International Journal of Hygiene and Environmental Health 220 (2017) 1133–1140

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Exposure to ambient dichloromethane in pregnancy and infancy from industrial sources and childhood cancers in California

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ARTICLE INFO

Article history:
Received 13 February 2017
Received in revised form 6 June 2017
Accepted 21 June 2017

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

Keywords:
Childhood cancer
Dichloromethane
Industrial release
Ambient exposure
Pregnancy

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 to 2012; i.e. 13,636 cases and a total of 270,673 controls. Information on industrial releases of dichloromethane within 3 km 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: 1.64, 95% CI 1.15–2.32 in the quadratic decay model). Risk estimates were similar in magnitude whether releases occurred in pregnancy or the child's first year of life.
Conclusion: Our findings suggest that exposure to industrial dichloromethane releases may be a risk factor for childhood germ cell tumors, teratomas, and possibly AML.

1. Introduction

Childhood cancers are the leading cause of death from disease among children less than 14 years of age in the United States (Ries et al., 1999). Incidence rates have been increasing and incidence in 2010 was 41% higher than it was in 1975 (Howlader et al., 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

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http://dx.doi.org/10.1016/j.ijheh.2017.06.006
1438-4639/

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 43 ug/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 h. 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 (<2.5 km) 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 (≤3 km) residences of pregnant women and infants living in California.

2. Methods

Cases and controls belong to an existing population-based study on childhood cancers, whose source population included all births in California from 1983 to 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 (Hall et al., 2016; Heck et al., 2012, 2013b, 2014, 2015, 2013c; Marcotte et al., 2014; 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 = 1895), children with improbable gestational lengths (<20 weeks; n = 131), children with missing or improbable birthweight (<500 g; 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.

2.1. Exposure assessment

Data on air releases of dichloromethane, in pounds per year, were obtained from the TRI database. Any amount of