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Maternal residential exposure to solvents from industrial sources during pregnancy and childhood cancer risk in California

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Abstract

Background: Maternal solvent exposure has been suspected to increase offspring cancer risk. The study aimed to evaluate the associations between maternal residential exposure to solvents from industrial pollution during pregnancy and childhood cancer.

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Declaration of competing interest

The authors declare they have no actual or potential competing financial interests.

CRediT authorship contribution statement

Yixin Chen: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation. **Darcy Van Deventer:** Writing – review & editing. **Roch Nianogo:** Writing – review & editing, Validation. **Marco Vinceti:** Writing – review & editing. **Wei Kang:** Writing – review & editing, Validation. **Myles Cockburn:** Writing – review & editing, Resources. **Noah Federman:** Writing – review & editing. **Julia E. Heck:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114388.

Methods: The present study included 15,744 cancer cases (aged 0–19 years at diagnosis) identified from California Cancer Registry and 283,141 controls randomly selected from California Birth Registry (20:1 frequency-matched by birth year: 1998–2016). We examined industrial releases of tetrachloroethylene and 1,1,1-trichloroethane within 3 km of the birth address, while we used a 5 km buffer for carbon disulfide. We calculated the total exposure from all linked Toxic Release Inventory sites during each index pregnancy and assigned "ever/never" and "high/low exposed/unexposed" exposure, using median values. We performed quadratic decay models to estimate cancer risks associated with maternal solvent exposure in pregnancy.

Results: 1,1,1-Trichloroethane was associated with rhabdomyosarcoma (adjusted Odds Ratio (aOR): 1.96; 95% Confidence Interval (CI): 1.16, 3.32) in the "ever exposed" group. Ever exposure to carbon disulfide was associated with increased risks of medulloblastoma (OR = 1.85, 95% CI 1.01, 3.40) and ependymoma (OR = 1.63 95% CI 0.97, 2.74).

Conclusions: Overall, our findings suggested maternal residential exposure to solvents from industrial sources might be associated with elevated childhood cancer risks.

Keywords

Industrial toxics; Solvents; Maternal exposure; Pregnancy; Childhood cancer

1. Introduction

Cancer ranked as the 2nd leading cause of death in children aged 0–19 years in the United States (US) (American Cancer Society, 2023), with only a few established risk factors including genetic predisposition (5–10% of cases), high-dose ionizing radiation, and prior chemotherapy (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Spector et al., 2015; Wakeford, 1995, 2013). Previous studies have identified potential environmental risk factors such as parental occupational exposures, pesticides, air pollution and air toxics exposures (Heck et al., 2013b; Lavigne et al., 2017; Malagoli et al., 2016; Rossides et al., 2022; Vinceti et al., 2012; Volk et al., 2019).

Multiple solvents are established or suspected carcinogens in studies of adults, with adverse reproductive and child health endpoints additionally reported (Gelbke et al., 2009; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2014; International Agency for Research on Cancer, 2022; Kalkbrenner et al., 2018; Sharma et al., 2022). With regards to childhood cancer, a study found residential proximity to industrial solvents was related to an increase in pediatric leukemia, and similar increases in retinoblastoma (García-Pérez et al., 2015, 2016b).

With regards to occupational exposures, maternal exposure to solvents on the job was related to increases in acute lymphoblastic leukemia in several but not all studies (Buckley et al., 1989; Lowengart et al., 1987; Schüz et al., 2000; Sung et al., 2008; Van Steensel-Moll et al., 1985). Maternal occupational exposure to tetrachloroethylene (PCE) was associated with an increased risk of childhood leukemia including acute nonlymphocytic leukemia (Buckley et al., 1989; Fagliano et al., 2003; Shu et al., 1999). Similarly, maternal occupational exposure

to 1, 1,1-trichloroethane (1,1,1-TCA) was associated with a higher risk of leukemia in offspring (Infante-Rivard et al., 2005).

In residential studies, residential vicinity to industrial pollution sources and childhood cancer identified sources releasing tetrachloromethane and observed associations with childhood leukemia (García-Pérez et al., 2019). However, assessing the distance to pollution sources as a proxy for exposure might introduce exposure misclassification. Utilizing air toxics data from monitoring stations, PCE was found to elevate the risk of Wilms tumor (Shrestha et al., 2014).

A working group has identified industrial agents considered high priority for evaluation by the IARC Monographs Program (Marques et al., 2019). Guided by these priorities, the study aimed to investigate the associations between childhood cancer and maternal residential exposure in pregnancy to three solvents (i.e., 1,1,1-TCA, PCE, carbon disulfide (CS_2)) tracked in California by the Environmental Protection Agency's Toxics Release Inventory (TRI) program.

2. Material and methods

We ascertained childhood and adolescent cancer cases (diagnosed 0–19 years) who were born 1998–2016 and diagnosed from 1998 to 2018 from the California Cancer Registry and classified cancers according to the International Classification of Childhood Cancer (ICCC) extended classification recode (Supplemental Table 1) (Steliarova-Foucher et al., 2005). Cases (89%) were matched to a California birth certificate by first and last names, dates of birth, and social security number if available, by using a probabilistic linkage program (LinkPlus; CDC, Atlanta, GA). Controls were randomly selected from California Birth Registry, frequency-matched by birth year (20:1 matching ratio) for births in the same years (Heck et al., 2013a).

We excluded children with missing or likely nonviable birthweight (<500 g; n = 344), with nonviable gestational age (<20 weeks; n = 138) and with missing sex information (n = 3) from the analysis. After exclusions, 15,744 cases and 283,141 controls were included for analysis (Fig. 1).

The U.S. EPA TRI program was created to monitor and document industrial management of toxic chemicals (Environmental Protection Agency, 2012). The program tracks 770 chemicals and 33 chemical categories that over 23,000 industrial and other facilities dispose of via releases, recycling, energy recovery, or treatment. Facilities are required to report releases if they fall under in the TRI-covered North America Industry Classification System (NAICS), have 10 or more full-time employees, and engage in the manufacturing, importing, processing, or use of TRI-listed chemicals in quantities surpassing EPA-established thresholds within a calendar year.

The TRI keeps record of air releases in addition to water and land releases for all listed chemicals and further classifies the air releases into "stack air" and "fugitive air". For our analysis, we assessed all ambient air releases (i.e., stack air and fugitive air combined), which account for 85% of all releases in California. We obtained the annual release data,

in pounds, of solvents commonly released in California (i.e., PCE, 1,1,1-TCA) and/or identified as high priority by IARC (i.e., CS_2) from the TRI database. Using ArcGIS 10.2 (ESRI, Redlands), we mapped ambient air release data to the location of each site based on geocoded address (i. e., latitude and longitude) provided by EPA.

We geocoded the exact residential addresses obtained from birth certificates, using a method designed to optimize geocoding of California addresses (Goldberg et al., 2008). We linked home address at birth of each subject to the location of each release site within the distance buffer with ArcGIS. In our analysis, we examined different distance thresholds (2 km, 3 km, 5 km) around the facilities to evaluate consistency in effect estimates across distances. We aimed to choose the smallest threshold which allowed for adequate statistical power for estimating effects for most solvents. Previous studies suggested excess risks of childhood cancer were associated with residency within 1–5 km of industrial sites (García-Pérez et al., 2015, 2016a, 2016c, 2019). Hence, we chose a 3-km threshold for solvents including PCE, and 1,1, 1-TCA, and a 5-km threshold for CS_2. If the home address at birth was beyond the distance buffer, we classified the child as unexposed to the chemical in pregnancy. Using ArcGIS, we calculated the straight-line distance from the home address at birth of subjects to TRI sites.

Based on the recommendations from the literature (Conley, 2011), we implemented quadratic decay models to account for the distance decay effects when estimating exposures during pregnancy. The quadratic decay model uses a modified equation (Equation (1)) from Cutter et al. (Cutter and Solecki, 1996). Here, K_{ir} is the impact of site i on residence r; v_i is the volume of releases from site i; d_{ir} is the distance between site i and residence r; and T is the threshold distance (Conley, 2011). Only the sites within the threshold distance from residence r were included in the calculation of this residence's exposures.

$$K_{ir} = v_i \times \left[1.0 - \left(d_{ir}^2 / T^2\right)\right] \quad (1)$$

A daily exposure amount was calculated by dividing the total annual release from all sites linked to each birth by 365.25 days. Multiplying the daily amount by the length of time exposed to a given year's releases allowed us to compute the total solvent exposure released to the air during pregnancy for each birth, taking into account the timing of pregnancy and gestational age. Children with a non-zero exposure amount were classified as "ever exposed" during pregnancy. We further categorized the exposure. We calculated the median value among the exposed controls living within the distance buffer and classified those with above median exposure as high exposed, and those with below median exposure but greater than zero as low exposed to evaluate possible exposure-response relationships. Descriptive statistics of solvent distributions during pregnancy, using the quadratic decay model, are presented in Supplemental Table 2.

We identified commonly released chemicals during the study period from the TRI database and further conducted Pearson correlation tests between the exposures to the top 25

chemicals, to address confounding by co-exposure to other industrial chemicals. Pearson correlation coefficients between each of the 3 solvents of interest and other commonly released chemicals were reported (Supplemental Table 3).

Unconditional logistic regression analyses (SAS 9.4 (SAS, Cary, NC)) were performed to evaluate the risk of childhood cancer among the “ever exposed” group as well as the “low exposed” and “high exposed” groups. In addition, we conducted sensitivity analysis to examine the association between the risk of childhood cancer and per interquartile range (IQR) increase in the exposure to each solvent, after confirming the linearity of each of the three pollutants. Covariates in addition to birth year (the matching factor) were selected based on previous literature, and we developed directed acyclic graphs (Suttorp et al., 2015) for the visual representation of causal assumptions (Supplemental Fig. 1) (Carozza et al., 2010; Pastor Jr et al., 2004; Spector et al., 2015; Zahnd et al., 2018).

California Cancer Registry records, birth certificates, and the years 2000 and 2010 census data provided information on gestational, demographic, and socioeconomic measures. Covariates adjusted in our models included maternal age (<20 years, 20–24 years, 25–29 years, 30–34 years, 35+ years), mother’s race and ethnicity (White non-Hispanic, Hispanic of any race, Black, Asian/Pacific Islander, American Indian), method of payment for prenatal care (private insurance vs. Medi-Cal, other government source, self-pay, or military; this variable is a proxy for socioeconomic status (Ritz et al., 2007)), a neighborhood SES-index variable, and residence in an urban/rural environment, as defined by the US Department of Agriculture (United States Department of Agriculture Economic Research Service, 2013). Census-tract socioeconomic status (SES) index is a 5-level variable created using principal components analysis based on seven neighborhood-level measures (percent blue-collar workers, average years of education, percent older than 16 years without employment, median household income, percent living 200% below poverty, median rent, and median house value) (Yost et al., 2001). We additionally adjusted for traffic-related fine particulate matter ($PM_{2.5}$) exposure in the subjects with available data on this variable, which was generated by using a California LINE Source Dispersion Model (CALINE4) (Heck et al., 2013b). Due to similar results to the main analyses, it was not included in the final model.

In statistical power analyses done before the study, we estimated that the exposure prevalence of 15% would be sufficient to estimate most cancer risks. For example, with the assumed exposure prevalence (15%), we had >90% power to observe an odds of 1.2 with 2800 children diagnosed with acute myeloid leukemia. In this study, carbon disulfide was examined only when power allowed in exploratory analyses.

We reported results in each category when exposed cases were ≥10.

3. Results

There were more non-Hispanic White mothers of cancer cases than of controls (Table 1). Mothers of cases were insured by private insurance/HMO/Blue Cross Blue Shield

more frequently than controls. Other demographic and socioeconomic characteristics were comparable between cases and controls.

Pearson correlation tests revealed only weak correlations between PCE, 1,1,1-TCA, CS_2 and other commonly released chemicals in California in 2000 (Supplemental Table 4).

We did not find associations between childhood cancer and PCE at any exposure level, although there were suggestive trends indicating that high level exposure to PCE might be associated with a higher risk of retinoblastoma (low: OR = 1.12; 95% CI 0.66, 1.91; high: OR = 1.45; 95% CI 0.85, 2.46) (Table 2).

1,1,1-TCA exposure was associated with an increased risk of rhabdomyosarcoma, among those ever exposed (OR = 1.96, 95% CI 1.16, 3.32) (Table 3). We did not have sufficient sample size to examine the risk among “low exposed” and “high exposed” groups. We also observed a trend with the risk of glioma (low: OR = 1.15; 95% CI 0.78, 1.68; high: OR = 1.35; 95% CI 0.94, 1.94).

For CS_2 (Table 4), we found increased risks of medulloblastoma (OR = 1.85, 95% CI 1.01, 3.40) and ependymoma (OR = 1.63, 95% CI 0.97, 2.74) associated with ever exposure but we lacked statistical power to further evaluate the risk by exposure levels.

In sensitivity analyses examining the risk per IQR increase for each solvent, we only observed slight increases in some cancer types, with all ORs ≤1.10 (Supplemental Tables 5–7): exposure to PCE and NHL, exposure to 1,1,1-TCA and rhabdomyosarcoma, as well as exposure to CS_2 and ALL.

4. Discussion

In this study, we used quadratic decay models to model solvent exposures from industrial sources and examined the risks of childhood cancer by exposure status during pregnancy. We assessed the risks by per IQR increase and by exposure levels and explored possible exposure-response associations. Our study is one of the few studies that investigated specific solvents released by industrial facilities. Our study is the first to provide epidemiologic evidence on the relation between 1,1,1-TCA and rhabdomyosarcoma, and on the relation between CS_2 and subtypes of CNS tumors.

1,1,1-TCA was classified by IARC as a Group 2A carcinogen, and it has been widely used as an industrial solvent in various products, including leather-treatment products with an average concentration of 66.5% of 1,1,1-TCA (International Agency for Research on Cancer, 2022). Tetrachloroethylene was classified by IARC as a Group 2A carcinogen, and is commonly used in dry cleaning, metal, and mining industries for cleaning purposes (Gold et al., 2008; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2014). CS_2 has not been evaluated by IARC. It is an industrial solvent mainly used in the manufacture of regenerated cellulose and viscose or as an intermediate to manufacture other chemicals (Printemps et al., 2022). Despite not being previously studied with rhabdomyosarcoma, 1,1,1-TCA was previously linked to excess risk of soft tissue sarcomas in the Swedish leather tanning industry (Mikoczy et al., 1994).

A number of studies have reported on central nervous system (CNS) toxicity with CS_2 exposure (Chuang et al., 2007; Huang et al., 1996; Krstev et al., 2003; Sun et al., 2009). Experimental studies have suggested CS_2 causes morphologic brain lesions (Beauchamp et al., 1983) and decreases in the number of nerve fiber bundles and migrating neurons (Ding et al., 2011). With regards to reproductive effects, CS_2 lowers sperm motility and antioxidant capacity (Guo et al., 2016). In addition, exposed female workers were more likely to experience adverse pregnancy outcomes including preterm birth, congenital malformations, emesis gravidarum, and pre-eclampsia (Zhou et al., 1988). Some of these adverse birth outcomes were linked to higher risks of CNS tumors (Askins et al., 2023; Oksuzyan et al., 2012; Schmidt et al., 2010). CS_2 can also be found in breast milk, suggesting that the child's early life exposures may also be relevant (Cai and Bao, 1981). CS_2 is understudied in cancer, but a prior study linked occupational exposure to greater lymphatic leukemia mortality in rubber industry workers (Wilcosky et al., 1984).

A high point estimate for CNS tumors was observed among children with low exposure to PCE in pregnancy, but no elevated risk was seen among the high exposed group, thus not substantially supporting a causal relation. On the other hand, live birth bias might influence the outcome, lowering our ability to detect any effect in the high exposed group (Liew et al., 2015). For example, although insufficient evidence indicated an increased risk of pregnancy loss with the exposure of PCE (Aschengrau et al., 2009; Brown Dzubow et al., 2010), PCE was shown to increase the risk of infertility (Aschengrau et al., 2020; Sallmén et al., 1995; Wesselink et al., 2018). Because our study only included live births and our study design excluded mothers who were unable to conceive, results may have been affected by live birth bias.

Our study identified specific solvents from the TRI and analyzed the total release amount from each industrial site. The weak correlations between the top 25 commonly released chemicals suggested minimal confounding from co-exposure to other industrial chemicals. The TRI database is considered the most comprehensive data source on industrial toxic emissions in the US (Chakraborty, 2004). Several studies have utilized this database to investigate the associations between industrial pollution and health outcomes (Chakraborty, 2004; Choi et al., 2006; Hendryx and Luo, 2013). Our group previously utilized the TRI data and reported associations between dichloromethane from industrial sources and several childhood cancer types (Park et al., 2017). The use of quadratic decay models was reported to have better model performance in analyzing TRI data (Conley, 2011). The geocoded addresses based on the exact home address of each birth also allowed us to model and assess comprehensive pollution exposure. Our geocoded addresses have high accuracy rates, because about 94.4% of our geocoded addresses were geocoded by building centroid, parcel, or street segment. Furthermore, our population-based cohort which is large for rare diseases allowed us to examine several types of childhood cancer with an adequate sample size. Recall bias for exposure data, covariate data and selective study participation were avoided by utilizing registry-based data.

Our study had limitations. Our study analysis was limited by the rarity of some cancer types as well as the generally low exposure prevalence. In addition, exposure misclassification might occur in our study. First, we assumed mothers did not move to places that had

different exposures to industrial pollutants in pregnancy (i.e., relied on home addresses at birth only). It is estimated that approximately 9–32% of pregnant mothers move in pregnancy with median distances moved ranging from 4.2 to 10 km (Bell and Belanger, 2012; Lupo et al., 2010; Pennington et al., 2017; Pereira et al., 2016). With a low to moderate percentage of women expected to move in pregnancy, and those who do, moved within small distances, our 3 and 5 km exposure buffers might have captured most residential exposure to industrial pollution. However, exposure misclassification might still occur for PCE, 1,1,1-TCA, and CS_2. Risk factors previously associated with greater mobility in pregnancy include low SES, lower maternal age and unmarried status (Bell and Belanger, 2012; Fell et al., 2004). As we adjusted for SES and maternal age in our analysis, we expect nondifferential exposure misclassification leading our estimates toward the null. Second, we were not able to account for environmental conditions such as temperature, wind stability, or atmospheric inversions. It is difficult to ascertain the direction of misclassification which occurred in both cases and controls, and thus this would lead to nondifferential misclassification resulting in underestimation of our results. We excluded participants (approximately 6.4–7.6% of total) with missing values on covariates and conducted a complete case analysis, which might introduce selection bias. Lastly, families might move to different areas after birth with different levels of industrial pollution, which may also contribute to the risk of childhood cancer. It is estimated that 20–34.5% of children moved in the first year of life (Ling et al., 2019; Urayama et al., 2009). Furthermore, our group previously reported moderate to strong correlations between pesticide exposure between birth and the first year of life (Ling et al., 2019) (Pearson correlation coefficients: 0.62–0.95). Therefore, our findings should be interpreted with caution as it may reflect exposures in early life.

Our study may contribute to a better understanding of the role of solvents from industrial sources in the etiology of childhood cancer. Excess risks of rhabdomyosarcoma and brain tumors (i.e., ependymoma and medulloblastoma) might be associated with maternal residential exposure to industrial 1,1,1-TCA and CS_2 in pregnancy, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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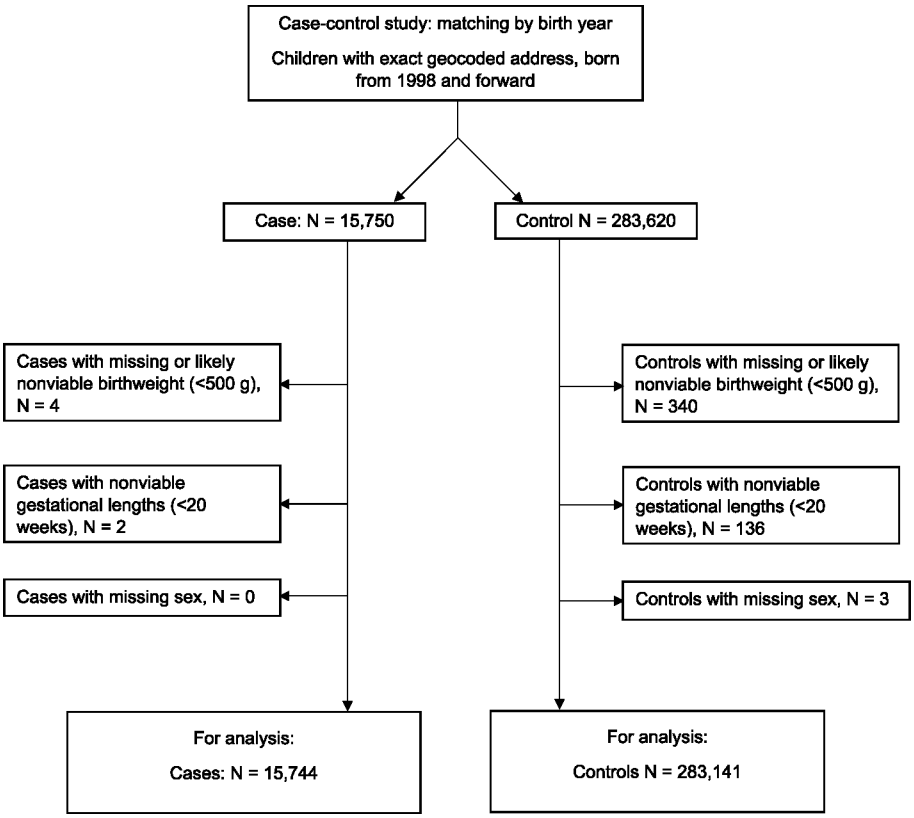

Fig. 1.

Study population flow diagram for children born from 1998 to 2016 in California and included for this case-control study.

Table 1

Demographic and socioeconomic characteristics of children born 1998–2016 in California.

Characteristics	Cases N = 15,744	Controls N = 283,141
Child's sex, N (%)		
Male	8505 (54.0)	144,218 (50.9)
Female	7239 (46.0)	138,923 (49.1)
Maternal age, N (%)		
19 or less	1315 (8.4)	26,304 (9.3)
20–24 years old	3188 (20.3)	63,009 (22.3)
25–29 years old	4020 (25.5)	75,279 (26.6)
30–34 years old	4117 (26.2)	69,862 (24.7)
35 and older	3104 (19.7)	48,687 (17.2)
Maternal birthplace, N (%)		
USA	9155 (58.2)	157,077 (55.5)
Outside of USA	6589 (41.9)	126,003 (44.5)
Missing	0	61
Maternal race and ethnicity, N (%)		
White non-Hispanic	5240 (33.3)	84,044 (30.0)
Hispanic of any race	7878 (50.0)	141,361 (49.9)
Black	643 (4.1)	16,243 (5.7)
Asian/Pacific Islander	1588 (10.1)	34,194 (12.1)
American Indian	61 (0.4)	1169 (0.4)
Other/not specified	118 (0.8)	2618 (0.9)
Missing	216	3512
Paternal race and ethnicity, N (%)		
White non-Hispanic	5077 (32.3)	81,041 (28.6)
Hispanic of any race	7312 (46.4)	130,559 (46.1)
Black	770 (4.9)	17,547 (6.2)
Asian/Pacific Islander	1387 (8.8)	29,791 (10.5)
American Indian	44 (0.3)	1006 (0.4)
Other/not specified	131 (0.8)	2420 (0.9)
Missing	1023	20,777
Source of payment for prenatal care, N (%)		
Private insurance/HMO/Blue Cross, Blue Shield	8716 (55.7)	141,721 (50.5)
Medi-Cal/other government/self-pay	6936 (44.3)	138,977 (49.5)
Missing	92	2443
Residency in rural/urban area, N (%)		
Rural	971 (6.2)	17,379 (6.1)
Urban	14,762 (93.8)	264,655 (93.5)
Missing	11	1107
Census tract level socioeconomic status		

Characteristics	Cases N = 15,744	Controls N = 283,141
Lowest	3993 (25.4)	78,316 (27.7)
Lower middle	3541 (22.5)	64,194 (22.7)
Middle	3114 (19.8)	53,429 (18.9)
Upper middle	2715 (17.2)	45,858 (16.2)
Highest	2351 (14.9)	39,559 (14.0)
Missing	30	1785
Age of cancer diagnosis, years (Mean ± Standard deviation)	5.7 ± 5.0	NA

Table 2

Associations between industrial tetrachloroethylene exposure during pregnancy and childhood cancers for births in CA between 1998 and 2016, using the quadratic decay model.

Chemical and Cancer type	Exposure category	Exposed cases,[a] N (%)	Crude model, OR (95% CI)[b]	Adjusted model, OR (95% CI)[c]
Tetrachloroethylene[d]				
Controls	Ever exposed	15,658 (5.5)	Ref	Ref
	Low	7806 (2.8)	Ref	Ref
	High	7852 (2.8)	Ref	Ref
ALL	Ever exposed	220 (5.5)	1.00 (0.87, 1.15)	0.99 (0.86, 1.14)
	Low	122 (3.0)	1.10 (0.92, 1.32)	1.10 (0.92, 1.32)
	High	98 (2.4)	0.89 (0.73, 1.10)	0.88 (0.72, 1.09)
AML	Ever exposed	38 (5.1)	0.96 (0.69, 1.34)	0.93 (0.67, 1.31)
	Low	19 (2.5)	0.94 (0.60, 1.49)	0.89 (0.56, 1.43)
	High	19 (2.5)	0.99 (0.62, 1.57)	0.98 (0.62, 1.56)
HL[e]	Ever exposed	21 (6.1)	0.69 (0.44, 1.07)	0.71 (0.45, 1.12)
NHL	Ever exposed	37 (6.0)	0.90 (0.64, 1.26)	0.97 (0.69, 1.38)
	Low	13 (2.1)	0.69 (0.40, 1.20)	0.70 (0.39, 1.24)
	High	24 (3.9)	1.07 (0.71, 1.63)	1.22 (0.80, 1.86)
CNS tumors (all)	Ever exposed	189 (5.9)	1.00 (0.86, 1.16)	1.09 (0.94, 1.27)
	Low	105 (3.3)	1.15 (0.95, 1.40)	1.24 (1.02, 1.51)
	High	84 (2.6)	0.86 (0.69, 1.07)	0.95 (0.76, 1.19)
Medulloblastoma	Ever exposed	23 (5.9)	1.05 (0.68, 1.60)	1.14 (0.74, 1.76)
	Low	13 (3.4)	1.20 (0.69, 2.09)	1.30 (0.74, 2.26)
	High	10 (2.6)	0.89 (0.47, 1.69)	0.99 (0.52, 1.88)
Glioma	Ever exposed	104 (5.4)	0.93 (0.76, 1.13)	1.01 (0.82, 1.24)
	Low	61 (3.2)	1.11 (0.86, 1.44)	1.20 (0.93, 1.56)
	High	43 (2.2)	0.74 (0.55, 1.01)	0.82 (0.60, 1.12)
Neuroblastoma	Ever exposed	38 (3.8)	0.83 (0.60, 1.16)	0.87 (0.62, 1.21)
	Low	20 (2.0)	0.80 (0.51, 1.25)	0.85 (0.55, 1.33)
	High	18 (1.8)	0.87 (0.54, 1.40)	0.89 (0.55, 1.45)
Retinoblastoma	Ever exposed	29 (5.8)	1.30 (0.89, 1.90)	1.27 (0.86, 1.86)
	Low	14 (2.8)	1.14 (0.67, 1.95)	1.12 (0.66, 1.91)
	High	15 (3.0)	1.50 (0.89, 2.55)	1.45 (0.85, 2.46)
Wilms tumor	Ever exposed	31 (4.1)	0.81 (0.56, 1.16)	0.84 (0.58, 1.21)
	Low	18 (2.4)	0.89 (0.56, 1.43)	0.93 (0.58, 1.48)
	High	13 (1.7)	0.71 (0.41, 1.24)	0.75 (0.43, 1.30)
Hepatoblastoma[e]	Ever exposed	10 (3.5)	0.78 (0.41, 1.47)	0.82 (0.43, 1.56)
Malignant bone tumors	Ever exposed	24 (5.4)	0.72 (0.47, 1.09)	0.76 (0.50, 1.15)
	Low	13 (2.9)	0.90 (0.52, 1.56)	0.94 (0.54, 1.64)
	High	11 (2.5)	0.58 (0.32, 1.06)	0.61 (0.33, 1.12)

Chemical and Cancer type	Exposure category	Exposed cases,[a] N (%)	Crude model, OR (95% CI)[b]	Adjusted model, OR (95% CI)[c]
Ewing's sarcoma[e]	Ever exposed	13 (8.6)	1.26 (0.71, 2.25)	1.33 (0.74, 2.39)
Rhabdomyosarcoma	Ever exposed	30 (6.9)	1.18 (0.81, 1.72)	1.23 (0.84, 1.81)
	Low	17 (3.9)	1.38 (0.85, 2.25)	1.44 (0.88, 2.35)
	High	13 (3.0)	0.98 (0.56, 1.72)	1.03 (0.59, 1.81)
Germ cell tumors	Ever exposed	39 (7.1)	1.15 (0.82, 1.60)	1.11 (0.79, 1.55)
	Low	15 (2.7)	0.94 (0.56, 1.57)	0.91 (0.55, 1.53)
	High	24 (4.3)	1.34 (0.88, 2.03)	1.28 (0.84, 1.96)

Abbreviation: ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CI: confidence interval; CNS tumors: central nervous system tumors; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; OR: odds ratio.

[a] Among children who have ever been exposed, participants were categorized into low and high exposure groups by the median.

[b] Adjusted for birth year, the matching variable.

[c] Adjusted for birth year, maternal age, race and ethnicity, source of payment for prenatal care, residence in rural/urban area, census tract SES-index.

[d] For tetrachloroethylene, the buffer size was 3 km distance.

[e] The results for low/high exposure were not reported because the number of exposed cases was less than 10.

Table 3

Associations between industrial 1,1,1-trichloroethane exposure during pregnancy and childhood cancers for births in CA between 1998 and 2016, using the quadratic decay model.

Chemical and Cancer type	Exposure category	Exposed cases,[a] N (%)	Crude model, OR (95% CI)[b]	Adjusted model, OR (95% CI)[c]
1,1,1-Trichloroethane[d]				
Controls	Ever exposed	4878 (1.7)	Ref	Ref
	Low	2441 (0.9)	Ref	Ref
	High	2437 (0.9)	Ref	Ref
ALL	Ever exposed	58 (1.4)	0.85 (0.65, 1.11)	0.83 (0.64, 1.09)
	Low	29 (0.7)	0.85 (0.59, 1.22)	0.86 (0.59, 1.24)
	High	29 (0.7)	0.86 (0.59, 1.24)	0.81 (0.55, 1.18)
AML[e]	Ever exposed	10 (1.3)	0.84 (0.45, 1.57)	0.84 (0.45, 1.58)
NHL[e]	Ever exposed	11 (1.8)	0.79 (0.44, 1.45)	0.89 (0.49, 1.63)
CNS tumors (all)	Ever exposed	60 (1.9)	0.99 (0.76, 1.28)	1.09 (0.84, 1.42)
	Low	33 (1.0)	1.11 (0.78, 1.56)	1.27 (0.90, 1.80)
	High	27 (0.8)	0.87 (0.59, 1.28)	0.94 (0.64, 1.37)
Glioma	Ever exposed	29 (1.5)	0.81 (0.56, 1.17)	0.91 (0.63, 1.32)
	Low	18 (0.9)	1.02 (0.64, 1.62)	1.19 (0.74, 1.89)
	High	11 (0.6)	0.61 (0.34, 1.10)	0.66 (0.36, 1.19)
Neuroblastoma[e]	Ever exposed	10 (1.0)	0.79 (0.42, 1.48)	0.86 (0.46, 1.61)
Rhabdomyosarcoma[e]	Ever exposed	15 (3.4)	1.86 (1.10, 3.14)	1.96 (1.16, 3.32)
Germ cell tumors[e]	Ever exposed	11 (2.0)	0.97 (0.53, 1.77)	0.94 (0.51, 1.72)

Abbreviation: ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CI: confidence interval; CNS tumors: central nervous system tumors; NHL: Non-Hodgkin lymphoma; OR: odds ratio.

[a] Among children who have ever been exposed, participants were categorized into low and high exposure groups by the median.

[b] Adjusted for birth year, the matching variable.

[c] Adjusted for birth year, maternal age, race and ethnicity, source of payment for prenatal care, residence in rural/urban area, census tract SES-index.

[d] For 1,1,1-trichloroethane, the buffer size was 3 km distance.

[e] The results for low/high exposure were not reported because the number of exposed cases was less than 10.

Table 4

Associations between industrial carbon disulfide exposure during pregnancy and childhood cancers for births in CA between 1998 and 2016, using the quadratic decay model.

Chemical and Cancer type	Exposure category	Exposed cases,[a] N (%)	Crude model, OR (95% CI)[b]	Adjusted model, OR (95% CI)[c]
Carbon disulfide[d] Controls	Ever exposed	7263 (2.6)	Ref	Ref
	Low	3631 (1.3)	Ref	Ref
	High	3632 (1.3)	Ref	Ref
ALL	Ever exposed	110 (2.7)	1.06 (0.88, 1.29)	1.04 (0.86, 1.27)
	Low	48 (1.2)	0.93 (0.70, 1.24)	0.88 (0.66, 1.18)
	High	62 (1.5)	1.20 (0.93, 1.54)	1.21 (0.93, 1.56)
AML[e]	Ever exposed	21 (2.8)	1.08 (0.70, 1.66)	1.08 (0.70, 1.67)
NHL[e]	Ever exposed	11 (1.8)	0.73 (0.40, 1.32)	0.77 (0.42, 1.39)
CNS tumors (all)	Ever exposed	91 (2.9)	1.14 (0.92, 1.40)	1.19 (0.96, 1.47)
	Low	48 (1.5)	1.18 (0.89, 1.58)	1.20 (0.90, 1.61)
	High	43 (1.3)	1.09 (0.80, 1.47)	1.17 (0.86, 1.58)
Ependymoma[e]	Ever exposed	11 (4.3)	1.70 (0.93, 3.11)	1.85 (1.01, 3.40)
Medulloblastoma[e]	Ever exposed	15 (3.9)	1.54 (0.92, 2.58)	1.63 (0.97, 2.74)
Glioma	Ever exposed	57 (3.0)	1.17 (0.90, 1.52)	1.25 (0.96, 1.63)
	Low	27 (1.4)	1.10 (0.75, 1.61)	1.15 (0.78, 1.68)
	High	30 (1.6)	1.24 (0.86, 1.78)	1.35 (0.94, 1.94)
Neuroblastoma[e]	Ever exposed	19 (1.9)	0.71 (0.45, 1.13)	0.71 (0.44, 1.13)
Retinoblastoma[e]	Ever exposed	17 (3.4)	1.29 (0.79, 2.09)	1.28 (0.79, 2.08)
Wilms tumor[e]	Ever exposed	18 (2.4)	0.89 (0.56, 1.42)	0.91 (0.57, 1.46)
Malignant bone tumors[e]	Ever exposed	10 (2.3)	0.95 (0.51, 1.78)	0.99 (0.53, 1.85)
Rhabdomyosarcoma[e]	Ever exposed	13 (3.0)	1.19 (0.69, 2.07)	1.23 (0.71, 2.14)
Germ cell tumors[e]	Ever exposed	13 (2.4)	0.95 (0.55, 1.64)	0.93 (0.53, 1.61)

Abbreviation: ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CI: confidence interval; CNS tumors: central nervous system tumors; NHL: Non-Hodgkin lymphoma; OR: odds ratio.

[a] Among children who have ever been exposed, participants were categorized into low and high exposure groups by the median.

[b] Adjusted for birth year, the matching variable.

[c] Adjusted for birth year, maternal age, race and ethnicity, source of payment for prenatal care, residence in rural/urban area, census tract SES-index.

[d] For carbon disulfide, the buffer size was 5 km distance.

[e] The results for low/high exposure were not reported because the number of exposed cases was less than 10.