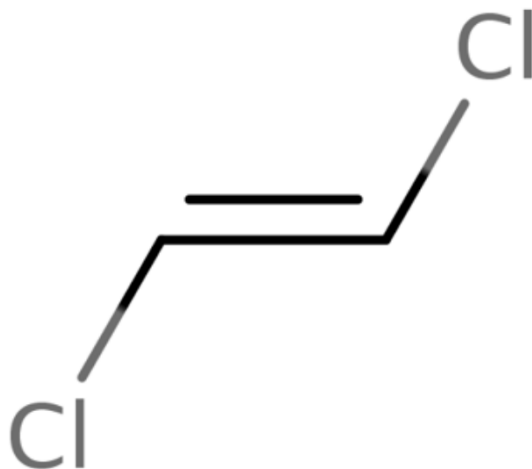

**Draft Data Quality Evaluation Information for
Human Health Hazard Epidemiology for
trans-1,2-Dichloroethylene**

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 156-60-5



June 2026

This supplemental file contains the data quality evaluation results for data sources that met the PECO screening criteria for the *Draft Risk Evaluation for trans-1,2-Dichloroethylene* and were used to characterize human health hazard in the *Draft Human Health and Environmental Hazard Assessment for trans-1,2-Dichloroethylene*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (e.g., statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol will be described in the *Draft Systematic Review Protocol for trans-1,2-Dichloroethylene*, to be released with the risk evaluation.

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HERO ID	Reference	Page
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Observational Epidemiology Studies

trans-1,2-Dichloroethylene

Cancer/Carcinogenesis

3489298	Ruckart, P. Z., Bove, F. J., Shanley, E., III, Maslia, M. (2015). Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: A case-control study. Environmental Health 14(1):74.	5
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Isomer: 1,2-Dichloroethylene

Cancer/Carcinogenesis

194820	Kernan, G. J., Ji, B. T., Dosemeci, M., Silverman, D. T., Balbus, J., Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. American Journal of Industrial Medicine 36(2):260-270.	7
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1069372	Young, T. B., Kanarek, M. S., Wolf, D. A., Wilson, D. A. (1990). Case-control study of colon cancer and volatile organics in Wisconsin municipal ground water supplies. :373-386.	9
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Endocrine

194820	Kernan, G. J., Ji, B. T., Dosemeci, M., Silverman, D. T., Balbus, J., Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. American Journal of Industrial Medicine 36(2):260-270.	11
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Gastrointestinal

1069372	Young, T. B., Kanarek, M. S., Wolf, D. A., Wilson, D. A. (1990). Case-control study of colon cancer and volatile organics in Wisconsin municipal ground water supplies. :373-386.	13
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Reproductive/Developmental

2799700	Brender, J. D., Shinde, M. U., Zhan, F. B., Gong, X., Langlois, P. H. (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environmental Health 13(1):96.	15
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Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)

Reproductive/Developmental

200239	Bove, F. J. (1996). Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicology and Industrial Health 12(2):255-266.	17
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194932	Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. American Journal of Epidemiology 141(9):850-862.	21
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Intentional Dosing Studies

trans-1,2-Dichloroethylene

trans-1,2-Dichloroethylene

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Neurological/Behavioral		
29046	Lehmann, K. B., Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116:131-268.	25
Ocular & Sensory		
29046	Lehmann, K. B., Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116:131-268.	27
Gastrointestinal		
29046	Lehmann, K. B., Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116:131-268.	29

Study Citation:	Ruckart, P. Z., Bove, F. J., Shanley, E., III, Maslia, M. (2015). Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: A case-control study. Environmental Health 14(1):74.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	male breast cancer		
Chemical:	trans-1,2-Dichloroethylene- Parent compound		
HERO ID:	3489298		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	The Department of Veteran's Affairs Central Cancer Registry was used to select cases and controls. Setting, eligibility criteria, reasons for exclusion, and number of participants at each stage were reported.
Metric 2:	Attrition	Medium	71/78 eligible cases and 373/400 eligible controls were included in the final analysis, so it is considered moderate loss. Exclusions were adequately described and analyzed.
Metric 3:	Comparison Group	Medium	Cases and controls were selected from the same pool of eligible participants. There were 5 controls for each case, and eligibility/inclusion criteria were described. Participant characteristics were compared in Table 1. Table 2 provides a comparison of characteristics of non-participating cases and controls. However, race was matched between cases and controls. In Table 1, the distribution of race in cases (92.7% is White) was different from that in controls (78.6% is White).
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Water modeling results, information from NPRC, housing records, and barrack location were used to establish exposure levels for each case and control.
Metric 5:	Exposure Levels	Medium	The range and distribution of exposure is adequate to develop exposure-response estimates and 3 levels of exposure were reported.
Metric 6:	Temporality	Medium	Seventy-one cases of male breast cancer were diagnosed with or treated for cancer from January 1, 1995. The exposure period was the earliest start date of a tour at Camp Lejeune and continued until the Marine left Camp Lejeune or December 31, 1985, whichever was earlier. Temporality is unclear for this exposure and outcome.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Male Marines were diagnosed with or treated for cancer at a Veteran's Affairs (VA) medical facility from January 1, 1995 (the start of Veteran's Affairs Central Cancer Registry) to May 5, 2013.
Metric 8:	Reporting Bias	High	A description of measured outcomes is reported, effect estimates are reported with a 95% confidence interval, and number of cases/controls and exposed/unexposed is reported for each analysis. Measures were taken to help account for bias.
Domain 4: Potential Confounding / Variability Control			
Metric 9:	Covariate Adjustment	High	All adjusted models included age at diagnosis and race because of their known association with male breast cancer. Thus, covariates were appropriately adjusted for in the analyses.

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Study Citation:	Ruckart, P. Z., Bove, F. J., Shanley, E., III, Maslia, M. (2015). Evaluation of contaminated drinking water and male breast cancer at Marine Corps Base Camp Lejeune, North Carolina: A case-control study. Environmental Health 14(1):74.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	male breast cancer			
Chemical:	trans-1,2-Dichloroethylene- Parent compound			
HERO ID:	3489298			
Domain	Metric	Rating	Comments	
	Metric 10: Covariate Characterization	High	Data were obtained from the National Personnel Record Center and 2 VA health record databases. Potential confounders listed in Table 1 were determined by comparing the unadjusted model for the exposure variable that included only those with complete data on the risk factor with the model adjusted for the risk factor using a 10% change in the estimate rule. Information about potential confounders was included.	
	Metric 11: Co-exposure Counfounding	Medium	Co-exposures to pollutants (other solvents in drinking water) were appropriately measured or either directly or indirectly adjusted for.	
Domain 5: Analysis	Metric 12: Study Design and Methods	High	The study design chosen (cross-sectional) was appropriate for the research question (male breast cancer risk). Exact and conditional logistic regressions were used. The study used two criteria to assess associations: the magnitude of the OR and the exposure-response relationship.	
	Metric 13: Statistical Power	Low	Some case numbers in the low and high exposure groups were very limited (n=1-3), so it is inadequate to detect an effect.	
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data.	
	Metric 15: Statistical Analysis	High	There were no identifiable logistic regression model assumption violations.	
Additional Comments:	A group of 71 marines with male breast cancer (cases) and 373 marines with cancers not known to be related to solvent exposure (controls) were assessed for male breast cancer risk associated with the time they resided at Camp Lejeune, NC, where drinking water was known to be contaminated with solvents, including t-1,2-dichloroethylene, from the 1950s to 1985. No significant increase in the risk of male breast cancer was observed with cumulative exposure to t-1,2-dichloroethylene for the low or high exposure groups, when cases and controls were compared.			

Overall Quality Determination

Medium

Study Citation:	Kernan, G. J., Ji, B. T., Dosemeci, M., Silverman, D. T., Balbus, J., Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. American Journal of Industrial Medicine 36(2):260-270.		
Health Outcome(s) Assessed:	Cancer/Carcinogenesis		
Reported Health Effect(s):	Death from pancreatic cancer		
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene		
HERO ID:	194820		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	The National Cancer Institute, National Institute of Occupational Safety and Health, and the National Center for Health Statistics reviewed death certificates from 24 states to select cases from those that had died from pancreatic cancer and matched controls. Controls with cause of death related to the outcome of interest (i.e. pancreatic diseases) were excluded from the study. All key elements of the study design were reported.
Metric 2:	Attrition	Medium	There was no direct evidence of subject loss or exclusion of subgroups from analyses. The authors provide the total number of cases and controls in the analysis. Case and control data were taken from a registry. It can be assumed that the data are complete for each subject.
Metric 3:	Comparison Group	High	Controls were selected from the same pool of death certificates from 24 states that cases were selected from. Controls with cause of death related to the outcome of interest were eliminated. Differences in baseline characteristics were controlled for via matching, stratification, and adjustment.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was assessed via occupation and industry data on death certificates. A job matrix was further applied to assess the likely levels of exposure. Probability and intensity of exposure were estimated across four levels for each occupation. Only employment captured on the death certificate could be considered, requiring extrapolation for earlier years.
Metric 5:	Exposure Levels	Medium	The study offers 4 levels of estimated probability and intensity of exposure (referent, low, medium, high).
Metric 6:	Temporality	Medium	Exposure was determined by occupational and industry codes on death certificates and indicate that exposure would precede disease, however, the timing and latency period is less clear.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Causes of mortality were determined from death certificates for both cases and controls. Death certificates were drawn from death registries of participating states (n=24). Causes of death were coded using ICD-9 codes, and pancreatic cancer was identified as ICD 157.
Metric 8:	Reporting Bias	Medium	Measured outcomes, effect estimates and confidence intervals are reported. Number of exposed cases is reported for each analysis, however the number of controls (exposed and unexposed) are not reported for analyses.

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Study Citation:	Kernan, G. J., Ji, B. T., Dosemeci, M., Silverman, D. T., Balbus, J., Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. American Journal of Industrial Medicine 36(2):260-270.
Health Outcome(s) Assessed:	Cancer/Carcinogenesis
Reported Health Effect(s):	Death from pancreatic cancer
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene
HERO ID:	194820

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	Medium	Potential confounders were accounted for in the following ways: matching (five year age group, state, race, and gender); adjustment in models (age, marital status, metropolitan, and residential status); and stratification (race and gender). Smoking was not included as a confounder.
	Metric 10: Covariate Characterization	Medium	Data used to assess potential confounders was derived from death certificates, an adequate measure. However, no information about cigarette smoking and other lifestyle factors were available for adjustment in the analysis.
	Metric 11: Co-exposure Counfounding	Medium	The variety of industries considered in the analysis diminishes concerns about co-exposures.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The case-control study design and statistical analysis methods were appropriate to assess the exposures/outcome of interest.
	Metric 13: Statistical Power	Medium	This study had an adequate sample size to detect an effect (n for cases = 63,097; n for controls = 252,386).
	Metric 14: Reproducibility of Analyses	Medium	The description of analysis was sufficient and would be reproducible.
	Metric 15: Statistical Analysis	High	The model to calculate risk estimates was transparent.
Additional Comments:	This case-control study examined the risk of death from pancreatic cancer in different occupational settings. Exposure was solely assessed using occupation/industry at time of death (reported on death certificate) and the application of a job matrix assessing likely levels of exposure for different positions. This means of estimating exposure may not fully represent a participant's exposure history. Additionally, the number of impacted participants (exposed cases) was inadequate to perform quality analyses for some exposure levels.		

Overall Quality Determination

High

Study Citation:	Young, T. B., Kanarek, M. S., Wolf, D. A., Wilson, D. A. (1990). Case-control study of colon cancer and volatile organics in Wisconsin municipal ground water supplies. :373-386.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	Colon cancer			
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene			
HERO ID:	1069372			
Domain	Metric	Rating	Comments	
Domain 1: Study Participation				
Metric 1:	Participant Selection	Medium	The study adequately describes participant recruitment and selection, study setting, and inclusion/exclusion criteria. Potential participants who died during recruitment could not be included in analysis. It is possible that those participants who died during the study period, particularly among cases, had higher exposure to chemicals of interest, which would not have been captured by the analysis.	
Metric 2:	Attrition	High	There was little subject withdrawal. An age stratum (<50) was eliminated from analysis due to a large number of female controls with breast cancer. This adjustment was deemed acceptable.	
Metric 3:	Comparison Group	High	Comparison groups and reasonable controls during analysis were both included in the study. Control groups included both cancer patients (with non-gastrointestinal/urinary cancers) and members of the general population. The use of both types of controls was considered a strength. Analysis considered age, sex, and urbanicity as potential confounders.	
Domain 2: Exposure Characterization				
Metric 4:	Measurement of Exposure	Low	Exposure was estimated via sampling data and modeling. Chemical levels from 1984-1985 were obtained from state sampling data. Information about participant place of residence across four time points (1951, 1961, 1971, and 1981) was used to estimate the exposure based on drinking water source and the previously mentioned state sampling data. VOCs are highly volatile and challenging to accurately sample, as the study discusses. As a result, it is unlikely that data from 1984-1985 accurately represent exposures during different time points.	
Metric 5:	Exposure Levels	Medium	The study reports 3 levels of exposure including the referent group, low exposure (2-10 micrograms/L), and high exposure (>=10 micrograms/L). While the exposure modeling method was not validated by previous measures or other modeling approaches, the likelihood of differential exposure misclassification is low.	
Metric 6:	Temporality	Low	The study examined cancer cases diagnosed in 1982-1983 and constructed exposure estimates for 1951, 1961, 1971, 1981. However, the data used to model historical exposures was collected from 1984-1986, and the modeling method could not be validated by historic sampling measurements.	
Domain 3: Outcome Assessment				
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Study Citation:	Young, T. B., Kanarek, M. S., Wolf, D. A., Wilson, D. A. (1990). Case-control study of colon cancer and volatile organics in Wisconsin municipal ground water supplies. :373-386.			
Health Outcome(s) Assessed:	Cancer/Carcinogenesis			
Reported Health Effect(s):	Colon cancer			
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene			
HERO ID:	1069372			
Domain	Metric	Rating	Comments	
	Metric 7:	Outcome Measurement or Characterization	Medium	Cases were selected based upon physician diagnosis, however the general population controls were selected from motor vehicle license registries. The authors do not explicitly discuss confirmation of the absence of colon cancer in this group. All subjects were followed for the same length of time.
	Metric 8:	Reporting Bias	High	Measured outcomes are reported. Odds ratios are reported with confidence intervals. The authors note the total number of cases and controls used for analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	High	The authors considered age, sex, and urbanicity as potential confounders. These variables were included in the analysis as covariates.
	Metric 10:	Covariate Characterization	High	Potential confounders were assessed via valid and reliable means.
	Metric 11:	Co-exposure Counfounding	Medium	Co-exposure chemicals that would bias the result were not likely to be present.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	Case-control was the appropriate study design chosen to examine chlorinated solvents in drinking water and colon cancer.
	Metric 13:	Statistical Power	Medium	The number of cases (n=347) and controls (639 cancer controls, 611 general population controls) is adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient, including transformation of variables for inclusion in the logistic regression models.
	Metric 15:	Statistical Analysis	High	The model is transparent. The authors reported included variables and a maximum likelihood analysis was conducted.
Additional Comments:	This study employed a case-control design to examine the association between colon cancer and exposure to 1,2-dichloroethylene (an isomer of trans-1,2-Dichloroethylene) and 1,1,1-trichloroethane (an isomer of 1,1,2-Trichloroethane) in Wisconsin municipal groundwater supplies. The study included a robust recruitment of control groups. Exposure modeling and estimates of historical exposure were the primary limitations, however any related misclassification would have been non-differential. Effect sizes were not large, and a dose-response relationship could not be established.			

Overall Quality Determination

Medium

Study Citation:	Kernan, G. J., Ji, B. T., Dosemeci, M., Silverman, D. T., Balbus, J., Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. American Journal of Industrial Medicine 36(2):260-270.		
Health Outcome(s) Assessed:	Endocrine		
Reported Health Effect(s):	Death from pancreatic cancer		
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene		
HERO ID:	194820		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	The National Cancer Institute, National Institute of Occupational Safety and Health, and the National Center for Health Statistics reviewed death certificates from 24 states to select cases from those that had died from pancreatic cancer and matched controls. Controls with cause of death related to the outcome of interest (i.e. pancreatic diseases) were excluded from the study. All key elements of the study design were reported.
Metric 2:	Attrition	Medium	There was no direct evidence of subject loss or exclusion of subgroups from analyses. The authors provide the total number of cases and controls in the analysis. Case and control data were taken from a registry. It can be assumed that the data are complete for each subject.
Metric 3:	Comparison Group	High	Controls were selected from the same pool of death certificates from 24 states that cases were selected from. Controls with cause of death related to the outcome of interest were eliminated. Differences in baseline characteristics were controlled for via matching, stratification, and adjustment.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Exposure was assessed via occupation and industry data on death certificates. A job matrix was further applied to assess the likely levels of exposure. Probability and intensity of exposure were estimated across four levels for each occupation. Only employment captured on the death certificate could be considered, requiring extrapolation for earlier years.
Metric 5:	Exposure Levels	Medium	The study offers 4 levels of estimated probability and intensity of exposure (referent, low, medium, high).
Metric 6:	Temporality	Medium	Exposure was determined by occupational and industry codes on death certificates and indicate that exposure would precede disease, however, the timing and latency period is less clear.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Causes of mortality were determined from death certificates for both cases and controls. Death certificates were drawn from death registries of participating states (n=24). Causes of death were coded using ICD-9 codes, and pancreatic cancer was identified as ICD 157.
Metric 8:	Reporting Bias	Medium	Measured outcomes, effect estimates and confidence intervals are reported. Number of exposed cases is reported for each analysis, however the number of controls (exposed and unexposed) are not reported for analyses.

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Study Citation:	Kernan, G. J., Ji, B. T., Dosemeci, M., Silverman, D. T., Balbus, J., Zahm, S. H. (1999). Occupational risk factors for pancreatic cancer: A case-control study based on death certificates from 24 U.S. states. American Journal of Industrial Medicine 36(2):260-270.
Health Outcome(s) Assessed:	Endocrine
Reported Health Effect(s):	Death from pancreatic cancer
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene
HERO ID:	194820

Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	Medium	Potential confounders were accounted for in the following ways: matching (five year age group, state, race, and gender); adjustment in models (age, marital status, metropolitan, and residential status); and stratification (race and gender). Smoking was not included as a confounder.
	Metric 10: Covariate Characterization	Medium	Data used to assess potential confounders was derived from death certificates, an adequate measure. However, no information about cigarette smoking and other lifestyle factors were available for adjustment in the analysis.
	Metric 11: Co-exposure Counfounding	Medium	The variety of industries considered in the analysis diminishes concerns about co-exposures.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The case-control study design and statistical analysis methods were appropriate to assess the exposures/outcome of interest.
	Metric 13: Statistical Power	Medium	This study had an adequate sample size to detect an effect (n for cases = 63,097; n for controls = 252,386).
	Metric 14: Reproducibility of Analyses	Medium	The description of analysis was sufficient and would be reproducible.
	Metric 15: Statistical Analysis	High	The model to calculate risk estimates was transparent.
Additional Comments:	This case-control study examined the risk of death from pancreatic cancer in different occupational settings. Exposure was solely assessed using occupation/industry at time of death (reported on death certificate) and the application of a job matrix assessing likely levels of exposure for different positions. This means of estimating exposure may not fully represent a participant's exposure history. Additionally, the number of impacted participants (exposed cases) was inadequate to perform quality analyses for some exposure levels.		

Overall Quality Determination

High

Study Citation:	Young, T. B., Kanarek, M. S., Wolf, D. A., Wilson, D. A. (1990). Case-control study of colon cancer and volatile organics in Wisconsin municipal ground water supplies. :373-386.			
Health Outcome(s) Assessed:	Gastrointestinal			
Reported Health Effect(s):	Colon cancer			
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene			
HERO ID:	1069372			
Domain	Metric	Rating	Comments	
Domain 1: Study Participation				
Metric 1:	Participant Selection	Medium	The study adequately describes participant recruitment and selection, study setting, and inclusion/exclusion criteria. Potential participants who died during recruitment could not be included in analysis. It is possible that those participants who died during the study period, particularly among cases, had higher exposure to chemicals of interest, which would not have been captured by the analysis.	
Metric 2:	Attrition	High	There was little subject withdrawal. An age stratum (<50) was eliminated from analysis due to a large number of female controls with breast cancer. This adjustment was deemed acceptable.	
Metric 3:	Comparison Group	High	Comparison groups and reasonable controls during analysis were both included in the study. Control groups included both cancer patients (with non-gastrointestinal/urinary cancers) and members of the general population. The use of both types of controls was considered a strength. Analysis considered age, sex, and urbanicity as potential confounders.	
Domain 2: Exposure Characterization				
Metric 4:	Measurement of Exposure	Low	Exposure was estimated via sampling data and modeling. Chemical levels from 1984-1985 were obtained from state sampling data. Information about participant place of residence across four time points (1951, 1961, 1971, and 1981) was used to estimate the exposure based on drinking water source and the previously mentioned state sampling data. VOCs are highly volatile and challenging to accurately sample, as the study discusses. As a result, it is unlikely that data from 1984-1985 accurately represent exposures during different time points.	
Metric 5:	Exposure Levels	Medium	The study reports 3 levels of exposure including the referent group, low exposure (2-10 micrograms/L), and high exposure (>=10 micrograms/L). While the exposure modeling method was not validated by previous measures or other modeling approaches, the likelihood of differential exposure misclassification is low.	
Metric 6:	Temporality	Low	The study examined cancer cases diagnosed in 1982-1983 and constructed exposure estimates for 1951, 1961, 1971, 1981. However, the data used to model historical exposures was collected from 1984-1986, and the modeling method could not be validated by historic sampling measurements.	
Domain 3: Outcome Assessment				
Continued on next page ...				

Human Health Hazard Epidemiology Evaluation

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Study Citation:	Young, T. B., Kanarek, M. S., Wolf, D. A., Wilson, D. A. (1990). Case-control study of colon cancer and volatile organics in Wisconsin municipal ground water supplies. :373-386.			
Health Outcome(s) Assessed:	Gastrointestinal			
Reported Health Effect(s):	Colon cancer			
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene			
HERO ID:	1069372			
Domain	Metric	Rating	Comments	
	Metric 7:	Outcome Measurement or Characterization	Medium	Cases were selected based upon physician diagnosis, however the general population controls were selected from motor vehicle license registries. The authors do not explicitly discuss confirmation of the absence of colon cancer in this group. All subjects were followed for the same length of time.
	Metric 8:	Reporting Bias	High	Measured outcomes are reported. Odds ratios are reported with confidence intervals. The authors note the total number of cases and controls used for analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 9:	Covariate Adjustment	High	The authors considered age, sex, and urbanicity as potential confounders. These variables were included in the analysis as covariates.
	Metric 10:	Covariate Characterization	High	Potential confounders were assessed via valid and reliable means.
	Metric 11:	Co-exposure Counfounding	Medium	Co-exposure chemicals that would bias the result were not likely to be present.
Domain 5: Analysis				
	Metric 12:	Study Design and Methods	High	Case-control was the appropriate study design chosen to examine chlorinated solvents in drinking water and colon cancer.
	Metric 13:	Statistical Power	Medium	The number of cases (n=347) and controls (639 cancer controls, 611 general population controls) is adequate to detect an effect in the exposed population.
	Metric 14:	Reproducibility of Analyses	Medium	The description of the analysis is sufficient, including transformation of variables for inclusion in the logistic regression models.
	Metric 15:	Statistical Analysis	High	The model is transparent. The authors reported included variables and a maximum likelihood analysis was conducted.
Additional Comments:	This study employed a case-control design to examine the association between colon cancer and exposure to 1,2-dichloroethylene (an isomer of trans-1,2-Dichloroethylene) and 1,1,1-trichloroethane (an isomer of 1,1,2-Trichloroethane) in Wisconsin municipal groundwater supplies. The study included a robust recruitment of control groups. Exposure modeling and estimates of historical exposure were the primary limitations, however any related misclassification would have been non-differential. Effect sizes were not large, and a dose-response relationship could not be established.			

Overall Quality Determination

Medium

Study Citation:	Brender, J. D., Shinde, M. U., Zhan, F. B., Gong, X., Langlois, P. H. (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environmental Health 13(1):96.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	birth defects (neural tube defects, limbs deficiencies, oral cleft defects, heart defects, spina bifida, anencephaly)		
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene		
HERO ID:	2799700		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	Participants were drawn from the Texas Birth Defects Registry (TBDR) for years 1996-2008. Controls were frequency matched from the same registry. Study authors state that neural tube cases were more likely to not be successfully geocoded which may introduce selection bias, however, the authors note that both cases and controls with addresses that could not be geocoded were similar. In spite of that, the inclusion criteria, methods of participant selection, and frequency match were reported.
Metric 2:	Attrition	Medium	13.3% case mother addresses and 12.8% control mother addresses were unable to be geocoded, however this most likely only lowered the precision of the study and most likely does not vary based on exposure level.
Metric 3:	Comparison Group	Medium	Controls were matched to cases and pulled from the same eligible population by year of delivery and public health service region. Other demographic factors, e.g., race was not matched in population selection. However, statistical analyses were adjusted for year of delivery, maternal age, race/ethnicity, education, and public health region of residence.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	Medium	Used Emission Weighted Proximity Model to estimate exposure at a given address based on proximity to emission sources and the specific amount or type of pollutant emitted. There may be some exposure misclassification due to mothers moving away from geocoded addresses. Previous studies indicate ~67% of mothers do not move between conception and delivery.
Metric 5:	Exposure Levels	Medium	Reports exposure as "exposure risk value" and groups the risk values into quartiles, with exposure risk values < 0 being the referent group
Metric 6:	Temporality	Medium	The study authors estimated exposure based on residence during pregnancy and evaluated birth outcomes. Temporality is established. Previous studies indicate ~67% mothers don't move between trimester and delivery. For mothers who moved during the pregnancy, the temporality is unknown.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	High	Outcomes determined by Texas Birth Defect Registry, checking for birth defect diagnosis. Birth certificates came from Center for Health Statistics at Texas Department of State Health Services
Metric 8:	Reporting Bias	High	Outcome data measured and reported clearly, stratified by specific type of birth defect
Domain 4: Potential Confounding / Variability Control			
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Human Health Hazard Epidemiology Evaluation

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Study Citation:	Brender, J. D., Shinde, M. U., Zhan, F. B., Gong, X., Langlois, P. H. (2014). Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: A case-control study. Environmental Health 13(1):96.
Health Outcome(s) Assessed:	Reproductive/Developmental
Reported Health Effect(s):	birth defects (neural tube defects, limbs deficiencies, oral cleft defects, heart defects, spina bifida, anencephaly)
Chemical:	trans-1,2-Dichloroethylene- Isomer: 1,2-Dichloroethylene
HERO ID:	2799700

Domain	Metric	Rating	Comments
	Metric 9: Covariate Adjustment	High	Cases were frequency matched by year of delivery and public health service region. Final models were adjusted for year of delivery, public health region, maternal age (<20, 20-24, 25-29, 30-34, 35-39, >39 years), education (<12 years, 12 years, >12 years), and race/ethnicity (Whit non-Hispanic, Black non-Hispanic, Hispanic, other non-Hispanic).
	Metric 10: Covariate Characterization	High	Used birth and death certificates for demographic information
	Metric 11: Co-exposure Confounding	Medium	other co-exposures were not described
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	study used logistic regression to measure association between exposure and birth defects
	Metric 13: Statistical Power	Medium	Overall adequate number of cases and controls - some effects have low cell counts, but at least one health effect has sufficient statistical power.
	Metric 14: Reproducibility of Analyses	Medium	Methods sufficiently detailed for reproducibility
	Metric 15: Statistical Analysis	High	No logistic regression model assumption violations were identified.

Additional Comments: This study examined the association between proximity to several point sources of chlorinated solvents and birth defects. Exposure was assessed using EPA's Toxic Release Inventory, and birth defects were assessed using Texas birth registries. The geocoded address of mothers on day of delivery and the amount of solvent was plugged into the Emission Weighted Probability model to assign each mother an exposure risk value. Limitations include limited evidence of temporality. Additionally, elective terminations lacked a vital record, which meant only 69% of mothers with neural tube defects were geocoded. Mothers highly exposed to 1,2-dichloroethylene were 1.6 times more likely to have the spina bifida birth defect and 1.19 times more likely to have septal heart defects than mothers who were not significantly exposed.

Overall Quality Determination

High

Study Citation:	Bove, F. J. (1996). Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicology and Industrial Health 12(2):255-266.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.		
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)		
HERO ID:	200239 Linked HERO ID(s): 194932, 200239		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This cross-sectional study (n=80,938) included all registered singleton live births and fetal deaths (>20 weeks' gestation) in 1985-88 in 75 New Jersey towns located in 4 counties with "some" water supplies contaminated with substances of interest and where: (i) residents were "mostly" served by public water systems; and (ii) births occurred "mostly" in state. Estimated proportions of residents served by public water systems, and of pregnancies/births captured, were not described. However, the inclusion of all eligible registered births, fetal deaths, and birth defects, as well as the selection of towns without knowledge of birth outcome prevalence, limited the likelihood of selection bias.
Metric 2:	Attrition	Medium	All registered births and fetal deaths were included. Attrition due to missing values for multiple variables was not quantified and is therefore uncertain. However, attrition was likely modest as the proportion of missing values for individual variables was relatively low: (i) ~6% of subjects were excluded from analyses of outcomes such as preterm birth due to invalid or missing gestational ages; and (ii) other covariates evaluated as confounders had up to 4.9% missing values.
Metric 3:	Comparison Group	High	After excluding plural pregnancies and chromosomal abnormalities, all registered live births during the study period in the areas included without the outcomes of interest were included in the comparison group. This comprehensive approach limited the potential for bias. Chromosomal abnormalities were not included as outcomes as they were not hypothesized to be associated with the exposures under study but were appropriately excluded given their uncertain etiology.
Domain 2: Exposure Characterization			
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Study Citation:	Bove, F. J. (1996). Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicology and Industrial Health 12(2):255-266.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.			
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)			
HERO ID:	200239 Linked HERO ID(s): 194932, 200239			
Domain	Metric	Rating	Comments	
	Metric 4: Measurement of Exposure	Medium	Along with several other contaminants, residential drinking water exposure to 'total dichloroethylenes' was assigned based on maternal town of residence at birth. The lack of separate estimates of association for the PECO included isomer trans-1,2-dichloroethylene and the PECO excluded contaminant 1,1-dichloroethylene, which were summed for analysis due to the low frequency of detection, is a limitation. The study also analyzed 1,2-dichloroethane and 1,1,1-trichloroethane. Exposure estimates were calculated using the average of water company sampling reports during the first trimester (for birth defects and fetal death) or the duration of pregnancy (for other outcomes). Detection limits and data availability were not specified in detail but were described as below 1 ppb, with reporting compliance >85%. A minimum of 1 sample per 6-month interval was required; variability in the number of measures available across water systems and towns was not described. Additional sources of measurement error included: changes in residence during pregnancy; water from alternate sources (ex. private wells, bottles, workplaces); variability in residential contaminant levels vs measured samples; unknown levels of tap water intake; and errors in estimated dermal and inhalation exposure while bathing or showering. While the extent of exposure misclassification is uncertain, there is no evidence to suggest it was differential rather than random.	
	Metric 5: Exposure Levels	Uninformative	The lack of separate estimates of association for the two measured dichloroethylenes, which were summed and evaluated as "total dichloroethylenes" means it is not possible to evaluate health effects of the PECO included chemical trans-1,2-dichloroethylene when not aggregated with the other measured dichloroethylene.	
	Metric 6: Temporality	High	Exposure levels were assigned based on contaminant exposures estimated during: (i) the first trimester for analyses of birth defects and fetal deaths; and (ii) the duration of pregnancy for other pregnancy outcomes.	
Domain 3: Outcome Assessment				
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Study Citation:	Bove, F. J. (1996). Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicology and Industrial Health 12(2):255-266.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.			
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)			
HERO ID:	200239 Linked HERO ID(s): 194932, 200239			
Domain	Metric	Rating	Comments	
	Metric 7: Outcome Measurement or Characterization	Medium	Outcomes included measures of birthweight (continuous among term births, low term birthweight, very low birthweight), prematurity, fetal death, and congenital anomalies in live births or fetal deaths. The anomalies analyzed included defects of the central nervous system, neural tube, oral cleft, total cardiac, major cardiac, ventricular septum, and any surveillance defect excluding chromosomal defects. All outcomes were identified using birth certificates, fetal death certificates (>20 weeks' gestation), and the NJ congenital birth defect registry (ICD codes provided). These registry data are likely to be sufficiently valid for late pregnancy outcomes. However, their limited ability to capture early pregnancy losses is a weakness. The sample included only 594 fetal deaths (less than 1% of the >80,000 sample). Typical estimates are that 10-20%, of recognized pregnancies ending in losses. Moreover, developmental defects contributing to early pregnancy losses were also not captured. A further limitation is that that potentially etiologically heterogeneous preterm birth types were analyzed together, as these data did not distinguish premature rupture of membranes vs idiopathic prematurity.	
	Metric 8: Reporting Bias	Medium	Models were constructed only for contaminants with associations > 1.0, and tables included only associations with odds ratios ≥1.5. No clear rationale was provided. Several positive odds ratios below the 1.5 cutoff were described in the results text (without confidence intervals), but no null/negative odds ratios were presented or described.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Medium	Potential confounding by maternal race, education, parity, and prior pregnancy loss, along with infant sex (for birth outcomes) and adequacy of prenatal care, was examined. Gestational age was addressed by analyzing birthweight among full term births, term low birth weight, and small size for gestational age. Only fully adjusted models were presented. In a companion case-control study (with low participation rates), adjustment for other variables not available on birth certificates (ex. maternal smoking, occupational exposures, medical history, and gestational weight gain) did not influence associations with other studied contaminants. This separate study reduces concerns for important confounding bias, but confounding cannot be ruled out.	
	Metric 10: Covariate Characterization	Medium	Data on covariates came from registry data: birth certificates, fetal death certificates, and the NJ congenital birth defects registry.	
	Metric 11: Co-exposure Counfounding	Medium	Co-exposure confounding by drinking water trihalomethane concentrations was evaluated. There was no evidence to suggest substantial confounding by this or other co-exposures.	
Domain 5: Analysis				

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Study Citation:	Bove, F. J. (1996). Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicology and Industrial Health 12(2):255-266.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.			
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)			
HERO ID:	200239 Linked HERO ID(s): 194932, 200239			
Domain	Metric	Rating	Comments	
	Metric 12: Study Design and Methods	High	Methods were appropriate. The study used logistic regression models to estimate odds ratios and confidence intervals for dichotomous outcomes, and linear regression for analysis of continuous birth weight.	
	Metric 13: Statistical Power	Medium	Statistical power was likely to have been limited as a consequence of the small proportion of the sample defined as having "elevated" residential water concentrations of the chemicals of interest. The range of exposure examined was limited, as cutoffs for elevated levels were close to the detection limits of 1 ppb. In addition, for most birth defect outcomes, fewer than 10 cases had elevated exposure.	
	Metric 14: Reproducibility of Analyses	Medium	The authors clearly described steps used to estimate exposure-outcome associations, including exposure category cutoffs and criteria for confounding. However, many results were not shown as tables included odds ratios ≥ 1.5 .	
	Metric 15: Statistical Analysis	High	The authors estimated coefficients, odds ratios and 95% confidence intervals using adequate methods. Confounding was based on 15% change-in-estimate comparing nested models. Effect modification (ex by infant sex) was not evaluated as there was no a priori evidence to suggest such analyses at that time.	
Additional Comments:	This study analyzed the association between several pregnancy outcomes size at birth, prematurity, fetal deaths > 20 weeks' gestation, and congenital birth defects) and estimated residential drinking water concentrations of several chlorinated solvents. Due to the low frequency of detection, the sum of trans-1,2-dichloroethylene and 1,1-dichloroethylene were analyzed as "total dichloroethylenes". Only 2.9% of the sample had elevated levels of total dichloroethylene (>2 ppb). The inability to separate any associations for trans-1,2-dichloroethylene vs. 1,1-dichloroethylene makes this study of limited utility for effects of this chemical. Another critical concern is the inability to capture early fetal deaths and any related malformations. Other limitations include potential exposure misclassification due to factors such as drinking water from other sources, changes in residence, exposure to these contaminants from other sources. No associations were significant. However, odds ratios above 1.5 for $\sum$ (trans-1,2-dichloroethylene & 1,1-dichloroethylene) >2 ppb included: OR = 2.60 (90% CI 0.93, 6.50) for neural tube defects and 1.71 (90% CI 0.62, 4.22) for oral cleft defects.			

Overall Quality Determination

Uninformative

Study Citation:	Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. American Journal of Epidemiology 141(9):850-862.		
Health Outcome(s) Assessed:	Reproductive/Developmental		
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.		
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)		
HERO ID:	194932 Linked HERO ID(s): 194932, 200239		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	Medium	This semi-ecological study (n=80,938) included all registered singleton live births and fetal deaths (>20 weeks) in 1985-88 in 75 New Jersey towns located in 4 counties with "some" water supplies contaminated with substances of interest and where: (i) residents were "mostly" served by public water systems; and (ii) births occurred "mostly" in state. Estimated proportions of residents served by public water systems, and of pregnancies/births captured, were not described. However, the inclusion of all eligible registered births, fetal deaths, and birth defects, as well as the selection of towns without knowledge of birth outcome prevalence, limited the likelihood of selection bias.
Metric 2:	Attrition	Medium	All registered births and fetal deaths were included. Attrition due to missing values for multiple variables was not quantified and is therefore uncertain. However, attrition was likely modest as the proportion of missing values for individual variables was relatively low: (i) ~6% of subjects were excluded from analyses of outcomes such as preterm birth due to invalid or missing gestational ages; and (ii) other covariates evaluated as confounders had up to 4.9% missing values.
Metric 3:	Comparison Group	High	After excluding plural pregnancies and chromosomal abnormalities, all registered live births during the study period in the areas included without the outcomes of interest were included in the comparison group. This comprehensive approach limited the potential for bias. Chromosomal abnormalities were not included as outcomes as they were not hypothesized to be associated with the exposures under study but were appropriately excluded given their uncertain etiology.
Domain 2: Exposure Characterization			
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Study Citation:	Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. American Journal of Epidemiology 141(9):850-862.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.			
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)			
HERO ID:	194932 Linked HERO ID(s): 194932, 200239			
Domain	Metric	Rating	Comments	
Metric 4:	Measurement of Exposure	Medium	Along with several other contaminants, residential drinking water exposure to 'total dichloroethylenes' (as well as 1,2-dichloroethane and 1,1,1-trichloroethane) was assigned based on maternal town of residence at birth. The lack of separate estimates of association for the PECO included isomer trans-1,2-dichloroethylene and the PECO excluded contaminant 1,1-dichloroethylene, which were summed for analysis due to the low frequency of detectable levels, is a limitation. Exposure estimates were calculated using the average of water company sampling reports during the first trimester (for birth defects and fetal death) or the duration of pregnancy (for other outcomes). Detection limits and data availability were not specified in detail but were described as below 1 ppb, with reporting compliance >85%. A minimum of 1 sample per 6-month interval was required; variability in the number of measures available across water systems and towns was not described. Additional sources of measurement error included: changes in residence during pregnancy; water from alternate sources (ex. private wells, bottles, workplaces); variability in residential contaminant levels vs measured samples; unknown levels of tap water intake; and errors in estimated dermal and inhalation exposure while bathing or showering. While the extent of exposure misclassification is uncertain, there is no evidence to suggest it was differential rather than random.	
Metric 5:	Exposure Levels	Uninformative	The lack of separate estimates of association for the two measured dichloroethylenes, which were summed and evaluated as "total dichloroethylenes" means it is not possible to evaluate health effects of the PECO included chemical trans-1,2-dichloroethylene when not aggregated with the other measured dichloroethylene.	
Metric 6:	Temporality	High	Exposure levels were assigned based on contaminant exposures estimated during: (i) the first trimester for analyses of birth defects and fetal deaths; and (ii) the duration of pregnancy for other pregnancy outcomes.	
Domain 3: Outcome Assessment				
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Study Citation:	Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. American Journal of Epidemiology 141(9):850-862.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.			
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)			
HERO ID:	194932 Linked HERO ID(s): 194932, 200239			
Domain	Metric	Rating	Comments	
	Metric 7: Outcome Measurement or Characterization	Medium	Outcomes included measures of birthweight (continuous among term births, low term birthweight, very low birthweight), prematurity, fetal death, and congenital anomalies in live births or fetal deaths. The anomalies analyzed included defects of the central nervous system, neural tube, oral cleft, total cardiac, major cardiac, ventricular septum, and any surveillance defect excluding chromosomal defects. All outcomes were identified using birth certificates, fetal death certificates (>20 weeks' gestation), and the NJ congenital birth defect registry (ICD codes provided). These registry data are likely to be sufficiently valid for late pregnancy outcomes. However, their limited ability to capture early pregnancy losses is a weakness. The sample included only 594 fetal deaths (less than 1% of the >80,000 sample). Typical estimates are that 10-20%, of recognized pregnancies ending in losses. Moreover, developmental defects contributing to early pregnancy losses were also not captured. A further limitation is that that potentially etiologically heterogeneous preterm birth types were analyzed together, as these data did not distinguish premature rupture of membranes vs idiopathic prematurity.	
	Metric 8: Reporting Bias	Low	Models were constructed only for contaminants with associations > 1.0, and tables included only associations with odds ratios ≥1.5. No clear rationale was provided. Several positive odds ratios below the 1.5 cutoff were described in the results text (without confidence intervals), but no null/negative odds ratios were presented or described.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Medium	Potential confounding by maternal race, education, parity, and prior pregnancy loss, along with infant sex (for birth outcomes) and adequacy of prenatal care, was examined. Gestational age was addressed by analyzing birthweight among full term births, term low birth weight, and small size for gestational age. Only fully adjusted models were presented. In a companion case-control study (with low participation rates), adjustment for other variables not available on birth certificates (ex. maternal smoking, occupational exposures, medical history, and gestational weight gain) did not influence associations with other studied contaminants. This separate study reduces concerns for important confounding bias, but confounding cannot be ruled out.	
	Metric 10: Covariate Characterization	Medium	Data on covariates came from registry data: birth certificates, fetal death certificates, and the NJ congenital birth defects registry.	
	Metric 11: Co-exposure Counfounding	Medium	Co-exposure confounding by drinking water trihalomethane concentrations was evaluated. There was no evidence to suggest substantial confounding by this or other co-exposures.	
Domain 5: Analysis				

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Study Citation:	Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., Savrin, J. E. (1995). Public drinking water contamination and birth outcomes. American Journal of Epidemiology 141(9):850-862.			
Health Outcome(s) Assessed:	Reproductive/Developmental			
Reported Health Effect(s):	Fetal growth and development: -Birthweight (term births), low birthweight (term births), very low birthweight, small for gestational age-Preterm birth-Fetal death (>20 weeks' gestation)-Congenital anomalies: (i) nervous system (central nervous system, neural tube defects); (ii) oral cleft; (iii) cardiovascular (total cardiac, major cardiac, ventricular septum defects); and (iv) any surveillance defect excluding chromosomal defects.			
Chemical:	trans-1,2-Dichloroethylene- Isomer: Total dichloroethylenes (summed with 1,1-dichloroethylene)			
HERO ID:	194932 Linked HERO ID(s): 194932, 200239			
Domain	Metric	Rating	Comments	
Metric 12:	Study Design and Methods	High	Methods were appropriate. The study used logistic regression models to estimate odds ratios and confidence intervals for dichotomous outcomes, and linear regression for analysis of continuous birth weight.	
Metric 13:	Statistical Power	Low	Statistical power was likely to have been limited as a consequence of the small proportion of the sample defined as having "elevated" residential water concentrations of the chemicals of interest. The range of exposure examined was limited, as cutoffs for elevated levels were close to the detection limits of 1 ppb. In addition, for most birth defect outcomes, fewer than 10 cases had elevated exposure. However, the authors emphasized the magnitude of associations rather than statistical significance and presented multiple confidence intervals to aid interpretation of the precision of estimates (50%, 90% and 99%).	
Metric 14:	Reproducibility of Analyses	Medium	The authors clearly described steps used to estimate exposure-outcome associations, including exposure category cutoffs and criteria for confounding. However, many results were not shown as tables included odds ratios ≥ 1.5 .	
Metric 15:	Statistical Analysis	High	The authors estimated coefficients, odds ratios and confidence intervals using adequate methods. Confounding was based on 15% change-in-estimate comparing nested models. Effect modification (ex by infant sex) was not evaluated as there was no a priori evidence to suggest such analyses at that time.	
Additional Comments:	This study analyzed the association between several pregnancy outcomes size at birth, prematurity, fetal deaths > 20 weeks gestation, and congenital birth defects) and estimated residential drinking water concentrations of several chlorinated solvents. Due to the low frequency of detection, the sum of trans-1,2-dichloroethylene and 1,1-dichloroethylene were analyzed as "total dichloroethylenes". Only 2.9% of the sample had elevated levels of total dichloroethylenes (>2 ppb) in the first trimester. The inability to separate any associations for trans-1,2-dichloroethylene vs. 1,1-dichloroethylene makes this study of limited utility for effects of this chemical. Another critical concern is the inability to capture early fetal deaths and any related malformations. Other limitations include potential exposure misclassification due to factors such as drinking water from other sources, changes in residence, exposure to these contaminants from other sources. No associations were significant. However, odds ratios above 1.5 for $\sum$ (trans-1,2-dichloroethylene & 1,1-dichloroethylene) >2 ppb included: OR = 2.60 (90% CI 0.93, 6.50) for neural tube defects and 1.71 (90% CI 0.62, 4.22) for oral cleft defects.			

Overall Quality Determination

Uninformative

Study Citation:	Lehmann, K. B., Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116:131-268.			
Health Outcome(s) Assessed:	Neurological/Behavioral			
Reported Health Effect(s):	Dizziness, drowsiness, intracranial pressure			
Chemical:	trans-1,2-Dichloroethylene- Parent compound			
HERO ID:	29046 Linked HERO ID(s): 29046, 4731490			
Domain	Metric	Rating	Comments	
Domain 1: Randomization	Metric 1A:	Was an adequate method used to randomize the administered dose or exposure level?	Medium	Randomization is not applicable; in this study the participants were the study researchers who exposed themselves to the same exposure doses of trans-1,2-dichloroethylene. There was no randomization to a placebo group.
Domain 2: Allocation Concealment and Blinding	Metric 2A:	Was allocation to study groups adequately concealed until recruitment was complete?	Medium	In this intentional dosing study, the researchers exposed themselves to the study chemical. There was no allocation to different groups. Therefore, lack of adequate allocation concealment would not appreciably bias results.
	Metric 2B:	Were the research personnel and human subjects blinded to the study group during the study?	Low	Since both study researchers intentionally exposed themselves to predetermined doses of the chemical at the same time, blinding was not possible for either the research team or the study participants.
Domain 3: Attrition	Metric 3A:	Were outcome data complete without attrition or exclusion from analysis?	High	No attrition was reported; two researchers exposed themselves to the study chemicals and there were no reported exclusions.
Domain 4: Exposure Measurement Bias	Metric 4A:	Can we be confident in the exposure characterization?	Medium	Trans-1,2-dichloroethylene was supplied by "I.G. Farbenindustrie A.G., Ludwigshafen on Rhine," and was reported to be in the purest commercial grade with "additional painstaking expert purification" via fractional distillation. While no specific purity level is described, there is indirect evidence that the purity of the supplied trans-1,2-dichloroethylene was confirmed.
Domain 5: Outcome Assessment	Metric 5A:	Can we be confident in the outcome assessment?	Low	The lack of blinding of the study subjects may have biased the results, as knowledge of exposure doses may have consciously or unconsciously influenced self-report of symptoms. Many of the outcomes examined were subjective self-reported symptoms that could not be independently verified.
	Metric 5B:	Selective Reporting: Were all measured outcomes reported?	Medium	All potentially measured outcomes appear to have been reported in the results.
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Study Citation:	Lehmann, K. B., Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116:131-268.
Health Outcome(s) Assessed:	Neurological/Behavioral
Reported Health Effect(s):	Dizziness, drowsiness, intracranial pressure
Chemical:	trans-1,2-Dichloroethylene- Parent compound
HERO ID:	29046 Linked HERO ID(s): 29046, 4731490

Domain	Metric	Rating	Comments
Additional Comments:	In this intentional dosing study, two of the study researchers directly exposed themselves to the chemical of interest, trans-1,2-dichloroethylene and self-reported symptoms that they experienced. Overall, there is limited information in this study and there is overall limited confidence in the findings given the small sample size (n=2) and the nature of assessing outcomes following self-exposure. Exposure appears to be reasonably well-characterized, but there was no standardized form of outcome assessment. Participants in this study experienced dizziness, burning of the eyes, intracranial pressure, drowsiness, and nausea following exposure to trans-1,2-dichloroethylene. Symptoms began at 825 ppm after a period of 10 minutes.		

Overall Quality Determination

Low

Study Citation:	Lehmann, K. B., Schmidt-Kehl, L. (1936). Die 13 wichtigsten Chlorkohlenwasserstoffe der Fettreihe von Standpunkt der Gewerbehygiene. Archiv fuer Hygiene und Bakteriologie 116:131-268.			
Health Outcome(s) Assessed:	Ocular & Sensory			
Reported Health Effect(s):	Eye burning			
Chemical:	trans-1,2-Dichloroethylene- Parent compound			
HERO ID:	29046 Linked HERO ID(s): 29046, 4731490			
Domain	Metric	Rating	Comments	
Domain 1: Randomization				
Metric 1A:	Was an adequate method used to randomize the administered dose or exposure level?	Medium	Randomization is not applicable; in this study the participants were the study researchers who exposed themselves to the same exposure doses of trans-1,2-dichloroethylene. There was no randomization to a placebo group.	
Domain 2: Allocation Concealment and Blinding				
Metric 2A:	Was allocation to study groups adequately concealed until recruitment was complete?	Medium	In this intentional dosing study, the researchers exposed themselves to the study chemical. There was no allocation to different groups. Therefore, lack of adequate allocation concealment would not appreciably bias results.	
Metric 2B:	Were the research personnel and human subjects blinded to the study group during the study?	Low	Since both study researchers intentionally exposed themselves to predetermined doses of the chemical at the same time, blinding was not possible for either the research team or the study participants.	
Domain 3: Attrition				
Metric 3A:	Were outcome data complete without attrition or exclusion from analysis?	High	No attrition was reported; two researchers exposed themselves to the study chemicals and there were no reported exclusions.	
Domain 4: Exposure Measurement Bias				
Metric 4A:	Can we be confident in the exposure characterization?	Medium	Trans-1,2-dichloroethylene was supplied by "I.G. Farbenindustrie A.G., Ludwigshafen on Rhine," and was reported to be in the purest commercial grade with "additional painstaking expert purification" via fractional distillation. While no specific purity level is described, there is indirect evidence that the purity of the supplied trans-1,2-dichloroethylene was confirmed.	
Domain 5: Outcome Assessment				
Metric 5A:	Can we be confident in the outcome assessment?	Low	The lack of blinding of the study subjects may have biased the results, as knowledge of exposure doses may have consciously or unconsciously influenced self-report of symptoms. Many of the outcomes examined were subjective self-reported symptoms that could not be independently verified.	
Metric 5B:	Selective Reporting: Were all measured outcomes reported?	Medium	All potentially measured outcomes appear to have been reported in the results.	
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Health Outcome(s) Assessed:	Ocular & Sensory
Reported Health Effect(s):	Eye burning
Chemical:	trans-1,2-Dichloroethylene- Parent compound
HERO ID:	29046 Linked HERO ID(s): 29046, 4731490

Domain	Metric	Rating	Comments
Additional Comments:	In this intentional dosing study, two of the study researchers directly exposed themselves to the chemical of interest, trans-1,2-dichloroethylene and self-reported symptoms that they experienced. Overall, there is limited information in this study and there is overall limited confidence in the findings given the small sample size (n=2) and the nature of assessing outcomes following self-exposure. Exposure appears to be reasonably well-characterized, but there was no standardized form of outcome assessment. Participants in this study experienced dizziness, burning of the eyes, intracranial pressure, drowsiness, and nausea following exposure to trans-1,2-dichloroethylene. Symptoms began at 825 ppm after a period of 10 minutes.		

Overall Quality Determination

Low

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Health Outcome(s) Assessed:	Gastrointestinal			
Reported Health Effect(s):	Nausea			
Chemical:	trans-1,2-Dichloroethylene- Parent compound			
HERO ID:	29046 Linked HERO ID(s): 29046, 4731490			
Domain	Metric	Rating	Comments	
Domain 1: Randomization				
Metric 1A:	Was an adequate method used to randomize the administered dose or exposure level?	Medium	Randomization is not applicable; in this study the participants were the study researchers who exposed themselves to the same exposure doses of trans-1,2-dichloroethylene. There was no randomization to a placebo group.	
Domain 2: Allocation Concealment and Blinding				
Metric 2A:	Was allocation to study groups adequately concealed until recruitment was complete?	Medium	In this intentional dosing study, the researchers exposed themselves to the study chemical. There was no allocation to different groups. Therefore, lack of adequate allocation concealment would not appreciably bias results.	
Metric 2B:	Were the research personnel and human subjects blinded to the study group during the study?	Low	Since both study researchers intentionally exposed themselves to predetermined doses of the chemical at the same time, blinding was not possible for either the research team or the study participants.	
Domain 3: Attrition				
Metric 3A:	Were outcome data complete without attrition or exclusion from analysis?	High	No attrition was reported; two researchers exposed themselves to the study chemicals and there were no reported exclusions.	
Domain 4: Exposure Measurement Bias				
Metric 4A:	Can we be confident in the exposure characterization?	Medium	Trans-1,2-dichloroethylene was supplied by "I.G. Farbenindustrie A.G., Ludwigshafen on Rhine," and was reported to be in the purest commercial grade with "additional painstaking expert purification" via fractional distillation. While no specific purity level is described, there is indirect evidence that the purity of the supplied trans-1,2-dichloroethylene was confirmed.	
Domain 5: Outcome Assessment				
Metric 5A:	Can we be confident in the outcome assessment?	Low	The lack of blinding of the study subjects may have biased the results, as knowledge of exposure doses may have consciously or unconsciously influenced self-report of symptoms. Many of the outcomes examined were subjective self-reported symptoms that could not be independently verified.	
Metric 5B:	Selective Reporting: Were all measured outcomes reported?	Medium	All potentially measured outcomes appear to have been reported in the results.	
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Health Outcome(s) Assessed:	Gastrointestinal
Reported Health Effect(s):	Nausea
Chemical:	trans-1,2-Dichloroethylene- Parent compound
HERO ID:	29046 Linked HERO ID(s): 29046, 4731490

Domain	Metric	Rating	Comments
Additional Comments:	In this intentional dosing study, two of the study researchers directly exposed themselves to the chemical of interest, trans-1,2-dichloroethylene and self-reported symptoms that they experienced. Overall, there is limited information in this study and there is overall limited confidence in the findings given the small sample size (n=2) and the nature of assessing outcomes following self-exposure. Exposure appears to be reasonably well-characterized, but there was no standardized form of outcome assessment. Participants in this study experienced dizziness, burning of the eyes, intracranial pressure, drowsiness, and nausea following exposure to trans-1,2-dichloroethylene. Symptoms began at 825 ppm after a period of 10 minutes.		

Overall Quality Determination

Low