired fertility.	
	Metric 18: Method Sensitivity	Low	A limit of detection (LOD) and limit of quantification (LOQ) for sperm weren’t reported.	
	Metric 19: Biomarker Stability	Medium	Samples were taken to the laboratory within an hour.	
	Metric 20: Sample Contamination	Medium	No information was included about potential contamination.	
	Metric 21: Method Requirements	Medium	The instrumentation was not fully described but there are no known interferants.	
	Metric 22: Matrix Adjustment	N/A	Matrix adjustment was not required.	

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Study Citation:	Takahashi, W., Wong, L., Rogers, B. J., Hale, R. W. (1981). Depression of sperm counts among agricultural workers exposed to dibromochloropropane and ethylene dibromide. Bulletin of Environmental Contamination and Toxicology 27(4):551-558.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	Semen Characteristics (sperm counts, morphology, and motility)
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62588

Domain	Metric	Rating	Comments
Additional Comments:	This cross-sectional study compared pineapple field workers to a reference group. A significant decrease in sperm count was found in the agricultural population compared to the reference group. There are substantial concerns with exposure measurement and potential co-exposure confounding in this study. Exposure to EDB was not measured directly and could not be separated from exposure to dibromochlorophane (DBCP), which was used simultaneously with EDB in the pineapple field.		

Overall Quality Determination

Low

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	fertility (number of children)		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	Participants were married current employees at an EDB factory "when concern over the potential effect of EDB on fertility arose, only factory B was in operation". Participation rates are not reported but it is implied that all eligible employees were included in the study.
Metric 2:	Attrition	High	No attrition is reported. Some characteristics of former employees, who were not included in the analysis sample, were reported and were similar to the current employees included in the analysis.
Metric 3:	Comparison Group	Medium	Age of employees is similar across exposure groups and all are male. Other characteristics are not reported.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	Exposure groups are based on type of job role and were categorized based on frequency of exposure, but not directly quantified.
Metric 5:	Exposure Levels	Medium	Four exposure levels are reported based on job roles. Employees are categorized as having none exposure to EDB, regular engagement with processing EDB, variable exposure, or irregular potential exposure.
Metric 6:	Temporality	Medium	Temporality is established by reporting the number of children fathered before versus after employees began working at the factor. Given variations in lengths of time worked, it is not entirely clear if the exposure window is relevant for the outcome.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Low	Outcome is measured as the number of children fathered while employed. The use of less sensitive or inferred metric for fertility gives reason to expect potential outcome misclassification.
Metric 8:	Reporting Bias	Medium	The outcome(s) of interests were reported in this study. Mean values and ranges were provided for relevant variables, but no confidence intervals or standard errors were reported.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	Low	No adjustments were made for confounders or covariates. Age is similar across all reporting groups, so confounding by age is not a major concern. However, there is variability in the number of children at the time of employment by exposure group, which could influence the number of children fathered while employed. Other confounding factors, such as socioeconomic status, are not accounted for.

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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	fertility (number of children)			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	54256			
Domain		Metric	Rating	Comments
	Metric 10:	Covariate Characterization	N/A	There was no information reported on covariates assessment or adjustment.
	Metric 11:	Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	Low	No statistical analyses were utilized to test significance of associations.
	Metric 13:	Statistical Power	Low	It's not clear if the number of participants would be adequate to detect an effect in the exposed population because the highest exposure group includes only 13 people. No statistical analyses were used to test significance of associations.
	Metric 14:	Reproducibility of Analyses	Medium	Analysis is straightforward and would be reproducible with access to the data.
	Metric 15:	Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for other potential confounders.
Additional Comments:	This study reports fertility rates among men employed in different roles at an ethylene dibromide manufacturing plant in Britain. Some concerns with this study include the lack of precision of exposure and outcome measurement. Further, no statistical methods were used to quantify the association between exposure and outcome, which limits interpretation of the results.			

Overall Quality Determination

Low

Study Citation:	Wong, O., Utidjian, D., H.M., Karten, V. S. (1979). Retrospective evaluation of reproductive performance of workers exposed to ethylene dibromide (EDB). Journal of Occupational and Environmental Medicine 21(2):98-102.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Fertility		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	94772 Linked HERO ID(s): 94772, 4822833, 12935803		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	The authors described methods of participant selection, but some key elements of the study, such as participation rate at most steps in the study or the subjects who withdrew or were excluded after study began were now reported for all sites. Available information however, indicates a low risk of bias.
Metric 2:	Attrition	Low	Very little information was provided with respect to the numbers of participants at each stage of the study, numbers of workers eligible vs numbers that participated, and/or reasons for non-participation.
Metric 3:	Comparison Group	High	Age, sex, and race adjustment as well as stratification is described and choice of reference population is reported. The study indicates that expected numbers of births were derived from national fertility tables compiled by the National Center for Health Statistics. Computations were made using maternal age, parity, and race.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	The authors did not look at individual exposure levels. The exposure methodology was not well-described. At least some of the exposure measurements were based on industrial hygiene surveys. Exposures at plant A ranged from < 0.5 to 5 ppm, and results were stratified according to exposures < 0.05 ppm and 0.5-5 ppm (individual exposure records not available for Plant D and they were excluded from the analyses). The study authors noted that job assignments were relatively stable (and exposures were fairly constant).
Metric 5:	Exposure Levels	Low	The study reports 2 levels of exposure (e.g., exposed/unexposed).
Metric 6:	Temporality	Medium	The study indicated that only births that occurred after nine months since exposure were included, and that these criteria may have possibly discounted premature births. Two births occurred 7 and 8 months after the onset of exposure.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Low	The authors did not use a diagnostic criteria to measure fertility in the subjects, such as sperm count, quality and motility. The authors used fertility/birth rate of the subject's spouse without taking into account any issues of fertility with the spouse. Fertility/birth rate which was used as a surrogate measure of male fertility is not the most direct/sensitive measure of the outcome.
Metric 8:	Reporting Bias	Medium	The measured outcome (birth rate) outlined in the methods is reported, but not in a way that would allow for detailed extraction (e.g., results were provided for each plant without estimates of variance).

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Study Citation:	Wong, O., Utidjian, D., H.M., Karten, V. S. (1979). Retrospective evaluation of reproductive performance of workers exposed to ethylene dibromide (EDB). Journal of Occupational and Environmental Medicine 21(2):98-102.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	Fertility
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	94772 Linked HERO ID(s): 94772, 4822833, 12935803

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	Medium	There is indirect evidence that results are age- and sex-adjusted.
	Metric 10: Covariate Characterization	Low	The study did not specify how information concerning covariates were obtained. The study states information pertaining to name, data of birth, race, marriages/divorces, spouse's information, dates of birth of children, history or vasectomy, dates of exposure and amounts of exposure were "collected" (not further specified). Some information was obtained through work histories. Factors pertaining to the spouse and/or the couple, such as employment status, income, and education were not available or factored into the analysis.
	Metric 11: Co-exposure Counfounding	Medium	The plants utilized for analyses were involved in EDB manufacturing (and were selected for that reason). However, it is noted in the methods that Plant A began producing di-bromochloropropane (DCB) in 1976, and plant C also produced other brominated compounds. Each plant was evaluated separately, but it does not appear that any adjustments were made for these potential co-exposures.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The retrospective study design chosen was appropriate for the research question and uses an appropriate statistical method (calculation of observed/expected birth rates).
	Metric 13: Statistical Power	Medium	A total of 297 couples from the 4 plants (A-D) were included in the study. From the 297 couples, a total of 1,097 person-years was under observation among the wives during the study period 1958-1977. The number of participants was adequate to detect an effect in the exposed population and/or subgroup of the total population.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand what has been done and to be conceptually reproducible.
	Metric 15: Statistical Analysis	High	The method for calculating risk estimates is transparent.

Additional Comments: Male workers from 4 EDB manufacturing plants in Texas and Arkansas were included in a cohort that was evaluated for effects on fertility via the assessment of birth rate of their spouses (a total of 297 couples were analyzed). The birth rate among male workers and their partners were compared with national birth rates taking into account maternal age, parity, and race. Based on the analysis of each plant individually, a significantly decreased birth rate was observed only in Plant D. Taking all of the plants into account, there was not a significant effect on birth rate. There were several limitations associated with the study, including inadequate information pertaining to exposure, how information about covariates was collected, lack of adjustments for possible co-exposures (dibromochloropropane at Plant A and 'other brominated compounds' at Plant C), and the use of a less sensitive/direct outcome to assess fertility (i.e., births in female partners as a surrogate for fertility in males rather than measurements of sperm count).

Overall Quality Determination

Low

Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	respiratory system cancer mortality, digestive system cancer mortality, all other site cancer mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	In this retrospective occupational cohort study, employees were identified from two facilities (Michigan and Texas). Each facility was described in detail. Job descriptions of those included in the study were provided. The study authors indicate they selected all employees from four specific job types that were likely to have had contact with EDB. Some details regarding the participation rate are unclear, however, there was no direct evidence to suggest selection bias. A total number of 261 subjects were reported.
Metric 2:	Attrition	Medium	Only one individual was reported to be untraced and three individuals did not have obtainable death certificates. Some employees were excluded from the analysis due to leaving the company prior to 1940, citing traceability issues. The number of participants excluded for this reason is unclear.
Metric 3:	Comparison Group	Low	Employees were compared to the US general population of white males, calculated in five year age groups. While all employees were reported to be male, other demographic characteristics such as race were not discussed, resulting in minor uncertainty about whether the reference group is wholly appropriate.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was determined by employment at one of the two facilities. The study authors note that detailed employment records exist for the two facilities, and that there was periodic environmental surveillance data for the 62 Michigan employees. The 99 Texas employees did not have routine environmental surveillance data, but job process documentation implies "significant EDB exposure might have occurred." for the selected jobs. For the 62 Michigan employees, the authors describe personal and area sampling (1950, 1952, 1971-1972) and ranges for each job type. Due to the incomplete surveillance data, only employment length for highest concern job types was used in the analysis. Overall, despite a disparity in levels of detail between the two population types, there is reasonable confidence that all employees were exposed to some level of EDB.
Metric 5:	Exposure Levels	Low	Number of observed and expected cases were calculated both by employment status (exposed/unexposed), and by employment length (three levels) as well as stratifying by interval since first exposure (three levels). Since none of these provide quantitative concentrations of EDB in a form useful for a dose-response assessment, this metric is rated Low.

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	respiratory system cancer mortality, digestive system cancer mortality, all other site cancer mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306			
Domain		Metric	Rating	Comments
	Metric 6:	Temporality	Medium	Employees were recruited if they had been employed after 1940 and were followed until 1976. Some individuals were still currently employed which may not allow for enough latency time for the outcome of interest, mortality. The healthy worker effect may also be of concern due to the use of an occupational cohort.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	Former employees were followed using Social Security checks. The evaluation and coding of death certificates was not detailed. ICD codes used to identify relevant mortalities were not provided. The source of US general population mortality rates was not detailed.
	Metric 8:	Reporting Bias	Medium	The number of observed cases and expected cases were provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Low	Only males were included in the study. The authors calculate age-stratified SMRs. Demographic characteristics of the participants was not provided, and only white male mortality data was utilized in the SMR calculation. It is not clear if race would be an applicable stratification factor in this population. Potentially relevant behaviors such as smoking and alcohol use are not discussed.
	Metric 10:	Covariate Characterization	Medium	Collection of potential confounders (sex, age) was not described but presumably based on employment records.
	Metric 11:	Co-exposure Counfounding	Low	Other co-exposures were described and included lead, bromine, ethylene, hydrogen, iodine, ammonia, silica, copper, nickel acetate, vinyl bromide, and numerous other chlorinated and/or brominated hydrocarbons. These exposures varied by job type. Five individuals suspected to be exposed to arsenic were evaluated separately. Adjustments or other considerations for co-exposures were not made.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	This study utilized a retrospective occupational cohort of men to evaluate the relationship between chronic EDB exposure and various cause-specific mortalities. No concerns about study design.
	Metric 13:	Statistical Power	Low	The sample size was somewhat small (n=161) with limited number of cases per cause of death and a total of only 35 reported deaths. Stratification by employment length and interval since first exposure may result in very small comparison groups and should be interpreted with caution.
	Metric 14:	Reproducibility of Analyses	Medium	Data was provided on employment length and interval since first exposure by facility. Other descriptions were sufficient to reproduce the main analysis and analyses stratified by employment duration/exposure interval.

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	respiratory system cancer mortality, digestive system cancer mortality, all other site cancer mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	Low	Expected deaths were calculated, however, standardized mortality ratios were not calculated.

Additional Comments: This study utilized a retrospective occupational cohort on 161 men to evaluate the relationship between EDB exposure and cause-specific mortality. Some concerns about this study include lack of information on participation rates, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants and cases. Additionally, there was a lack of information on the study population characteristics, and expected cases were calculated without a measure of variance. Urine bromine was measured, however, this was not used for the analysis and study authors indicate this would be non-specific for EDB exposure.

Overall Quality Determination

Low

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:	Ethylene Dibromide- 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 ethylene dibromide, 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:	Ethylene Dibromide- 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:	Ethylene Dibromide- 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:	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:	Ethylene Dibromide- 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:	Ethylene Dibromide- 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:	Ethylene Dibromide- 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:	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Chemosphere 16(8-9):2095-2099.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	soft-tissue sarcoma deaths		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	1357737		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	Low	The paper reported that the target population was 37,000 individuals who worked for at least one year at a chemical production facility in Midland, Michigan. From this population, all death certificates that had an underlying or contributing cause of death that mentioned cancer were reviewed to determine whether the cancer type was soft-tissue sarcoma. A concern is that the authors did not specify how many of the study subjects had died, how many of those had death certificates available, or how many of the death certificates mentioned cancer. From the death certificates that mentioned cancer, 10 probable and 12 questionable cases of soft-tissue sarcoma were identified. Death certificates, medical records, and histology reports for these 22 individuals were reviewed and 15 were determined to meet the case definition. Referents were matched 9 to 1 to cases. Inclusion and exclusion criteria for the referents were specified but randomization in selection of referents was not mentioned.
	Metric 2: Attrition	Medium	Of the 15 cases identified, no matching controls were found for one case. Therefore, this case was excluded from the analyses.
	Metric 3: Comparison Group	Medium	Cases and controls were obtained from the same eligible population. The target population was described as having worked at the chemical production facility for at least one year between January 1, 1940 and December 31, 1979 but it is unclear whether that was a requirement for inclusion for cases. Referents had to have worked at the facility for at least one year and had to have been employed "during or after 1940 but before 1978". It is unclear why potential controls who worked at the facility in 1979 were excluded. The referents were matched with cases on sex and race, and "with a few exceptions," year of birth and year of hire. The exceptions were not explained further.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Low	Work histories for cases and referents were coded and reviewed by an industrial hygienist to determine potential exposure to the chemical of interest. The industrial hygienist was blinded to case/control status. The paper noted that the use of employee exposure and work histories enabled the study "to avoid the potential problem" of recall bias. However, measured concentrations of the chemicals were not reported and the exposure assessment was based on "presumptive chemical exposures".
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Study Citation:	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Chemosphere 16(8-9):2095-2099.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	soft-tissue sarcoma deaths			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	1357737			
Domain	Metric	Rating	Comments	
	Metric 5:	Exposure Levels	Low	Exposure was considered as a dichotomous variable with categories of ever exposed vs never exposed. No quantitative information was reported on exposure levels or range of exposures, other than duration of exposure. Latency periods and duration of exposure were not adequately addressed in the analyses. The authors reported that "the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his 6 referents ranged from 66 days to 9.4 years."
	Metric 6:	Temporality	Low	Temporality of exposure and outcome is established. It is unclear if the interval between exposure and outcome is sufficient for soft tissue sarcoma outcomes. Duration of exposure was not adequately addressed in the analyses. The authors reported that "the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his 6 referents ranged from 66 days to 9.4 years."
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Medium	To identify soft-tissue sarcoma deaths, all death certificates that had "an underlying or contributing cause of death which mentioned cancer" were reviewed. These included ICD codes 140 to 239. From the death certificates that mentioned cancer, 10 probable and 12 questionable cases of soft-tissue sarcoma were identified. The probable cases had a "cause of death listed as a malignant soft-tissue sarcoma according to the classification of Morton and Eilber". The questionable cases were listed as "sarcoma-undefined site" or "lymphoma". For these 22 potential cases, the authors reported that "attempts were made to obtain copies of medical records, pathology reports, and tissue specimens" and the final determination was based on the "best available medical information: death certificates, medical records, or histopathology report". The proportion of cases determined by each of these methods was not reported.The referents "must not have died from ill-defined cancers possibly of soft-tissue origin". The referents "must have survived at least as long as the case". Therefore, the outcome was assessed well in the referents, except for the potential that the referents might have had cancer but might not have died from it.
	Metric 8:	Reporting Bias	High	Numbers of cases and controls were reported in Table 3. Maximum likelihood estimate odds ratios with 95% confidence intervals were reported for ethylene dibromide and other chemicals.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Medium	The referents were matched with cases on sex and race, and "with a few exceptions," year of birth and year of hire. The exceptions were not explained further. The authors also reported that the medical records of cases and referents were reviewed for information on "various heritable syndromes, family history of cancer, history of lymphedema, steroids, throrotrast, foreign body implants, chronic extensive scarring, radiation therapy, and immunologic defects". However, it is unclear how that information was used.

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Study Citation:	Sobel, W., Bond, G. G., Skowronski, B. J., Brownson, P. J., Cook, R. R. (1987). A soft tissue sarcoma case control study in a large multi-chemical manufacturing facility. Chemosphere 16(8-9):2095-2099.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	soft-tissue sarcoma deaths			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	1357737			
Domain	Metric	Rating	Comments	
	Metric 10:	Covariate Characterization	High	Potential covariates were assessed using medical and work records.
	Metric 11:	Co-exposure Counfounding	Low	In addition to ethylene dibromide, the study identified 12 other chemicals used at the same facility that were determined by the National Toxicology Program to be associated with soft-tissue sarcoma. The authors noted that some individuals were exposed to multiple chemicals during their employment history and therefore were counted multiple times in the results table (Table 3). Co-exposures do not appear to have been adjusted for in the analyses.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	Soft tissue sarcoma is a group of rare cancers, so a case-control study design is appropriate. Odds ratios are appropriate for assessing case-control studies.
	Metric 13:	Statistical Power	Low	The study included a small sample size of 14 cases and 126 matched controls. One case and 6 controls were identified as having ethylene dibromide exposure. No statistically significant associations were found for any of the 13 chemicals that had been associated with soft-tissue sarcomas by the National Toxicology Program. Therefore, the statistical power might not have been sufficient to detect an association.
	Metric 14:	Reproducibility of Analyses	Low	The study calculated odd ratios and 95% confidence intervals. The analyses appear to have accounted for the matching of cases and controls, but those details are not adequately described.
	Metric 15:	Statistical Analysis	Low	Full details of the analyses and assumptions were not reported. The analyses appear to have accounted for the matching of cases and controls, but those details are not adequately described.
Additional Comments:	This case-control study assessed soft-tissue sarcoma deaths in workers at a facility that used 13 chemicals potentially associated with soft-tissue sarcomas including ethylene dibromide. Some of the reporting of methods lacked sufficient details. The study included a small sample size of 14 cases and 126 matched controls. No statistically significant associations were found for any of the 13 chemicals that had been associated with soft-tissue sarcomas by the National Toxicology Program. Therefore, the statistical power might not have been sufficient to detect an association. One case and 6 controls were identified as having ethylene dibromide exposure. Duration of exposure and latency periods were not adequately addressed in this study. The exposure was assessed as dichotomous ever exposed vs never exposed. However, the authors reported that "the single case related to ethylene dibromide had been exposed for 40.6 years. The duration for his 6 referents ranged from 66 days to 9.4 years."			
Overall Quality Determination		Low		

Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	all malignant neoplasms, colon and rectum cancer, other digestive cancers, larynx cancer, lung cancer (including trachea and bronchus), genitourinary cancer, lymphatic cancers, brain and central nervous system cancer, other cancers		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62587		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cohort was identified using several record sources. Females were excluded. All males who worked at the plant for at least one day from 1952 - 1977 were included. Computer tapes identified employees from 1960-1976 but other record sources were used for 1952-1959 and 1977, so there might have been some inconsistency in selection into the study. There is no information provided on the accuracy of the sources, but it is considered likely that identifying the subjects who worked in the plant would not omit subjects based on exposure or outcome.
Metric 2:	Attrition	High	There was only 1% loss to follow-up.
Metric 3:	Comparison Group	Medium	Standardized mortality ratios (SMRs) were calculated using race-specific person years at risk for 5-year categories of age with the expected numbers for males in the United States, stratified by race, 5-year age group, and 5-year calendar time period. Mortality for workers was compared to mortality for the general population so there is the potential for healthy worker effect.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	The study does not include assessment of industrial hygiene sampling for EDB, nor any personal monitoring for EDB, nor use of biomarkers for EDB, nor use of job matrices that would indicate EDB exposure, nor any other way to distinguish exposure to EDB from exposures to the other chemicals at the plant including tetraethyl lead (TEL), etc. The only measurements of exposure are work at the plant (SMRs: cause-specific mortality rates for males who worked at the plant vs cause-specific mortality rates of males in the U.S.) and duration of exposure measured by length of exposure. These are not adequate measures to quantify exposure specific to EDB.
Metric 5:	Exposure Levels	Low	Exposed workers were compared to the general population, so there were only two levels of exposure.
Metric 6:	Temporality	Medium	Since mortality is the endpoint, exposure would have to precede the outcome. It is unclear whether the exposures fall within the relevant exposure window.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Vital status was determined using company records, Social Security, IRS, and the Texas Bureau of Safety and Vital Statistics. The cause of death was coded by a nosologist using the ICD codes in effect at the time of death.
Metric 8:	Reporting Bias	High	SMRs were appropriately reported.
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Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	all malignant neoplasms, colon and rectum cancer, other digestive cancers, larynx cancer, lung cancer (including trachea and bronchus), genitourinary cancer, lymphatic cancers, brain and central nervous system cancer, other cancers
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62587

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	SMRs were adjusted for race, age, and sex.
	Metric 10: Covariate Characterization	Low	Information was obtained from work records. Study subjects "whose race was white or unknown, and individuals with Hispanic surnames, were classified as white." All others were classified as non-white. Thus, there was potential misclassification of race. Only a small proportion of the workers were female. Females "were excluded from the study because historically they held nonproduction positions."
	Metric 11: Co-exposure Counfounding	Low	In addition to EDB, exposure was noted to include tetraethyl lead, ethylene dichloride, inorganic lead, and vinyl chloride monomer. It was noted that work histories lacked sufficient data to identify specific jobs in processing and manufacturing areas. Therefore, results cannot be separated by chemical nor can it be known if there was exposure to more than one of these chemicals for any specific job.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The analyses were appropriate and well described.
	Metric 13: Statistical Power	Medium	There were 2493 subjects included with 156 deaths.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was appropriate.
	Metric 15: Statistical Analysis	High	The method for calculating Standardized Mortality Ratios (SMR) is transparent.
Additional Comments:	The main limitations of this study are the lack of EDB-specific quantitative exposure data, the inability to separate out the exposure of interest from other co-exposures, and the potential for healthy worker effect.		

Overall Quality Determination

Medium

Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	Cancer mortality		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	54256		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	Medium	The authors provided limited detail on the participants selection process, but numbers of individuals employed and individuals with health records is reported, allowing calculation of an inclusion rate. The main inclusion criteria were having worked at either factory for at least 4 years. This excludes employees with shorter tenure and therefore the lower end of the exposure distribution, but is not expected to be a major source of bias.
	Metric 2: Attrition	Medium	In Factory A, all known employees of 4 plus years had outcome data, but the total number of employees is unknown, so it is difficult to assess selection and attrition rates. In Factory B, 198 employees had been employed for 4 plus years and 3 were not included in analysis for "lack of information". There is no reason to assume that attrition is associated with outcomes.
	Metric 3: Comparison Group	Low	The unexposed comparison group was drawn from the general local population, but no information was reported to determine if the local population and exposed population were similar.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Low	Exposure assignment is based only on having worked at a factory; detailed employment records are not reported.
	Metric 5: Exposure Levels	Low	The only 2 reported levels of exposure for total mortality and cancer mortality are exposed (factory population) and unexposed (local population). Although years of employment are available elsewhere in the article and could serve to help distinguish levels of exposure, this is not accounted for in measures of mortality outcomes.
	Metric 6: Temporality	Medium	Temporality appears to be established, but some individuals may not have been followed for a sufficient period of time given the latency period of cancer and other outcomes.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	Low	The outcome (mortality and cause of death) measurement appears to differ slightly for exposed vs. unexposed populations: The factory population reports death rate per 1000 person-years, but the comparison group from the local population instead reports annual death rates for only select years.
	Metric 8: Reporting Bias	Medium	All described outcomes are reported, but there are no confidence intervals or errors reported.
Domain 4: Potential Confounding / Variability Control			
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Study Citation:	Turner, D., Barry, I., P.S. (1979). An epidemiological study of workers in plants manufacturing ethylene dibromide. Arhiv za Higijenu Rada i Toksikologiju / Archives of Industrial Hygiene and Toxicology 30:621-626.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Cancer mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	54256

Domain	Metric	Rating	Comments
	Metric 9: Covariate Adjustment	Medium	Results are stratified by age and only men are included in the study population so confounding by sex is not a concern. No other adjustments for potential confounders are made.
	Metric 10: Covariate Characterization	N/A	There was no information reported on covariates assessment or adjustment.
	Metric 11: Co-exposure Counfounding	Medium	The introduction suggests that co-exposures to other chemicals is unlikely because the factories are separate from other chemical industrial activity. However, potential co-exposure may be possible to other chemicals involved in bromine extraction and EDB production.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	Low	Overall, there were no statistical analyses utilized. Cancer mortality and total mortality rates were reported for exposed and unexposed groups, but there was no statistical comparison between them.
	Metric 13: Statistical Power	Medium	The study population of 117 employees from factory A and 234 (n=195 analytic sample) employees from factory B is likely sufficient to detect an effect.
	Metric 14: Reproducibility of Analyses	Low	There were no statistical analyses utilized. Additionally, there are minimal details on how mortality rates were calculated, particularly for the local population.
	Metric 15: Statistical Analysis	N/A	The authors did not use statistical analyses to adjust for other potential confounders.
Additional Comments:	This occupational study reports mortality rates for factory workers and the general local population. However, no statistical analyses were conducted to determine differences between the two populations. There are also several concerns with exposure assessment and outcome measurement that contribute to low confidence in the overall results.		

Overall Quality Determination

Low

Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Lung/Respiratory
Reported Health Effect(s):	emphysema mortality, chronic bronchitis mortality, asthma mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	In this retrospective occupational cohort study, employees were identified from two facilities (Michigan and Texas). Each facility was described in detail. Job descriptions of those included in the study were provided. The study authors indicate they selected all employees from four specific job types that were likely to have had contact with EDB. Some details regarding the participation rate are unclear, however, there was no direct evidence to suggest selection bias. A total number of 261 subjects were reported.
Metric 2:	Attrition	Medium	Only one individual was reported to be untraced and three individuals did not have obtainable death certificates. Some employees were excluded from the analysis due to leaving the company prior to 1940, citing traceability issues. The number of participants excluded for this reason is unclear.
Metric 3:	Comparison Group	Low	Employees were compared to the US general population of white males, calculated in five year age groups. While all employees were reported to be male, other demographic characteristics such as race were not discussed, resulting in minor uncertainty about whether the reference group is wholly appropriate.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was determined by employment at one of the two facilities. The study authors note that detailed employment records exist for the two facilities, and that there was periodic environmental surveillance data for the 62 Michigan employees. The 99 Texas employees did not have routine environmental surveillance data, but job process documentation implies "significant EDB exposure might have occurred." for the selected jobs. For the 62 Michigan employees, the authors describe personal and area sampling (1950, 1952, 1971-1972) and ranges for each job type. Due to the incomplete surveillance data, only employment length for highest concern job types was used in the analysis. Overall, despite a disparity in levels of detail between the two population types, there is reasonable confidence that all employees were exposed to some level of EDB.
Metric 5:	Exposure Levels	Low	Number of observed and expected cases were calculated both by employment status (exposed/unexposed), and by employment length (three levels) as well as stratifying by interval since first exposure (three levels). Since none of these provide quantitative concentrations of EDB in a form useful for a dose-response assessment, this metric is rated Low.

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.			
Health Outcome(s) Assessed:	Lung/Respiratory			
Reported Health Effect(s):	emphysema mortality, chronic bronchitis mortality, asthma mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306			
Domain	Metric	Rating	Comments	
	Metric 6:	Temporality	Medium	Employees were recruited if they had been employed after 1940 and were followed until 1976. Some individuals were still currently employed which may not allow for enough latency time for the outcome of interest, mortality. The healthy worker effect may also be of concern due to the use of an occupational cohort.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	Former employees were followed using Social Security checks. The evaluation and coding of death certificates was not detailed. ICD codes used to identify relevant mortalities were not provided. The source of US general population mortality rates was not detailed.
	Metric 8:	Reporting Bias	Medium	The number of observed cases and expected cases were provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Low	Only males were included in the study. The authors calculate age-stratified SMRs. Demographic characteristics of the participants was not provided, and only white male mortality data was utilized in the SMR calculation. It is not clear if race would be an applicable stratification factor in this population. Potentially relevant behaviors such as smoking and alcohol use are not discussed.
	Metric 10:	Covariate Characterization	Medium	Collection of potential confounders (sex, age) was not described but presumably based on employment records.
	Metric 11:	Co-exposure Counfounding	Low	Other co-exposures were described and included lead, bromine, ethylene, hydrogen, iodine, ammonia, silica, copper, nickel acetate, vinyl bromide, and numerous other chlorinated and/or brominated hydrocarbons. These exposures varied by job type. Five individuals suspected to be exposed to arsenic were evaluated separately. Adjustments or other considerations for co-exposures were not made.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	This study utilized a retrospective occupational cohort of men to evaluate the relationship between chronic EDB exposure and various cause-specific mortalities. No concerns about study design.
	Metric 13:	Statistical Power	Low	The sample size was somewhat small (n=161) with limited number of cases per cause of death and a total of only 35 reported deaths. Stratification by employment length and interval since first exposure may result in very small comparison groups and should be interpreted with caution.
	Metric 14:	Reproducibility of Analyses	Medium	Data was provided on employment length and interval since first exposure by facility. Other descriptions were sufficient to reproduce the main analysis and analyses stratified by employment duration/exposure interval.

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Lung/Respiratory
Reported Health Effect(s):	emphysema mortality, chronic bronchitis mortality, asthma mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	Low	Expected deaths were calculated, however, standardized mortality ratios were not calculated.

Additional Comments: This study utilized a retrospective occupational cohort on 161 men to evaluate the relationship between EDB exposure and cause-specific mortality. Some concerns about this study include lack of information on participation rates, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants and cases. Additionally, there was a lack of information on the study population characteristics, and expected cases were calculated without a measure of variance. Urine bromine was measured, however, this was not used for the analysis and study authors indicate this would be non-specific for EDB exposure.

Overall Quality Determination

Low

Study Citation:	Hoppin, J. A., Umbach, D. M., London, S. J., Henneberger, P. K., Kullman, G. J., Coble, J., Alavanja, M. C., Freeman, Beane, L. E., Sandler, D. P. (2009). Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. European Respiratory Journal 34(6):1296-1303.		
Health Outcome(s) Assessed:	Lung/Respiratory		
Reported Health Effect(s):	Adult-onset asthma		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	5556064		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	High	This paper presented a "cross-sectional analysis of enrollment data from the Agricultural Health Study (AHS)". The AHS is a large prospective cohort study with methodology reviewed by the AHS Executive Committee and extensively described in multiple publications. Selection into the present study was limited to male private pesticide applicators who returned both the AHS enrollment questionnaire and a second postal questionnaire, including complete information on the questions of interest. The questionnaires are available online (www.aghealth.org/questionnaires.html). It is possible that those who returned both questionnaires differed from those who didn't, but substantial differences in the exposure-outcome distributions are unlikely. The authors noted that applicators who did not return the second questionnaire "were similar regarding demographics, farming practices and medical history."
	Metric 2: Attrition	High	The analysis was cross-sectional. All male private pesticide applicators aged greater than or equal to 20 years old "with complete information on smoking, asthma history, age, body mass index (BMI) and HPEEs were included in the present analysis." Additionally, "the analysis was restricted to those exposures with at least five exposed cases." The authors also stated that "given the interest in adult asthma and occupational exposures, individuals diagnosed with asthma before the age of 20 yrs (n = 545) were excluded."
	Metric 3: Comparison Group	Medium	Key elements of the study design are reported in this paper and previous Agricultural Health Study publications. A comparison of demographic, medical, and farming characteristics is presented in Table 1 of the paper. As the authors noted, "males with asthma tended to be older and heavier and slightly more likely to have smoked than those without asthma."
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	Low	Exposure was measured using self-reported questionnaire data provided by participants on pesticides applied. Additionally, participants reported if they ever experienced pesticide poisoning (self-report/doctor diagnosis) or high pesticide exposure events (based on response to the questionnaire question "Have you ever had an incident or experience while using any type of pesticide which caused you unusually high personal exposure?").
	Metric 5: Exposure Levels	Medium	The study included a control group plus two exposure levels defined based on the median of an intensity-adjusted exposure metric.
	Metric 6: Temporality	Low	In this cross-sectional study, the temporality of exposure and outcome is uncertain.

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Study Citation:	Hoppin, J. A., Umbach, D. M., London, S. J., Henneberger, P. K., Kullman, G. J., Coble, J., Alavanja, M. C., Freeman, Beane, L. E., Sandler, D. P. (2009). Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study. European Respiratory Journal 34(6):1296-1303.			
Health Outcome(s) Assessed:	Lung/Respiratory			
Reported Health Effect(s):	Adult-onset asthma			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5556064			
Domain	Metric	Rating	Comments	
Domain 3: Outcome Assessment				
Metric 7:	Outcome Measurement or Characterization	Medium	The outcome was defined based on self-report of doctor-diagnosed asthma after the age of 19 yrs old, and was further sub-divided based on allergic status defined by self-reported doctor diagnosed eczema or hay fever.	
Metric 8:	Reporting Bias	High	All relevant data were reported in sufficient detail.	
Domain 4: Potential Confounding / Variability Control				
Metric 9:	Covariate Adjustment	High	Appropriate considerations were made for potential confounders, including adjusting for covariates.	
Metric 10:	Covariate Characterization	High	Potential confounders were assessed using Agricultural Health Study questionnaires.	
Metric 11:	Co-exposure Counfounding	Medium	Correlations among pesticide exposures were assessed.	
Domain 5: Analysis				
Metric 12:	Study Design and Methods	High	The cross-sectional study design and polytomous logistic regression were appropriate for assessing the research question.	
Metric 13:	Statistical Power	Medium	There were 127 cases of allergic asthma, 314 cases of non-allergic asthma, and 19263 controls in the study. In the analyses for ethylene dibromide, there were 10 cases of allergic asthma, 16 cases of non-allergic asthma, and 818 controls.	
Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand what was done. The analysis is conceptually reproducible with access to the analytic data.	
Metric 15:	Statistical Analysis	High	The regression modeling was transparent. The paper includes details on how and why variables were included in the models.	
Additional Comments:	This cross-sectional study assessed the association between occupational exposures to pesticides in male farmers and the occurrence of adult-onset asthma, defined as self-reported doctor-diagnosed asthma after the age of 19 years. The study was generally well-conducted, but the cross-sectional design precludes determination of causality. Another limitation is that exposure was based on self-reported data rather than direct measurements.			

Overall Quality Determination

Medium

Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.		
Health Outcome(s) Assessed:	Lung/Respiratory		
Reported Health Effect(s):	nonmalignant respiratory diseases		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62587		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cohort was identified using several record sources. Females were excluded. All males who worked at the plant for at least one day from 1952 - 1977 were included. Computer tapes identified employees from 1960-1976 but other record sources were used for 1952-1959 and 1977, so there might have been some inconsistency in selection into the study. There is no information provided on the accuracy of the sources, but it is considered likely that identifying the subjects who worked in the plant would not omit subjects based on exposure or outcome.
Metric 2:	Attrition	High	There was only 1% loss to follow-up.
Metric 3:	Comparison Group	Medium	Standardized mortality ratios (SMRs) were calculated using race-specific person years at risk for 5-year categories of age with the expected numbers for males in the United States, stratified by race, 5-year age group, and 5-year calendar time period. Mortality for workers was compared to mortality for the general population so there is the potential for healthy worker effect.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	The study does not include assessment of industrial hygiene sampling for EDB, nor any personal monitoring for EDB, nor use of biomarkers for EDB, nor use of job matrices that would indicate EDB exposure, nor any other way to distinguish exposure to EDB from exposures to the other chemicals at the plant including tetraethyl lead (TEL), etc. The only measurements of exposure are work at the plant (SMRs: cause-specific mortality rates for males who worked at the plant vs cause-specific mortality rates of males in the U.S.) and duration of exposure measured by length of exposure. These are not adequate measures to quantify exposure specific to EDB.
Metric 5:	Exposure Levels	Low	Exposed workers were compared to the general population, so there were only two levels of exposure.
Metric 6:	Temporality	Medium	Since mortality is the endpoint, exposure would have to precede the outcome. It is unclear whether the exposures fall within the relevant exposure window.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Vital status was determined using company records, Social Security, IRS, and the Texas Bureau of Safety and Vital Statistics. The cause of death was coded by a nosologist using the ICD codes in effect at the time of death.
Metric 8:	Reporting Bias	High	SMRs were appropriately reported.
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Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.
Health Outcome(s) Assessed:	Lung/Respiratory
Reported Health Effect(s):	nonmalignant respiratory diseases
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62587

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	SMRs were adjusted for race, age, and sex.
	Metric 10: Covariate Characterization	Low	Information was obtained from work records. Study subjects "whose race was white or unknown, and individuals with Hispanic surnames, were classified as white." All others were classified as non-white. Thus, there was potential misclassification of race. Only a small proportion of the workers were female. Females "were excluded from the study because historically they held nonproduction positions."
	Metric 11: Co-exposure Counfounding	Low	In addition to EDB, exposure was noted to include tetraethyl lead, ethylene dichloride, inorganic lead, and vinyl chloride monomer. It was noted that work histories lacked sufficient data to identify specific jobs in processing and manufacturing areas. Therefore, results cannot be separated by chemical nor can it be known if there was exposure to more than one of these chemicals for any specific job.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The analyses were appropriate and well described.
	Metric 13: Statistical Power	Medium	There were 2493 subjects included with 156 deaths.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was appropriate.
	Metric 15: Statistical Analysis	High	The method for calculating Standardized Mortality Ratios (SMR) is transparent.
Additional Comments:	The main limitations of this study are the lack of EDB-specific quantitative exposure data, the inability to separate out the exposure of interest from other co-exposures, and the potential for healthy worker effect.		

Overall Quality Determination

Medium

Study Citation:	Beard, J. D., Umbach, D. M., Hoppin, J. A., Richards, M., Alavanja, M. C., Blair, A., Sandler, D. P., Kamel, F. (2014). Pesticide exposure and depression among male private pesticide applicators in the agricultural health study. Environmental Health Perspectives 122(9):984-991..			
Health Outcome(s) Assessed:	Neurological/Behavioral			
Reported Health Effect(s):	Depression			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5554770			
Domain	Metric	Rating	Comments	
Domain 1: Study Participation				
	Metric 1:	Participant Selection	Medium	Those who did not complete the follow-up phone interview for other reasons (20,640) may have been more depressed, leading to selection of a healthier population. Limited evidence (Montgomery et al., 2010) suggests dropout was random.
	Metric 2:	Attrition	Medium	Relatively high loss to follow up (>50%), mostly due to death or unexplained refusal, but exclusions are documented in Figure 1 and the text.
	Metric 3:	Comparison Group	Medium	Authors did not address differences between exposure groups but conducted several analyses to identify potential confounders.
Domain 2: Exposure Characterization				
	Metric 4:	Measurement of Exposure	Medium	History of pesticide use was self-reported on a retrospective questionnaire and may have been subject to recall bias.
	Metric 5:	Exposure Levels	Medium	Pesticide users were categorized into tertiles based on cumulative days of use.
	Metric 6:	Temporality	Low	The PRE outcome groups may have been diagnosed with depression prior to the pesticide exposure. The POST group theoretically had a new case in the 12 years after enrollment. The authors suggest reverse causation is unlikely.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	The outcome was based on self-report of a physician diagnosis, and the three data sources (two written questionnaires and phone questionnaire) asked different versions of the question. The authors stated reporting rates were likely lower on the follow-up phone questionnaire (due to social desirability bias), and could not report on prevalence for this reason. Awareness of depression in men, diagnostic criteria, and physician screening practices may have also changed over the decades included in the study. Some participants reported different ever-diagnosed information at different times. However, differential reporting of outcome by exposure status is unlikely.
	Metric 8:	Reporting Bias	High	Sample size, odds ratio, and 95% confidence intervals are shown in results tables.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	High	Minimally sufficient weighting or adjustment was applied for age, diabetes diagnosis (an indicator of chronic disease), education level, and state. Confounder selection methods were explained.
	Metric 10:	Covariate Characterization	High	Validated questionnaires were used to characterize covariates.
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Study Citation:	Beard, J. D., Umbach, D. M., Hoppin, J. A., Richards, M., Alavanja, M. C., Blair, A., Sandler, D. P., Kamel, F. (2014). Pesticide exposure and depression among male private pesticide applicators in the agricultural health study. Environmental Health Perspectives 122(9):984-991..			
Health Outcome(s) Assessed:	Neurological/Behavioral			
Reported Health Effect(s):	Depression			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5554770			
Domain	Metric		Rating	Comments
	Metric 11:	Co-exposure Counfounding	Medium	Exposure to any pesticide, pesticide classes, and individual pesticides were considered in separate analyses.
Domain 5: Analysis	Metric 12:	Study Design and Methods	High	Rather than a repeat sampling design, three case groups were nested within the cohort based on combinations of outcome measurement at two time points. Linear, logistic, or ordinal logistic regression methods were applied, depending on the nature of the exposure variable.
	Metric 13:	Statistical Power	Medium	Some results (e.g., any EDB exposure) had fewer than 30 people in the case groups and fairly wide confidence intervals, although these were still adequate to consistently detect an effect.
	Metric 14:	Reproducibility of Analyses	Medium	Statistical approach was sufficiently explained.
	Metric 15:	Statistical Analysis	High	Data were not transformed, but four criteria were applied to evaluate the appropriateness of weights and multiple assumptions were tested with sensitivity analyses.
Additional Comments:	Although the exposure and outcome were self-reported, the statistical methods aimed to account for these limitations. The noncases were similar to the cases in terms of employment history and other characteristics, and the odds of depression (at baseline or baseline and follow-up) were elevated among those with a history of EDB use.			
Overall Quality Determination			Medium	

Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.		
Health Outcome(s) Assessed:	Neurological/Behavioral		
Reported Health Effect(s):	Mortality due to transportation accidents, falls, other accidents, suicide, and homicide		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	62587		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cohort was identified using several record sources. Females were excluded. All males who worked at the plant for at least one day from 1952 - 1977 were included. Computer tapes identified employees from 1960-1976 but other record sources were used for 1952-1959 and 1977, so there might have been some inconsistency in selection into the study. There is no information provided on the accuracy of the sources, but it is considered likely that identifying the subjects who worked in the plant would not omit subjects based on exposure or outcome.
Metric 2:	Attrition	High	There was only 1% loss to follow-up.
Metric 3:	Comparison Group	Medium	Standardized mortality ratios (SMRs) were calculated using race-specific person years at risk for 5-year categories of age with the expected numbers for males in the United States, stratified by race, 5-year age group, and 5-year calendar time period. Mortality for workers was compared to mortality for the general population so there is the potential for healthy worker effect.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Low	The study does not include assessment of industrial hygiene sampling for EDB, nor any personal monitoring for EDB, nor use of biomarkers for EDB, nor use of job matrices that would indicate EDB exposure, nor any other way to distinguish exposure to EDB from exposures to the other chemicals at the plant including tetraethyl lead (TEL), etc. The only measurements of exposure are work at the plant (SMRs: cause-specific mortality rates for males who worked at the plant vs cause-specific mortality rates of males in the U.S.) and duration of exposure measured by length of exposure. These are not adequate measures to quantify exposure specific to EDB.
Metric 5:	Exposure Levels	Low	Exposed workers were compared to the general population, so there were only two levels of exposure.
Metric 6:	Temporality	Medium	Since mortality is the endpoint, exposure would have to precede the outcome. It is unclear whether the exposures fall within the relevant exposure window.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Vital status was determined using company records, Social Security, IRS, and the Texas Bureau of Safety and Vital Statistics. The cause of death was coded by a nosologist using the ICD codes in effect at the time of death.
Metric 8:	Reporting Bias	High	SMRs were appropriately reported.
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Study Citation:	Sweeney, M. H., Beaumont, J. J., Waxweiler, R. J., Halperin, W. E. (1986). An investigation of mortality from cancer and other causes of death among workers employed at an east Texas chemical plant. Archives of Environmental Health 41(1):23-28.
Health Outcome(s) Assessed:	Neurological/Behavioral
Reported Health Effect(s):	Mortality due to transportation accidents, falls, other accidents, suicide, and homicide
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	62587

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	SMRs were adjusted for race, age, and sex.
	Metric 10: Covariate Characterization	Low	Information was obtained from work records. Study subjects "whose race was white or unknown, and individuals with Hispanic surnames, were classified as white." All others were classified as non-white. Thus, there was potential misclassification of race. Only a small proportion of the workers were female. Females "were excluded from the study because historically they held nonproduction positions."
	Metric 11: Co-exposure Counfounding	Low	In addition to EDB, exposure was noted to include tetraethyl lead, ethylene dichloride, inorganic lead, and vinyl chloride monomer. It was noted that work histories lacked sufficient data to identify specific jobs in processing and manufacturing areas. Therefore, results cannot be separated by chemical nor can it be known if there was exposure to more than one of these chemicals for any specific job.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The analyses were appropriate and well described.
	Metric 13: Statistical Power	Medium	There were 2493 subjects included with 156 deaths.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was appropriate.
	Metric 15: Statistical Analysis	High	The method for calculating Standardized Mortality Ratios (SMR) is transparent.
Additional Comments:	The main limitations of this study are the lack of EDB-specific quantitative exposure data, the inability to separate out the exposure of interest from other co-exposures, and the potential for healthy worker effect.		

Overall Quality Determination**Medium**

Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Immune/Hematological
Reported Health Effect(s):	influenza mortality, pneumonia mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	In this retrospective occupational cohort study, employees were identified from two facilities (Michigan and Texas). Each facility was described in detail. Job descriptions of those included in the study were provided. The study authors indicate they selected all employees from four specific job types that were likely to have had contact with EDB. Some details regarding the participation rate are unclear, however, there was no direct evidence to suggest selection bias. A total number of 261 subjects were reported.
Metric 2:	Attrition	Medium	Only one individual was reported to be untraced and three individuals did not have obtainable death certificates. Some employees were excluded from the analysis due to leaving the company prior to 1940, citing traceability issues. The number of participants excluded for this reason is unclear.
Metric 3:	Comparison Group	Low	Employees were compared to the US general population of white males, calculated in five year age groups. While all employees were reported to be male, other demographic characteristics such as race were not discussed, resulting in minor uncertainty about whether the reference group is wholly appropriate.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was determined by employment at one of the two facilities. The study authors note that detailed employment records exist for the two facilities, and that there was periodic environmental surveillance data for the 62 Michigan employees. The 99 Texas employees did not have routine environmental surveillance data, but job process documentation implies "significant EDB exposure might have occurred." for the selected jobs. For the 62 Michigan employees, the authors describe personal and area sampling (1950, 1952, 1971-1972) and ranges for each job type. Due to the incomplete surveillance data, only employment length for highest concern job types was used in the analysis. Overall, despite a disparity in levels of detail between the two population types, there is reasonable confidence that all employees were exposed to some level of EDB.
Metric 5:	Exposure Levels	Low	Number of observed and expected cases were calculated both by employment status (exposed/unexposed), and by employment length (three levels) as well as stratifying by interval since first exposure (three levels). Since none of these provide quantitative concentrations of EDB in a form useful for a dose-response assessment, this metric is rated Low.

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.			
Health Outcome(s) Assessed:	Immune/Hematological			
Reported Health Effect(s):	influenza mortality, pneumonia mortality			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306			
Domain	Metric	Rating	Comments	
	Metric 6:	Temporality	Medium	Employees were recruited if they had been employed after 1940 and were followed until 1976. Some individuals were still currently employed which may not allow for enough latency time for the outcome of interest, mortality. The healthy worker effect may also be of concern due to the use of an occupational cohort.
Domain 3: Outcome Assessment				
	Metric 7:	Outcome Measurement or Characterization	Low	Former employees were followed using Social Security checks. The evaluation and coding of death certificates was not detailed. ICD codes used to identify relevant mortalities were not provided. The source of US general population mortality rates was not detailed.
	Metric 8:	Reporting Bias	Medium	The number of observed cases and expected cases were provided.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	Low	Only males were included in the study. The authors calculate age-stratified SMRs. Demographic characteristics of the participants was not provided, and only white male mortality data was utilized in the SMR calculation. It is not clear if race would be an applicable stratification factor in this population. Potentially relevant behaviors such as smoking and alcohol use are not discussed.
	Metric 10:	Covariate Characterization	Medium	Collection of potential confounders (sex, age) was not described but presumably based on employment records.
	Metric 11:	Co-exposure Counfounding	Low	Other co-exposures were described and included lead, bromine, ethylene, hydrogen, iodine, ammonia, silica, copper, nickel acetate, vinyl bromide, and numerous other chlorinated and/or brominated hydrocarbons. These exposures varied by job type. Five individuals suspected to be exposed to arsenic were evaluated separately. Adjustments or other considerations for co-exposures were not made.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	This study utilized a retrospective occupational cohort of men to evaluate the relationship between chronic EDB exposure and various cause-specific mortalities. No concerns about study design.
	Metric 13:	Statistical Power	Low	The sample size was somewhat small (n=161) with limited number of cases per cause of death and a total of only 35 reported deaths. Stratification by employment length and interval since first exposure may result in very small comparison groups and should be interpreted with caution.
	Metric 14:	Reproducibility of Analyses	Medium	Data was provided on employment length and interval since first exposure by facility. Other descriptions were sufficient to reproduce the main analysis and analyses stratified by employment duration/exposure interval.

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Study Citation:	Dow Chemical, (1992). Initial submission: The mortality experience of 161 employees exposed to ethylene dibromide in two production units with cover letter dated 060492.
Health Outcome(s) Assessed:	Immune/Hematological
Reported Health Effect(s):	influenza mortality, pneumonia mortality
Chemical:	Ethylene Dibromide- Parent compound
HERO ID:	5591185 Linked HERO ID(s): 5591185, 5494306

Domain	Metric	Rating	Comments
	Metric 15: Statistical Analysis	Low	Expected deaths were calculated, however, standardized mortality ratios were not calculated.

Additional Comments: This study utilized a retrospective occupational cohort on 161 men to evaluate the relationship between EDB exposure and cause-specific mortality. Some concerns about this study include lack of information on participation rates, lack of information on how death certificates were retrieved and coded, and a relatively small number of participants and cases. Additionally, there was a lack of information on the study population characteristics, and expected cases were calculated without a measure of variance. Urine bromine was measured, however, this was not used for the analysis and study authors indicate this would be non-specific for EDB exposure.

Overall Quality Determination

Low

Study Citation:	Lebailly, P., Vigreux, C., Lechevrel, C., Ledemeney, D., Godard, T., Sichel, F., Letalaer, J. Y., Henry-Amar, M., Gauduchon, P. (1998). DNA damage in mononuclear leukocytes of farmers measured using the alkaline comet assay: Discussion of critical parameters and evaluation of seasonal variations in relation to pesticide exposure. Cancer Epidemiology Biomarkers and Prevention 7(10):917-927.		
Health Outcome(s) Assessed:	Immune/Hematological		
Reported Health Effect(s):	leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cells, platelets		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	5621630		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Low	In this cross-sectional study, participants were drawn from farmers exposed to pesticides while spraying fields, however, the method of identification and recruitment was not entirely clear. Details on participation rates were not provided. This study utilized farmers which may introduce healthy worker bias effect and result in lower incidences of negative health outcomes. The study reports that "55 farmers, all men, were prospectively enrolled in four groups" between 1995-1996.
Metric 2:	Attrition	Low	The study reports that 55 farmers were initially enrolled, but blood samples were only obtained for 29 farmers, which were used to determine outcome status. There is no explanation provided for why samples were unable to be collected for the remaining 26 farmers, which comprises nearly half of the original sample.
Metric 3:	Comparison Group	Medium	Demographic descriptions of the farmers were provided and important characteristics (age, alcohol, smoking, and prescription meds) were considered during statistical analyses. While farmers were recruited in different batches, which may indicate differences in seasonality, but there is no specific evidence of inappropriate comparisons.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Uninformative	Exposure was evaluated by interviews with farmers and expressed as acreage and hours spent spraying pesticides. EDB is mentioned in the introduction as one potential pesticide among several, and the study authors do not indicate which pesticides were commonly applied by these farmers. Farmers did not inventory which specific pesticides were used. This could result in serious misclassification.
Metric 5:	Exposure Levels	Uninformative	Exposure is measured in terms of acreage and time spent spraying, however, EDB was not the only pesticide in use and the information provided is inadequate to determine differences in EDB exposure.
Metric 6:	Temporality	Medium	Temporality is established by inventorying the number of days without pesticide use before collecting blood samples. Blood samples for immunotoxicity endpoints were collected at the beginning of the spraying season, at an intermediate period, and at the end of spraying season.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Methods to collect blood were described and appeared to be conducted consistently. Hematological parameters were evaluated using an automated counter (Coultronix), and normal values for the various parameters were provided.

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Study Citation:	Lebailly, P., Vigreux, C., Lechevrel, C., Ledemeney, D., Godard, T., Sichel, F., Letalaer, J. Y., Henry-Amar, M., Gauduchon, P. (1998). DNA damage in mononuclear leukocytes of farmers measured using the alkaline comet assay: Discussion of critical parameters and evaluation of seasonal variations in relation to pesticide exposure. Cancer Epidemiology Biomarkers and Prevention 7(10):917-927.			
Health Outcome(s) Assessed:	Immune/Hematological			
Reported Health Effect(s):	leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cells, platelets			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5621630			
Domain		Metric	Rating	Comments
	Metric 8:	Reporting Bias	High	Individual data for famers’ exposure was provided. Data on hematological endpoints was provided with means and standard errors. All outcomes discussed in the abstract, introduction, and methods was provided in the results.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	High	All important confounders (age, alcohol, smoking, and prescription meds) were considered in the statistical analysis. The study only included men.
	Metric 10:	Covariate Characterization	Medium	Covariates were collected by face-to-face questionnaire. This was not reported to be structured or validated, but there are no specific concerns.
	Metric 11:	Co-exposure Counfounding	Low	Other specific pesticides were cited as being potentially used and implicated in the relevant outcome, including 2,4-dichlorophenoxyacetic acid and malathion, and farmers did not inventory specific chemicals applied to fields. Some farmers may have had apprecia- bly different mixtures of pesticides with varying proportions of EDB.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	This study evaluates changes in hematological parameters across spraying seasons in a cross-sectional group of farmers, which is an appropriate design to assess the relation- ship between pesticide exposure and hematology parameters.
	Metric 13:	Statistical Power	Low	The study population was relatively small with some groups containing less than 10 individuals, with a final total of only 29 participants. This may impact the ability to detect an effect.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis was sufficient that it could be repeated if given original data.
	Metric 15:	Statistical Analysis	High	The study authors state that ”scores” were normally distributed, meeting model assump- tions. ANOVA was used to assess differences in hematological parameters between exposure groups. The method for accounting for participants with multiple blood sam- ples was to do a second round of ANOVA, where only sample per farmer was selected, with preference to the most recent sample.
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16:	Use of Biomarker of Exposure	N/A	N/A, no biomarkers of exposure were measured.
	Metric 17:	Effect Biomarker	High	The hematological parameters are typically reliable metrics for hematological injury. Study authors cite evidence of increased lymphatic and hematopoietic system cancers in agricultural populations linked to pesticide exposure. Specific evidence of a relationship between lymphatic or hematopoietic system injury for EDB was not provided.

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Study Citation:	Lebailly, P., Vigreux, C., Lechevrel, C., Ledemeney, D., Godard, T., Sichel, F., Letalaer, J. Y., Henry-Amar, M., Gauduchon, P. (1998). DNA damage in mononuclear leukocytes of farmers measured using the alkaline comet assay: Discussion of critical parameters and evaluation of seasonal variations in relation to pesticide exposure. Cancer Epidemiology Biomarkers and Prevention 7(10):917-927.			
Health Outcome(s) Assessed:	Immune/Hematological			
Reported Health Effect(s):	leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cells, platelets			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	5621630			
Domain	Metric		Rating	Comments
	Metric 18:	Method Sensitivity	Medium	There was no indication that hematological and immune cells were not detected in study participants.
	Metric 19:	Biomarker Stability	Low	Sample storage history between collection and hematological analysis was not described. Cells were later stored at -80 degrees C for the genotoxicity analysis.
	Metric 20:	Sample Contamination	Medium	Samples were collected in EDTA-treated tubes. No other information was provided.
	Metric 21:	Method Requirements	Medium	Hematological and immune cell counts were performed using an automated S+ counter (Coultronix).
	Metric 22:	Matrix Adjustment	N/A	N/A, matrix adjustment was not relevant for these biomarkers.
Additional Comments:	This study utilized a cross-sectional group of farmers in France during different periods of the growing season to evaluate hematological effects of spraying pesticides. There were a few major deficiencies in the study design with regard to specificity to EDB. Exposure was measured by quantifying spraying activity and chemical inventories of the sprayed chemicals was not provided which may result in serious exposure misclassification. This study contains mechanistic data (genotoxicity).			

Overall Quality Determination

Uninformative

Study Citation:	Wang, Z., Chen, D., Peng, L., Wang, X., Ding, Q., Li, L., Xu, T. (2024). Exposure to volatile organic compounds is a risk factor for diabetes retinopathy: A cross-sectional study. <i>Frontiers in Public Health</i> 12:1347671.			
Health Outcome(s) Assessed:	Nutrition & Metabolic			
Reported Health Effect(s):	diabetes, diabetes retinopathy			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	12791626			
Domain	Metric	Rating	Comments	
Domain 1: Study Participation				
Metric 1:	Participant Selection	Medium	This cross-sectional analysis of NHANES 2011-2018 data examines the associations between ethylene dibromide concentrations in whole blood and diabetes and diabetes retinopathy. Recruitment details, participation rates at each step, and reasons for exclusions are reported. NHANES uses a sampling approach that results in a demographically representative study population. Additionally, the study uses propensity score matching (PSM) to match cases of diabetes and non-diabetic subjects based on age and gender only. No more detail is provided as to whether PSM was utilized on other covariates.	
Metric 2:	Attrition	Medium	Initially, of 39,156 eligible participants, 2,213 refused to participate, did not know or had missing outcome data, and 17,547 had missing exposure data. There is no evidence that missing data was related to outcome status or exposure level.	
Metric 3:	Comparison Group	Low	Body mass index (BMI) and race varied statistically significant across groups, and statistical analysis (logistic regression) appear to be univariate only.	
Domain 2: Exposure Characterization				
Metric 4:	Measurement of Exposure	Uninformative	The measurement of mVOCs in human whole blood wascarried out by capillary gas chromatography and massspectrometry with selected-ion monitoring detection and isotope dilution.	
Metric 5:	Exposure Levels	Uninformative	The differences in reported ethylene dibromide levels between groups were due to differences in rounding in the NHANES dataset.	
Metric 6:	Temporality	Low	This study uses cross-sectional design approach, so exposure and outcome data were collected at the same time. Specific timing of other temporal information was not reported in this study.	
Domain 3: Outcome Assessment				
Metric 7:	Outcome Measurement or Characterization	High	An specific questionnaire within the NHANES survey was utilized to to assess whether participants have the outcomes of interest.	
Metric 8:	Reporting Bias	Low	Both diabetes and diabetes retinopathy results are reported as odds ratio and 95% confidence intervals (CIs). However, reported outcomes were not based on direct measures. Results from the weighted quantile sum and Bayesian kernel machine regression model were reported. While some results were presented not all were reported in a table or graphic format.	
Domain 4: Potential Confounding / Variability Control				
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Study Citation:	Wang, Z., Chen, D., Peng, L., Wang, X., Ding, Q., Li, L., Xu, T. (2024). Exposure to volatile organic compounds is a risk factor for diabetes retinopathy: A cross-sectional study. <i>Frontiers in Public Health</i> 12:1347671.			
Health Outcome(s) Assessed:	Nutrition & Metabolic			
Reported Health Effect(s):	diabetes, diabetes retinopathy			
Chemical:	Ethylene Dibromide- Parent compound			
HERO ID:	12791626			
Domain	Metric	Rating	Comments	
	Metric 9: Covariate Adjustment	Low	This study used propensity score matching to select subjects based on age and sex; however, it appears that in their logistic regression models, the study authors did not further adjust for other potential confounders, including BMI and race/ethnicity. When utilizing weighted quantile sum and Bayesian kernel machine regression model, the authors adjusted for age, sex, BMI, education levels and race/ethnicity.	
	Metric 10: Covariate Characterization	High	Age, sex, race/ethnicity and education levels were obtained from the demographic data, BMI was collected from examination data.	
	Metric 11: Co-exposure Counfounding	Medium	It appears that there is no evidence of present and unaddressed co-exposures.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	Low	The study design (cross-sectional) was appropriate for the research question. However, the causal relationship between exposure to ethylene dibromide and the risk of diabetes can not be verified.	
	Metric 13: Statistical Power	Low	The number of participants (n=2,932; diabetes n=1,479 and non-diabetes n=1,453) are adequate to detect an effect. However, there is insufficient information about number of participants used in final regression models.	
	Metric 14: Reproducibility of Analyses	Medium	The analytical approaches utilized in the study were adequately explained. For example, it used propensity score matching, logistic regression and weighted quantile sum to assess the associations between mVOCs (individually or combined) and diabetes and diabetes retinopathy.	
	Metric 15: Statistical Analysis	Low	Propensity score matching to match on age and sex were used to create more comparable groups. Odds ratios and 95% CIs are reported as effect estimate evaluating the associations between individual mVOCs exposure and diabetes and diabetes retinopathy. Also, odds ratios and 95% CIs are reported as effect estimate evaluating the associations between combined mVOCs exposure and diabetes and diabetes retinopathy. Furthermore, exposure-response functions between mVOCs and diabetes mellitus and diabetes retinopathy. However, the final logistic models did not further adjust for potential confounders.	
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16: Use of Biomarker of Exposure	High	Ethylene dibromide was directly measured in whole blood.	
	Metric 17: Effect Biomarker	N/A	No biomarkers of effect were measured or assessed in this study.	
	Metric 18: Method Sensitivity	Medium	LOD and % <LOD not reported in this study, but NHANES laboratory procedures are publicly available.	
	Metric 19: Biomarker Stability	Low	Storage and stability details were not reported in this study, but were probably appropriate.	
	Metric 20: Sample Contamination	Medium	No evidence of contamination was reported.	

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Study Citation:	Wang, Z., Chen, D., Peng, L., Wang, X., Ding, Q., Li, L., Xu, T. (2024). Exposure to volatile organic compounds is a risk factor for diabetes retinopathy: A cross-sectional study. Frontiers in Public Health 12:1347671.		
Health Outcome(s) Assessed:	Nutrition & Metabolic		
Reported Health Effect(s):	diabetes, diabetes retinopathy		
Chemical:	Ethylene Dibromide- Parent compound		
HERO ID:	12791626		

Domain	Metric		Rating	Comments
	Metric 21:	Method Requirements	Medium	Capillary gas chromatography and mass spectrometry with selected-ion monitoring detection and isotope dilution were used.
	Metric 22:	Matrix Adjustment	Low	While no direct information regarding matrix adjustment is discussed, the study authors refer to exploring "detailed methods and information of mVOCs could be found on the web of NHANES" for more information.

Additional Comments: Study is based on NHANES data, so exposure and outcome measurement methods are likely reliable and valid, though some specific details were not reported in this publication and metrics were scored without referencing NHANES documentation or prior publications. The statistical analyses were appropriate, though the regression was not sophisticated in that it did not adjust for covariates. Age and sex were considered through matching. This study has several limitations including using imputed estimates from NHANES, which were the same for all of the individuals in each group.

Overall Quality Determination **Uninformative**

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Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cross-sectional analysis of NHANES 2011-2018 data examines the associations between ethylene dibromide concentrations in whole blood and diabetes and diabetes retinopathy. Recruitment details, participation rates at each step, and reasons for exclusions are reported. NHANES uses a sampling approach that results in a demographically representative study population. Additionally, the study uses propensity score matching (PSM) to match cases of diabetes and non-diabetic subjects based on age and gender only. No more detail is provided as to whether PSM was utilized on other covariates. Initially, of 39,156 eligible participants, 2,213 refused to participate, did not know or had missing outcome data, and 17,547 had missing exposure data. There is no evidence that missing data was related to outcome status or exposure level. Body mass index (BMI) and race varied statistically significant across groups, and statistical analysis (logistic regression) appear to be univariate only.
Metric 2:	Attrition	Medium	
Metric 3:	Comparison Group	Low	
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Uninformative	The measurement of mVOCs in human whole blood wascarried out by capillary gas chromatography and massspectrometry with selected-ion monitoring detection and isotope dilution.
Metric 5:	Exposure Levels	Uninformative	The differences in reported ethylene dibromide levels between groups were due to differences in rounding in the NHANES dataset.
Metric 6:	Temporality	Low	This study uses cross-sectional design approach, so exposure and outcome data were collected at the same time. Specific timing of other temporal information was not reported in this study.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	An specific questionnaire within the NHANES survey was utilized to to assess whether participants have the outcomes of interest.
Metric 8:	Reporting Bias	Low	Both diabetes and diabetes retinopathy results are reported as odds ratio and 95% confidence intervals (CIs). However, reported outcomes were not based on direct measures. Results from the weighted quantile sum and Bayesian kernel machine regression model were reported. While some results were presented not all were reported in a table or graphic format.
Domain 4: Potential Confounding / Variability Control			
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HERO ID:	12791626			
Domain	Metric	Rating	Comments	
	Metric 9:	Covariate Adjustment	Low	This study used propensity score matching to select subjects based on age and sex; however, it appears that in their logistic regression models, the study authors did not further adjust for other potential confounders, including BMI and race/ethnicity. When utilizing weighted quantile sum and Bayesian kernel machine regression model, the authors adjusted for age, sex, BMI, education levels and race/ethnicity.
	Metric 10:	Covariate Characterization	High	Age, sex, race/ethnicity and education levels were obtained from the demographic data, BMI was collected from examination data.
	Metric 11:	Co-exposure Counfounding	Medium	It appears that there is no evidence of present and unaddressed co-exposures.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	Low	The study design (cross-sectional) was appropriate for the research question. However, the causal relationship between exposure to ethylene dibromide and the risk of diabetes can not be verified.
	Metric 13:	Statistical Power	Low	The number of participants (n=2,932; diabetes n=1,479 and non-diabetes n=1,453) are adequate to detect an effect. However, there is insufficient information about number of participants used in final regression models.
	Metric 14:	Reproducibility of Analyses	Medium	The analytical approaches utilized in the study were adequately explained. For example, it used propensity score matching, logistic regression and weighted quantile sum to assess the associations between mVOCs (individually or combined) and diabetes and diabetes retinopathy.
	Metric 15:	Statistical Analysis	Low	Propensity score matching to match on age and sex were used to create more comparable groups. Odds ratios and 95% CIs are reported as effect estimate evaluating the associations between individual mVOCs exposure and diabetes and diabetes retinopathy. Also, odds ratios and 95% CIs are reported as effect estimate evaluating the associations between combined mVOCs exposure and diabetes and diabetes retinopathy. Furthermore, exposure-response functions between mVOCs and diabetes mellitus and diabetes retinopathy. However, the final logistic models did not further adjust for potential confounders.
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16:	Use of Biomarker of Exposure	High	Ethylene dibromide was directly measured in whole blood.
	Metric 17:	Effect Biomarker	N/A	No biomarkers of effect were measured or assessed in this study.
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Overall Quality Determination	Uninformative
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