HHS Public Access

Author manuscript

Int J Hyg Environ Health. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Int J Hyg Environ Health. 2017 October ; 220(7): 1133–1140. doi:10.1016/j.ijheh.2017.06.006.

Exposure to Ambient Dichloromethane in Pregnancy and Infancy from Industrial Sources and Childhood Cancers in California

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Abstract

Background—The incidence of childhood cancers has been increasing, and environmental exposure to air toxics has been suggested as a possible risk factor. This study aims to explore ambient exposure to dichloromethane (methylene chloride).

Methods—We frequency matched by birth year approximately 20 cancer-free controls identified from birth records to all childhood cancers ages 0–5 in the California Cancer Registry diagnosed from 1988–2012; i.e. 13,636 cases and a total of 270,673 controls. Information on industrial releases of dichloromethane within 3km of birth addresses was retrieved from mandatory industry reports to the EPA's Toxics Release Inventory (TRI). We derived exposure to dichloromethane within close vicinity of birth residences using several modeling techniques including unconditional logistic regression models with multiple buffer distances, inverse distance weighting, and quadratic decay models.

Results—We observed elevated risks for germ cell tumors [Odds Ratio (OR): 1.52, 95% Confidence Interval (CI) 1.11, 2.08], particularly teratomas (OR: 2.08, 95% CI 1.38–3.13), and possible increased risk for acute myeloid leukemias (AML) (OR: 1.29, 95% CI 0.93, 1.77). Risk estimates were similar in magnitude whether releases occurred in pregnancy or the child's first year of life.

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pregnancy Chemical compounds studied in this article: dichloromethane (PubChem CID: 6344)

Conclusion—Our findings suggest that exposure to industrial dichloromethane releases may be a risk factor for childhood germ cell tumors, teratomas, and possibly AML.

Keywords

Childhood cancer; dichloromethane; industrial release; ambient exposure

Introduction

Childhood cancers are the leading cause of death from disease among children less than 14 years of age in the United States (Ries, 1999). Incidence rates have been increasing and incidence in 2010 was 41% higher than it was in 1975 (Howlader, 2013). Still, not much is known about the causes of childhood cancers. Evidence is slowly growing for several possible causal associations. Ionizing radiation and prior chemotherapy have been shown to cause childhood cancers (Spector et al., 2015). In addition, males have a slightly higher risk of developing most childhood cancers. Older parental age and race/ethnicity also play a role in the development of malignancies in infancy with highest rates observed among whites (Spector et al., 2015).

Pregnancy and early life exposures are important in the study of childhood cancer etiology due to possible damage and toxicity during the sensitive period of organism development. Some studies of parental occupational exposures and childhood cancers found increased risk among children born to parents exposed to solvents, diesel exhaust, air pollution and paint during pregnancy (Ghosh et al., 2013; Greenop et al., 2014; Peters et al., 2013). There is also possible support for a role of environmental exposures including ambient air pollution and pesticides (Heck et al., 2013c; Ward et al., 2009; Zahm and Ward, 1998).

Dichloromethane (also called methylene chloride) is a solvent used in paint removers, adhesives, aerosols, pharmaceuticals, chemical processes, and metal cleaning. This chlorinated hydrocarbon has also been used in many household products including adhesive removers, paint thinners, and as a propellant in aerosols such as insect sprays and automotive products (NTP, 2011). Potential routes of human exposure to dichloromethane include inhalation, dermal contact, and ingestion (NTP, 1986). Dichloromethane is highly volatile and because its vapors are heavier than air it tends to stay close to the ground becoming an inhalation hazard. Worldwide, background levels in ambient air are reported at ~ 0.17 ug/m^3 while urban areas and hazardous waste sites may reach up to 43ug/m^3 (IARC, 1999). According to the Occupational Safety & Health Administration, the permissible exposure limit (PEL) is set at 86.8 mg/m^3 with an action level at 43.4 mg/m^3 calculated over as an eight-hour time-weighted average. If the PEL is exceeded, respiratory protection is mandatory while exceeding the action level signals that compliance activities such as monitoring and surveillance must be initiated (USDL, 2003). Dichloromethane has a half-life of 53–127 days in air and is broken down through photochemical reactions that generate hydroxyl radicals. Once inhaled, the body metabolizes dichloromethane fairly rapidly and releases its metabolites through exhalation and urine within 48 hours. However, physical activity or high body fat can lead to accumulation in body tissue, mainly in fat since physical activity increases the amount inhaled and fat stores dichloromethane. Dichloromethane

accumulated in fat is slowly released back into the bloodstream over a longer period of time compared to those with lower body fat. In a previous study, dichloromethane was found in 100% of the breast milk of eight lactating women living near an industrial facility; furthermore, a simulation study suggested that lactational transfer may occur in occupationally exposed mothers (Fisher et al., 1997; Pellizzari et al., 1982). In adults, dichloromethane can affect the respiratory, gastrointestinal, hepatic, and neurological systems, but research on possible health effects in children is scarce (ATSDR, 2000).

The International Agency for Research on Cancer (IARC) recently classified dichloromethane as a probable human carcinogen (Group 2A) based upon studies in mice which found increased incidence of hepatocellular and lung tumors. In humans, the most compelling evidence supports an association with cancers of the liver and biliary tract. (IARC, 1999, 2016). A recent review summarizing results from cohort and case-control studies reported increased risks of lung cancer and non-Hodgkin lymphoma as well as possible associations with brain, breast, and liver cancers (Cooper et al., 2011). Most of the studies included in this review examined adult cancers in occupationally exposed workers, who are exposed at much higher levels than measured in ambient air ($3 – 4000+mg/m^3$). Exposure levels in industrial settings in the US measurements ranged from 247 mg/m^3 to 1736 mg/m^3 in a study of factories located in Massachusetts (IARC, 1999; Roelofs and Ellenbecker, 2003). Two studies assessed childhood leukemia, one examining maternal occupational dichloromethane exposures in the 2 years before pregnancy and another measuring residential proximity to industrial sites (<2.5km) which released the chemical and exposed children in early childhood. These studies estimated 11%–65% increases in risk of all leukemia in children 0–14 and 0–9 years old, respectively (Garcia-Perez et al., 2015; Infante-Rivard et al., 2005). A third study in Texas focusing on CNS tumors and dichloromethane exposures, measured annual average ambient chlorinated solvents at the census-tract level using the EPA's 1999 Assessment System for Population Exposure Nationwide (ASPEN) model and reported associations with childhood medulloblastoma and primitive neuroectodermal tumors (PNET) among children <18 years of age (OR: 4.5) (Lupo et al., 2012).

After two chemical plant disasters in India and West Virginia in 1984 and 1985 respectively, Congress passed the Emergency Planning and Community Right-to-Know Act (EPCRA) to enable public access to data regarding chemical releases in their communities. As part of this act, the Toxic Release Inventory (TRI) program was created in 1986 to track and record industrial management of toxic chemicals. Currently, over 650 chemicals are reported through the TRI Program. The TRI reporting is mandated for facilities which are included in the TRI-covered North American Industry Classification System (NAICS), have 10 or more full-time employees, and the facility manufactures or imports, processes, or uses any EPCRA chemicals in quantities greater than the EPA established thresholds over the course of a calendar year (US EPA, 2015).

The purpose of the present study was to investigate the association between childhood cancers and exposures to dichloromethane releases from industrial plants, as reported to the TRI, near (≤3km) residences of pregnant women and infants living in California.

Methods

Cases and controls belong to an existing population-based study on childhood cancers, whose source population included all births in California from 1983–2011; that study has been described in detail elsewhere (Heck et al., 2013a). In brief, cases were collected from the California Cancer Registry (CCR) from among those diagnosed 1988–2013 with any cancer, younger than age 6, and born in California. Birth certificates were linked to cases using a probabilistic linkage program (LinkPlus, CDC) using first names, last names, dates of birth, and social security numbers when available. As a result, 89% of all cases were matched to a California birth certificate. Twenty controls for each case were randomly selected from California birth records and frequency-matched by year of birth to all cases. To be eligible, controls had to not appear in the CCR prior to the age of 6 in California. As this was a record-based study, we did not seek informed consent from individual subjects. The demographic and gestational characteristics of cases and controls have been previously reported (Abrahao et al., 2015; Hall et al., 2016; Heck et al., 2012; Heck et al., 2013b; Heck et al., 2014, 2015; Heck et al., 2013c; Shrestha et al., 2013).

Residential addresses were obtained from electronic birth certificates, which contain street addresses. If the exact address was unavailable, we calculated the most precise address information available, whether it was intersections, city centroids or zip code centroids. Prior to 1998, California birth certificates only included zip code information. As such, zip code centroids were used as the geocoded point of residence for estimating exposures.

Covariate information was obtained from California Cancer Registry records, birth certificates, and the year 2000 census data. Birth dates and gestational ages, as measured from date of last menstruation, were obtained from birth certificates. To identify control children who died of other causes, we obtained California death certificates and linked these to the participants. After exclusion of controls who died prior to age 6 (n = 1,895), children with improbable gestational lengths (<20 weeks; n = 131), children with missing or improbable birthweight (< 500g; n = 41), and children with an unclear/missing socioeconomic status information (n = 317), 13,636 cases and 270,673 controls remained for this study. The SES-index variable is a 5-level SES census-tract/block level measure 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). For those lacking exact addresses, zip code centroids were used to determine the SES-index.

Cancer types were classified according to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program International Classification of Childhood Cancer (ICCC) main and extended classification recodes. International Classification of Diseases for Oncology (ICD-O-3) codes were used in conjunction with ICCC codes to identify specific histologic subtypes. Here we report only on cancer subtypes with at least 10 exposed cases.

Exposure Assessment

Data on air releases of dichloromethane, in pounds per year, were obtained from the TRI database. Any amount of dichloromethane released by a TRI facility was considered in our analyses. Releases from individual sites ranged from 2.8 pounds to 1,016,106 pounds per year with a median of 5,562 pounds and a mean of 34,147.87 pounds. Using ArcGIS 10.2 (ESRI, Redlands), we mapped ambient air release data to the location of the site of release based on the latitude and longitude for each site provided by EPA. TRI classifies ambient air releases as “stack air” and “fugitive air” and these account for 85% of all releases in California. “Stack air” releases refer to gases created during mixing or heating of substances that are then processed and released through the smokestack, e.g. releases that are unable to be reclaimed or recaptured and escape to the external environment. “Fugitive air” releases refer to particles or gases created during processes such as cutting or molding where the air is not directly captured for processing. The resulting pollutants leak into the ambient environment through doors and windows of the building. A majority (~85%) of dichloromethane releases are into the air while water and land releases are fairly infrequent (~2% and ~12% respectively), thus, we chose to focus on ambient air releases only (IARC, 1999).

Since TRI data are reported annually, exposures were estimated using an average exposure over the course of the year, and then assigned to individuals based on timing of pregnancy in the year. This was accomplished by creating an average amount for the length of time exposed to a given year’s releases either during pregnancy or during the first year of life.

Based on recommendations from the literature (Conley, 2011), we implemented several models to estimate exposures: a) a buffer model; b) an inverse-distance weighting model; and c) a quadratic decay model. First, we drew buffers of different sizes around the industrial site and classified children inside a radius of 3, 5, 8 or 10km as exposed. We determined the smallest buffer size that still allowed for an adequate sample size; in final analyses we present the 3km distance as it allowed for adequate sample size for most cancer types. Using an inverse-distance weighting approach, we applied a decay function ($J_{ir} = 1/d_{ir}^2$) to an exposure total summed over multiple sites denoted by i and residences denoted by r, where J is the total exposure amount. The quadratic decay model uses a modified equation based on equation 1 from Cutter et al.(Cutter and Solecki, 1996) The following equation shows K_{ir} which 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). The threshold distance is based on the radius used in the buffer model.

$$K_{ir} = v_i \left(1.0 - \left((d_{ir})^2 / \left(T^2\right)\right)\right).$$

We determined straight line distance between residences of subjects and TRI sites using ArcGIS. For the exposures modeled based on inverse-distance weighting or the quadratic decay models, we utilized the pounds of air toxics released and distance to the sources. Exposures were assigned to individual’s residences by utilizing each of the three approaches. We assigned “ever/never” exposures based on birth addresses being within 3km of any industrial release of dichloromethane reported to the TRI or outside of the 3km

distance. To determine if higher exposures were relevant for disease risk, we also calculated the median exposure in controls and examined this in the inverse-distance weighted and quadratic decay models. Those with above median exposure were classified as “exposed” while those below the median, including non-exposed, were considered “unexposed.” The median value for the inverse-distance weighted model was 1,321 pounds while the median value for the quadratic decay model was 1,833 pounds. Analyses using the inverse-distance weighted and quadratic decay models both use all years of data and the entire study population.

Statistical Analyses

Unconditional logistic regression (SAS 9.3 (SAS, Cary, NC)), was performed with adjustment for birth year, the matching factor. Selection of additional covariates was based upon factors previously associated with childhood cancers in our data and possibly associated with dichloromethane exposure, and/or the criterion of a >10% change in effect estimate. Covariates we considered for inclusion in models included mother’s age (<20 years, 20–24 years, 25–29 years, 30–34 years, 35+ years), mother’s educational attainment (<8 years, 9–11 years, 12 years, 13–15 years, 16+ years), the socioeconomic (SES)-index variable, child’s sex, mother’s race, method of prenatal care payment (private insurance vs. Medi-Cal, other government source, self-pay, military), father’s race, and residence in an urban/rural environment, as defined from census tract information (ERS, 2016).

We also explored adjustment for traffic pollution, as measured by fine particulate matter ($PM_{2.5}$) which was calculated using a CAlifornia LINE Source Dispersion Model (CALINE4) as detailed previously (Heck et al., 2013c). Covariates included in the final models were birth year, SES, mother’s age, mother’s education, rural/urban status, and child’s sex.

We examined the difference in effect estimates across the 3 modeling methods. We found that results were similar across all models. We present only the results from the smallest buffer with sufficient sample size for exposed cases (3km).

Because exact address was only available starting from 1998, we additionally conducted sensitivity analyses restricting to those children born after 1997. Prior to 1998, only zip codes were available.

Results were fairly consistent across the models except when exposed case counts were relatively low, which is expected as small changes in counts can greatly impact effect estimates. Thus, we present results from only the 3km buffer model, which was the model that allowed for the largest sample size. We additionally examined dose-response, comparing never exposed (i.e. >3km distance from a emitting facility) to low exposed (below the median) and high exposure (above the median).

Results

Demographics are presented in Tables 1a and 1b. Mothers exposed to dichloromethane tended to be younger, less educated, of lower SES, and more often Black or Hispanic.

Compared to controls, germ cell tumors had higher percentages exposed, while ependymomas had fewer. Cases and controls were fairly similar in terms of most demographic factors (Supplemental Table 1a and 1b). Several of the cancer types were more common among male children, and cancer incidence also differed by maternal race/ethnicity for some types.

We observed a slight increase in germ cell cancers (OR: 1.52, 95% CI 1.11–2.08), particularly in teratomas (OR:2.08, 95% CI 1.38–3.13), in the 3km buffer exposure model; results were similar when we instead relied on the inverse-weighted and quadratic exposure assessment models, but the latter produced wider confidence intervals (Table 2). We estimated the strongest associations for teratomas with this cancer being mostly responsible for the elevated odds ratio for all germ cell tumors (OR: 2.08, 95% CI 1.38–3.13). Effect estimates were also elevated for AML with stronger associations found for exposures in the first year of life (OR: 1.29, 95% CI 0.93–1.77). The negative association between dichloromethane and neuroblastoma disappeared when we limited the analysis to children for whom we had exact addresses, i.e. the association crossed the null (OR: 1.11, 95% CI 0.74–1.68).

Results from the inverse-distance weighted and quadratic decay models are presented in Table 3. In these models, we found similar elevated odds ratios with AML and teratomas (Table 3) during pregnancy. In sensitivity analyses (Supplemental Table 2) we saw slightly increased odds ratios in two cancers with sufficient sample size after restriction to the years for which we had exact home address; leukemias (all types; OR:1.08, 95% CI 0.88, 1.32) and ALL (OR:1.12, 95% CI 0.89, 1.39).

The dose-response analysis is shown in table 4. Risk for AML was highest in the high exposure group, while for teratomas, results were elevated in both low and high exposed groups.

Discussion

We observed positive effects for germ cell tumors, specifically teratomas, and possibly ALL and AML in children under age 6 with exposures to ambient levels of industrial dichloromethane pollution in pregnant women and infants living in close proximity to dichloromethane releasing facilities in California. Ambient air levels of dichloromethane in California are comparable to levels elsewhere, as the median and maximum monitored ambient concentrations in California in 1999 were 1.735 and 16.6 ug/m^3 (CA EPA, 2001); while worldwide background levels in ambient air have been ranging from 0.17 – 43 ug/m^3 (IARC, 1999). When TRI reporting began in 1987, 130 facilities in 16 CA counties reported over 6 million pounds of air releases for dichloromethane that year. The number of facilities declined steadily over the next decade to 37 facilities in 12 counties releasing approximately 1 million pounds in 1997 and this has continued to decline since. However, the South Coast Air Quality Management District, which monitors air toxics in the South Coast Air Basin (SCAB) including Orange county and the non-desert regions of Los Angeles County, San Bernardino County, and Riverside County, detected increases in ambient dichloromethane from 2009–2012, with average levels increasing from 0.7–1.0 ug/m^3 to 4.9–8.3 ug/m^3 due to

recent spikes of high exposure in Rubidoux, a city in Los Angeles County (Wallerstein, 2015).

In sensitivity analyses, we restricted to the years with exact addresses to reduce misclassification error, and found that estimates were stable across the three models. Our sensitivity analyses lend support to the results of two previous studies that examined maternal occupational dichloromethane exposures and reported elevated odds of both childhood leukemias (all types) and ALL specifically (OR: 1.65, 95% CI 1.11–2.45, OR: 1.34, 95% CI 0.54–3.34) (Garcia-Perez et al., 2015; Infante-Rivard et al., 2005). In the Infante-Rivard paper, exposures were assessed based on maternal occupation coded using Canadian industrial titles and job titles to determine exposures to specific solvents, thus exposures were possibly elevated compared to the ambient exposures in our study. Our analyses using exact addresses (1998+) only found slightly elevated point estimates, with wide confidence intervals, for childhood leukemia (all types) and ALL.

The effect estimates were similar for exposures in pregnancy and first year of life exposures, but TRI reports are collected annually and thus exposure estimates for these two periods of interest frequently overlapped especially if the mother and child remained at the same addresses and the facility did not change operations. Thus, our ability to determine the most relevant time period for carcinogenicity of dichloromethane exposure was limited.

To the best of our knowledge, this is the first study to report an association between dichloromethane and germ cell tumors. Previous studies have shown that prenatal and early life exposures play a role in germ cell tumor carcinogenesis (Chen et al., 2005; Moller, 1997). Type 1 germ cell tumors consist of teratomas and yolk sac tumors that are found in neonates and children <5 years of age and most often are located in the testes, ovaries, retroperitoneum, in the hypophyseal region of the brain, and in the head and neck regions. The origins of these type 1 germ cell tumors have been traced to early primordial germ cells based on a partially erased biparental pattern of genomic imprinting (Bussey et al., 2001; Neumann et al., 2011; Oosterhuis and Looijenga, 2005; Schneider et al., 2001). Based on these findings, we hypothesize that the association seen in germ cell tumors with dichloromethane exposure could be due to effects of dichloromethane metabolites on differentiation and migration of the early primordial germ cells during neonatal development.

The two primary mechanistic pathways for dichloromethane transformation involve *CYP2E1* dependent oxidative metabolism that yields carbon monoxide, and glutathione S-transferase theta 1 (*GSTT1*) that yields carbon dioxide. The *CYP2E1* route of degradation saturates at fairly low levels and CO levels alone have not been sufficiently linked to genotoxicity. However, at larger concentrations of dichloromethane, the *GSTT1*-based mechanism creates S-haloalkylglutathione and formaldehyde as intermediates which are both more toxic than the parent compound (Olvera-Bello et al., 2010). These increases, especially in formaldehyde, have been linked to carcinogenic potential (Hu et al., 2006). Since dichloromethane is released from industrial facilities, we also found that 1,1,1-trichloroethane was co-released from approximately one-third of the sites. The effects of dichloromethane on the cancers we observed may be in part due to exposure to 1,1,1-

trichloroethane, though it is a less toxic substance. One study reported maternal occupational exposure to, 1,1-trichloroethane was related to increased risk of leukemia in offspring (Infante-Rivard et al., 2005).

One limitation of this study is that possible residential mobility of mothers during and shortly after pregnancy would introduce exposure misclassification if mothers' addresses at child's birth are different from their actual residences earlier in the pregnancy or later in the child's 1st year of life. Previous studies showed that changes in residence between birth and diagnosis for leukemia did not affect the type of residence (urban/rural) for most children (<20% change) and when families move they typically stay in the same municipality (~62%) (Fell et al., 2004; Urayama et al., 2009). There is a possibility of differential exposure misclassification if case mothers moved more frequently than control mothers. The direction of bias is difficult to ascertain as case mothers may have moved into areas or out of areas of exposure. The resulting differential exposure misclassification could bias the associations away or toward the null. However, differential exposure misclassification is unlikely prior to diagnosis in cases and controls. risk factors previously associated with higher mobility are low SES, lower maternal age, unmarried status (Bell and Belanger, 2012; Fell et al., 2004). We adjusted for SES and in sensitivity analyses, for maternal age. Therefore, we expect non-differential exposure misclassification which would likely bias our estimates toward the null.

One of the major strengths of this study is the large sample size. Using the California Cancer Registry and California birth certificates, we are able to examine specific childhood cancer subtypes. In addition, this is a registry-based study and therefore, recall bias and selective study participation are not a concern with regards to exposure assessment. Also, the three models generally found comparable results.

In conclusion, our study presents some evidence that dichloromethane releases from industrial facilities may play a role for several childhood cancers including germ cell tumors and teratomas, and possibly AML. The findings for leukemias supports the results of previous studies (Garcia-Perez et al., 2015; Infante-Rivard et al., 2005).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the US National Institutes of Health (grants R21ES018960 and R21ES019986). Dr. Cockburn was supported in part by the National Cancer Institute's Surveillance, Epidemiology and End Results Program (contract HHSN261201000140C, Cancer Prevention Institute of California; contract HHSN261201000035C, University of Southern California; and contract HHSN261201000034C, Public Health Institute) and the Centers for Disease Control and Prevention's National Program of Cancer Registries (under U58DP003862-01, California Department of Public Health). Mr. Park was supported by the Iris Cantor-UCLA Women's Health Center Tarlow Eisner Moss Research Fund and the David Lucile Packard Foundation and the UCLA Career Development Program in Population-Based Cancer Prevention and Control Research (National Cancer Institute, R25CA087949).

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Table 1a

Dichloromethane exposure patterns in relation to demographic characteristics

	Ever Exposed*	Never Exposed
Total N = 284,309	25,200 (8.9%)	259,109 (91.1%)
Child's Sex		
Male	12,830 (8.8%)	132,872 (91.2%)
Female	12,370 (8.9%)	126,237 (91.1%)
Maternal age		
<20	2,954 (9.9%)	26,931 (90.1%)
20–24	6,549 (9.6%)	61,847 (90.4%)
25–29	7,315 (9.3%)	71,483 (90.7%)
30–34	5,504 (8.3%)	60,911 (91.7%)
35+	2,868 (7.0%)	37,895 (93.0%)
Missing	10	42
Maternal education (1989+)		
< 8 years	4,196 (13.7%)	26,515 (86.3%)
9–11 years	4,594 (10.2%)	40,261 (89.8%)
12 years	5,774 (8.3%)	63,520 (91.7%)
13–15 years	3,456 (7.0%)	46,136 (93.0%)
16+	2,906 (5.9%)	46,703 (94.1%)
Missing	195	4,451
Neighborhood SES-Index Variable		
1 (lowest)	8,520 (12.0%)	62,455 (88.0%)
2	6,949 (10.1%)	62,146 (89.9%)
3	4,280 (6.8%)	58,743 (93.2%)
4	3,084 (6.9%)	41,891 (93.1%)
5 (highest)	2,367 (6.5%)	33,874 (93.5%)
Method of Payment for Prenatal Care (1989+)		
Private, HMO, Blue Cross, Blue Shield	11,052 (9.0%)	111,735 (91.0%)
Medi-Cal, Government, Self-pay, Military	9,841 (8.0%)	113,558 (92.0%)
Missing	228	2,546
Mother's Race		
White Non-Hispanic	5,772 (5.8%)	94,070 (94.2%)
Hispanic	14,930 (11.4%)	115,536 (88.6%)
Black	1,793 (9.6%)	16,919 (90.4%)
Other/refused	2,705 (7.7%)	32,584 (92.3%)
Father's Race		
White Non-Hispanic	5,537 (6.3%)	81,967 (93.7%)
Hispanic	14,445 (11.7%)	109,394 (88.3%)
Black	1,894 (10.1%)	16,945 (89.9%)
Other/refused	3,324 (6.2%)	50,803 (93.8%)
Urban/Rural		

	Ever Exposed*	Never Exposed
Metropolitan	25,200 (9.7%)	233,856 (90.3%)
Micropolitan/Small Town	0 (0%)	11,987 (100%)
Rural	0 (0%)	13,266 (100%)

* Children and pregnant women living within 3km of dichloromethane releases

Table 1b

Dichloromethane exposures at 3km and childhood cancers

	ICCC/ICD-O-3** Codes	Ever Exposed*	Never Exposed
Hematopoietic cancers	011–015, 021–025	559 (9.8%)	5162 (90.2%)
Leukemias	011–015	492 (9.6%)	4608 (90.4%)
ALL	011	399 (9.7%)	3722 (90.3%)
AML	012	72 (9.7%)	668 (90.3%)
Lymphomas	021–025	67 (10.8%)	554 (89.2%)
Non-Hodgkin's Lymphoma	022–023	16 (9.5%)	152 (90.5%)
CNS tumors	031–037	218 (9.2%)	2162 (90.8%)
Ependymoma	031	22 (7.7%)	264 (92.3%)
Astrocytoma	032	83 (8.3%)	918 (91.7%)
Neuroblastoma	041	106 (7.7%)	1275 (92.3%)
Retinoblastoma	050	68 (9.2%)	675 (90.9%)
Unilateral RB	050	46 (9.0%)	467 (91.0%)
Bilateral RB	050	22 (9.9%)	201 (90.1%)
Wilms tumor	061	92 (8.7%)	965 (91.3%)
Hepatoblastoma	071	28 (8.2%)	314 (91.8%)
Soft Tissue sarcomas	091–095	67 (9.5%)	639 (90.5%)
Germ Cell tumors	101–105	61 (13.5%)	388 (86.5%)
Yolk Sac tumors	101–105, **9071	22 (12.2%)	159 (87.9%)
Teratomas	101–105, **9080	34 (16.4%)	171 (83.6%)
Controls		23,956 (8.9%)	246,717 (91.1%)

*Children and pregnant women living within 3km of dichloromethane releases

**ICD-O-3 Code

Table 2

Associations of dichloromethane exposure and childhood cancers within a 3km buffer between residences and releasing facilities during pregnancy and first year of life for births in CA between 1983–2011

	Pregnancy			First Year of Life		
Cancer	**Cases (n)** ***	**OR***	**OR****	**Cases (n)** ***	**OR***	**OR****
Hematopoietic cancers	456	1.03	0.99 (0.90, 1.10)	405	1.03	1.01 (0.90, 1.12)
Leukemias	408	1.02	0.99 (0.89, 1.10)	367	1.03	1.01 (0.90, 1.13)
ALL	337	1.00	0.97 (0.86, 1.09)	313	1.00	0.98 (0.87, 1.11)
AML	57	1.18	1.15 (0.86, 1.52)	45	1.27	1.29 (0.93, 1.77)
Lymphomas	48	1.11	1.01 (0.74, 1.37)	38	1.01	0.96 (0.68, 1.35)
Non-Hodgkin's Lymphoma	11	0.95	0.91 (0.48, 1.73)	9	0.77	NA
CNS tumors	182	0.99	1.06 (0.91, 1.25)	136	0.89	0.95 (0.79, 1.14)
Ependymoma	17	0.92	0.93 (0.56, 1.54)	10	0.69	0.67 (0.35, 1.29)
Astrocytoma	72	0.87	0.95 (0.74, 1.22)	57	0.86	0.89 (0.67, 1.18)
Neuroblastoma	92	0.88	0.92 (0.74, 1.14)	45	0.71	0.75 (0.55, 1.02)
Retinoblastoma	60	1.12	1.04 (0.79, 1.37)	37	1.13	1.11 (0.78, 1.58)
Unilateral RB	40	1.04	0.98 (0.70, 1.38)	32	1.11	1.14 (0.78, 1.66)
Bilateral RB	20	1.32	1.17 (0.72, 1.89)	5	1.21	NA
Wilms tumor	67	0.94	0.88 (0.68, 1.14)	47	0.85	0.74 (0.55, 1.00)
Hepatoblastoma	24	1.13	1.17 (0.76, 1.80)	15	1.05	1.28 (0.74, 2.22)
Soft tissue sarcomas	57	1.07	1.16 (0.88, 1.55)	35	0.83	0.92 (0.64, 1.31)
Germ Cell tumors	50	1.69	1.52 (1.11, 2.08)	21	1.58	1.41 (0.87, 2.27)
Yolk Sac tumors	16	1.41	1.15 (0.67, 1.98)	9	1.24	NA
Teratomas	31	2.23	2.08 (1.38, 3.13)	11	4.54	6.07 (2.69, 13.66)

*Adjusted for matching factor only (birth year)

**Adjusted for birth year, SES, mother's age, mother's education, rural/urban status, and child's sex

***Those with missing covariate information were not included in this analysis

Table 3

Associations of dichloromethane exposures and childhood cancers within a 3km buffer between residences and releasing facilities for births in CA between 1983–2011 using the inverse-distance weighting and quadratic decay models in pregnancy

	Inverse-distance weighting			Quadratic decay		
Cancer	**Cases (n)**	**OR***	**OR****	**Cases (n)**	**OR***	**OR****
Hematopoietic cancers	223	1.03	0.99 (0.86, 1.14)	237	1.09	1.07 (0.93, 1.23)
Leukemias	194	1.00	0.96 (0.83, 1.11)	209	1.08	1.05 (0.91, 1.22)
ALL	153	0.93	0.88 (0.74, 1.04)	166	1.00	0.97 (0.83, 1.14)
AML	33	1.46	1.47 (1.02, 2.12)	36	1.61	1.64 (1.15, 2.32)
Lymphomas	29	1.25	1.27 (0.86, 1.88)	28	1.21	1.24 (0.84, 1.84)
Non-Hodgkin's Lymphoma	8	1.42	NA	8	1.55	NA
CNS tumors	89	0.99	1.08 (0.87, 1.35)	88	0.99	1.08 (0.87, 1.35)
Ependymoma	8	0.77	0.97 (0.47, 2.00)	11	1.05	1.38 (0.74, 2.58)
Astrocytoma	37	0.91	1.02 (0.72, 1.43)	36	0.91	0.99 (0.70, 1.40)
Neuroblastoma	45	0.89	0.96 (0.71, 1.30)	40	0.82	0.85 (0.62, 1.18)
Retinoblastoma	28	1.18	1.02 (0.69, 1.51)	25	1.07	0.91 (0.60, 1.37)
Unilateral RB	18	1.05	0.92 (0.57, 1.50)	16	0.95	0.82 (0.49, 1.37)
Bilateral RB	10	1.52	1.24 (0.64, 2.38)	9	1.38	NA
Wilms tumor	26	0.88	0.72 (0.48, 1.07)	25	0.84	0.69 (0.46, 1.04)
Hepatoblastoma	10	1.22	1.11 (0.58, 2.13)	10	1.21	1.12 (0.58, 2.14)
Soft Tissue sarcomas	26	1.04	1.11 (0.74, 1.67)	22	0.91	0.93 (0.60, 1.44)
Germ Cell tumors	22	1.44	1.34 (0.86, 2.09)	19	1.26	1.14 (0.71, 1.83)
Yolk Sac tumors	5	1.10	NA	4	0.97	NA
Teratomas	15	2.01	1.93 (1.11, 3.36)	14	1.86	1.78 (1.01, 3.15)

*Adjusted for matching factor only (birth year)

**Adjusted for birth year, SES, mother's age, mother's education, rural/urban status, and child's sex

Table 4

Associations of dichloromethane exposures and childhood cancers within a 3km buffer between residences and releasing facilities for births in CA between 1983–2011 using the inverse-distance weighting and quadratic decay models in pregnancy using high and low exposure versus no exposure

	Inverse-distance weighting			Quadratic decay		
Cancer	**Cases (n)**	**OR***	**OR****	**Cases (n)**	**OR***	**OR****
Hematopoietic cancers						
No exposure		1.00	Ref		1.00	Ref
Low	233	1.03	0.99 (0.87, 1.14)	219	0.97	0.93 (0.81, 1.06)
High	223	1.03	0.99 (0.86, 1.14)	237	1.09	1.06 (0.93, 1.22)
Leukemias						
No exposure		1.00	Ref		1.00	Ref
Low	214	1.04	1.02 (0.88, 1.17)	199	0.97	0.94 (0.81, 1.09)
High	194	1.00	0.96 (0.83, 1.12)	209	1.08	1.05 (0.91, 1.21)
ALL						
No exposure		1.00	Ref		1.00	Ref
Low	184	1.06	1.05 (0.90, 1.22)	171	0.99	0.97 (0.83, 1.13)
High	153	0.93	0.88 (0.75, 1.04)	166	1.00	0.97 (0.82, 1.14)
AML						
No exposure		1.00	Ref		1.00	Ref
Low	24	0.93	0.90 (0.59, 1.35)	21	0.81	0.78 (0.50, 1.21)
High	33	1.46	1.46 (1.01, 2.11)	36	1.59	1.61 (1.13, 2.28)
Lymphomas						
No exposure		1.00	Ref		1.00	Ref
Low	19	0.97	0.78 (0.49, 1.24)	20	1.00	0.81 (0.52, 1.28)
High	29	1.24	1.25 (0.85, 1.85)	28	1.21	1.22 (0.82, 1.81)
Non-Hodgkin's Lymphoma						
No exposure		1.00	Ref		1.00	Ref
Low	3	0.50	N/A	3	0.38	N/A
High	8	1.37	N/A	8	1.49	N/A
CNS tumors						
No exposure		1.00	Ref		1.00	Ref

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Cancer	Inverse-distance weighting			Quadratic decay		
	Cases (n)	OR*	OR**	Cases (n)	OR*	OR**
Low	93	0.99	1.04 (0.84, 1.29)	94	1.00	1.05 (0.85, 1.29)
High	89	0.99	1.09 (0.87, 1.36)	88	0.99	1.08 (0.87, 1.35)
Ependymoma						
No exposure		1.00	Ref		1.00	Ref
Low	9	1.06	N/A	6	0.82	N/A
High	8	0.78	N/A	11	1.04	1.34 (0.71, 2.50)
Astrocytoma						
No exposure		1.00	Ref		1.00	Ref
Low	35	0.84	0.89 (0.64, 1.26)	36	0.84	0.91 (0.65, 1.28)
High	37	0.90	1.01 (0.72, 1.41)	36	0.90	0.99 (0.70, 1.39)
Neuroblastoma						
No exposure		1.00	Ref		1.00	Ref
Low	47	0.87	0.89 (0.66, 1.19)	52	0.94	0.98 (0.74, 1.29)
High	45	0.89	0.95 (0.70, 1.29)	40	0.82	0.85 (0.61, 1.17)
Retinoblastoma						
No exposure		1.00	Ref		1.00	Ref
Low	32	1.05	1.05 (0.73, 1.51)	35	1.15	1.14 (0.81, 1.62)
High	28	1.18	1.03 (0.69, 1.52)	25	1.08	0.92 (0.61, 1.39)
Unilateral RB						
No exposure		1.00	Ref		1.00	Ref
Low	22	1.03	1.03 (0.67, 1.60)	24	1.12	1.12 (0.74, 1.70)
High	18	1.05	0.93 (0.57, 1.51)	16	0.96	0.83 (0.50, 1.38)
Bilateral RB						
No exposure		1.00	Ref		1.00	Ref
Low	10	1.13	1.10 (0.58, 2.10)	11	1.25	1.21 (0.65, 2.24)
High	10	1.53	1.25 (0.64, 2.41)	9	1.40	N/A
Wilms tumor						
No exposure		1.00	Ref		1.00	Ref
Low	41	0.99	1.03 (0.75, 1.41)	42	1.03	1.05 (0.76, 1.44)
High	26	0.88	0.72 (0.48, 1.07)	25	0.84	0.69 (0.46, 1.04)

	Inverse-distance weighting			Quadratic decay		
Cancer	**Cases (n)**	**OR***	**OR****	**Cases (n)**	**OR***	**OR****
Hepatoblastoma						
No exposure		1.00	Ref		1.00	Ref
Low	14	1.05	1.19 (0.69, 2.05)	14	1.05	1.19 (0.69, 2.05)
High	10	1.22	1.13 (0.59, 2.16)	10	1.22	1.13 (0.59, 2.17)
Soft Tissue sarcomas						
No exposure		1.00	Ref		1.00	Ref
Low	31	1.09	1.19 (0.83, 1.72)	35	1.21	1.33 (0.94, 1.89)
High	26	1.05	1.13 (0.75, 1.70)	22	0.92	0.96 (0.62, 1.49)
Germ Cell tumors						
No exposure		1.00	Ref		1.00	Ref
Low	28	1.85	1.62 (1.09, 2.40)	31	2.01	1.78 (1.22, 2.60)
High	22	1.51	1.41 (0.90, 2.21)	19	1.34	1.22 (0.75, 1.96)
Yolk Sac tumors						
No exposure		1.00	Ref		1.00	Ref
Low	11	1.67	1.50 (0.80, 2.80)	12	1.79	1.63 (0.89, 2.98)
High	5	1.14	N/A	4	1.01	N/A
Teratomas						
No exposure		1.00	Ref		1.00	Ref
Low	16	2.29	2.06 (1.22, 3.48)	17	2.42	2.18 (1.30, 3.64)
High	15	2.17	2.10 (1.20, 3.67)	14	2.02	1.96 (1.10, 3.47)

*Adjusted for matching factor only (birth year)

**Adjusted for birth year, SES, mother's age, mother's education, rural/urban status, and child's sex