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Prenatal and Early Life Exposures and the Risk of Childhood Cancers: An Examination of Ambient Pesticides, Dichloromethane, and Survivor Bias

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Prenatal and Early Life Exposures and the Risk of Childhood Cancers: An Examination of Ambient Pesticides, Dichloromethane, and Survivor Bias

A dissertation submitted in partial satisfaction

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Doctor of Philosophy in Epidemiology

by

Andrew Park

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ABSTRACT OF THE DISSERTATION

Prenatal and Early Life Exposures and the Risk of Childhood Cancers: An Examination of Ambient Pesticides, Dichloromethane, and Survivor Bias

by

Andrew Park

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2017

Professor Beate R. Ritz, Chair

The etiology of childhood cancer remains unexplained in a majority of cases. Cancer is the leading cause of death by disease in children in the US. Ionizing radiation and certain genetic abnormalities have been well-established as risk factors for childhood cancers. In addition, several environmental factors including pesticides and air toxics have been implicated in previous studies. Utilizing a statewide population-based case-control study in California, we examined the effects of ambient agricultural pesticides and industrial dichloromethane releases on childhood cancers. Cases less than age six were obtained from the California Cancer Registry diagnosed between 1988-2012 and linked to birth certificates. Controls were then randomly selected from birth certificates and frequency matched by year of birth. Pesticide exposure estimates were obtained using a sophisticated geographic information system (GIS) based program. The GIS-based Residential Ambient Pesticide Estimation System (GRAPES) combined

agricultural Pesticide Use Reports (PUR), Land Use Surveys (LUR), and the Public Land Survey System (PLSS) to create estimates based on distance to the child's residence at birth. We analyzed the effects of individual pesticides on childhood acute lymphoblastic leukemia (ALL) using semi-Bayesian hierarchical logistic modeling. Our findings suggest an increased risk of childhood ALL among those exposed to any carcinogenic pesticides, or 2,6-dinitroanilines, anilides, ureas classes of pesticides, and specifically diuron, phosmet, kresoxim-methyl, and propanil.

Additionally, we investigated the effects of dichloromethane exposure among children born to mothers living in proximity to industrial facilities. Using the Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI), we estimated exposure to dichloromethane based on distance from the residence to the facility using three exposure modeling methods. We observed elevated risks in germ cell tumors, particularly teratomas, and a possible increase in risk for ALL and acute myeloid leukemias (AML).

Lastly, we explored a possible explanation for the null and often inverse associations seen in maternal smoking and childhood ALL. We simulated populations based on priors obtained from the Danish National Registries and estimated the effect of a possible survivor bias, also known as 'live-birth bias,' to determine the strength of the bias. Based on our results, it is unlikely that this survivor bias can solely explain the inconsistent associations seen with maternal smoking.

The dissertation of Andrew Park is approved.

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2017

DEDICATION

This dissertation is dedicated to my parents, whose sacrifice have afforded me the ability to complete this work. Also, to my brother and his family, my friends, and my teachers.

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASPEN	Assessment System for Population Exposure Nationwide
CALINE4	CAlifornia LINE Source Dispersion Model
CCR	California Cancer Registry
CDPR	California Department of Pesticide Regulation
CML	Chronic myeloid leukemia
CNS	Central nervous system
CPD	Cigarettes per day
DAG	Directed acyclic graph
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
GIS	Geographic Information System
HLM	Hierarchical logistic modeling
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
ICD-O-3	International Classification of Diseases for Oncology

NAICS	North American Industry Classification System
OR	Odds Ratio
PAN	Pesticide Action Network
PEL	Permissible exposure limit
PLSS	Public Land Survey System
PTSD	Post-traumatic stress disorder
PUR	Pesticide Use Reports
RUCA	Rural-urban commuting area
SCAB	South Coast Air Basin
SEER	Surveillance, Epidemiology and End Results
SES	Socio-economic status
TCR	T-cell antigen receptor
TRI	Toxics Release Inventory

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Chapter 1. Introduction

1.1 Childhood Cancer

Childhood cancers are the leading cause of death from disease among children less than 14 years of age in the United States.[1] According to the National Cancer Institute there will be an estimated 10,270 new cases and 1,190 deaths to occur among children (≤14 years) in 2017.[2] Childhood cancers total approximately 1% of all new cancer diagnoses in the US.[3] Acute lymphoblastic leukemia (ALL) (26%), brain and central nervous system (CNS) cancer (21%), and neuroblastoma (7%) are the most common childhood cancers.[3] Statistics show that the 5-year survival rates as an aggregate have been improving steadily over the past 20 years (up from 60% in 1975-79 to 82% in 2005). However, incidence rates have also been increasing, as incidence in 2010 was 41% higher than it was in 1975.[4]

Burden of Childhood Cancers

For all childhood cancers, 5-year relative survival rates for the years 2003-2009 were reported at 81.8% for children aged between 0-14. As of January 1, 2010, there were 379,112 childhood cancer survivors between 0-19 years of age living in the US.[4]

With the high survival rates, childhood cancer survivors face a lifetime of late effects. The increased risk of development of a second primary cancer is one of the most worrisome.[5] Cancer survivors are vulnerable to many cancer-related sequelae that increase their morbidity and mortality. These sequelae, labeled as "late effects" when persisting or developing 5 years after the first diagnosis can affect growth and development, fertility and reproduction, vital organ

function, and carcinogenesis. These late effects can be especially detrimental to younger patients in their growth and development since it is during critical growth periods.[6] Previous studies have found 6 to 11-fold higher risks of a new cancer among childhood cancer survivors compared to the general population. This may be due to underlying genetic predisposition or effects of radiation and chemotherapies in young patients. Excesses of breast, thyroid, CNS, bone and stomach cancers have been associated with radiotherapy during childhood.[7, 8] In addition, survivors tend to have higher risks of emotional problems and psychosocial problems such as post-traumatic stress disorder (PTSD).[9-11] Survivors also may suffer from delayed social development and chronic psychological and cognitive impairments that decrease quality of life in all childhood cancers after treatment.[12]

Childhood cancers also negatively affect the parents or caregivers. Studies reported on the effects of childhood cancers on parents in terms of financial costs, as well as psychological and social distress. A recent study found that rates of serious, debilitating psychological distress (16%) were higher among parents of childhood cancer patients compared to the general population (2-3%).[13] A review of financial costs found that treatment costs ranged from 0.2% to >200% of family income.[14] These costs include indirect costs such as lost earnings due to having to quit a job, reduced productivity, and unperformed tasks at home, such as laundry.[14]

Acute Lymphoblastic Leukemia

Leukemia, constituting 40% of all childhood cancers, is the most frequent of the major types of childhood malignancies. Acute lymphoblastic leukemia (ALL) alone accounts for 25% of all childhood malignancies in children younger than 15 years of age.[4, 15] It is the most common

subtype of childhood leukemia and accounts for approximately 78% of all childhood leukemia cases. Even so, it is a rare disease with an incidence rate of approximately 38 cases per million per year in the United States, with a peak between ages 2-5 and with highest incidence among Hispanics.[16] Few risk factors have been established aside from ionizing radiation and specific genetic abnormalities.

A number of studies have investigated potential risk factors for ALL. Paternal smoking during preconception, pregnancy and after birth have been associated with ALL. In a recent review of 18 epidemiological studies, paternal smoking was found to be a risk factor in all exposure windows (lifetime, preconception, during pregnancy, after birth) (OR = 1.11, 95%CI [1.05-1.18] for lifetime ever smokers, OR = 1.24 95%CI [1.07-1.43] during pregnancy). It seems counterintuitive though that maternal smoking has not been associated with ALL.[17] Other suspected risk factors for ALL include Down syndrome, topoisomerase inhibitors during pregnancy, such as chemotherapy drugs, benzene metabolites, and pesticides, decreased folate levels before and during pregnancy, infections, and extremely low-frequency magnetic fields.[18-21]

Currently, there exist three major hypotheses related to childhood ALL. The first is the two-hit hypothesis initially put forth by Knudson upon researching retinoblastoma, which predicts that two or more genetic mutations or events must occur for the development of cancer.[22, 23] If this is also true for ALL, it is hypothesized that the first hit may occur as early as during fetal haematopoiesis.[24] The first hit in childhood ALL tends to affect more mature lymphoid progenitor cells.[25, 26] In contrast, the first hit in adult ALL occurs in multipotent stem cells, which

may be the reason behind the differing prognoses.[27] The second hit is thought to occur during the proliferation of B-lymphocyte progenitor cells during early childhood.[28] A second hypothesis, proposed by Kinlen, suggests the possibility of an infectious agent in the cause of ALL.[29] By examining areas with high rates of population mixing, after accounting for possible environmental exposures, this theory suggests that there are causative infectious agents related to the contact between different populations. One explanation posits that infections previously not encountered cause lymphoproliferative stress in the immune systems of the original residents and the immigrants.[30] Several studies have examined this hypothesis by researching several different population clusters but none identified a specific infectious agent.[31-33] Another explanation given by Kinlen suggests ALL may be due to a rare immune response to a highly prevalent, likely subclinical, infection rather than a rare infectious agent.[34] Around the same time, Greaves suggested that reduced or delayed exposure to common infectious agents during early childhood may lead to leukemia.[35] Among those experiencing delayed exposure, those with a higher risk for hyper-reactive immune responses and lower immune modulation will likely experience immune dysregulation and this subsequently may lead to proliferation of immune cells that are not properly differentiated.[36]

The hypotheses put forth by Kinlen and Greaves are compatible with circumstances in which population mixing is related in some way to delayed exposures to infectious agents. Termed the "infective lymphoid recovery hypothesis" researchers theorize that mild infections early in life act to prime the immune adaptive response, while recurrent infections later in childhood provide for the accumulation of oncogenic mutations leading to the promotion of ALL.[37, 38]

1.2 Literature Review

Ambient Agricultural Pesticides and ALL

In 2012, 186 million pounds of pesticide active ingredients were reportedly used in California treating approximately 84 million acres. Pesticide use categories include production agriculture, post-harvest fumigation, structural pest control, and landscape maintenance, in order of decreasing usage. The largest type of pesticide use was fungicide/insecticides, followed by fumigants, insecticides, herbicides, and fungicides by poundage. The following commodities accounted for 71% of active ingredient used in 2011: almonds, wine grapes, table and raisin grapes, cotton, alfalfa, processing tomatoes, rice, walnuts, pistachios, oranges, strawberries, peaches and nectarines, and carrots. Since 1998, pesticide use has decreased from 223 million pounds to 186 million pounds; however, it is likely that this is not due to fewer farmers using pesticides, but rather to improvements in pesticide formulations which necessitate a smaller poundage for the same effect.[39] The top active ingredients by poundage in 2012 were sulfur, petroleum and mineral oils, 1,3-dichloropropene, glyphosate, and chloropicrin. 1,3-dichloropropene is considered a Group B2 carcinogen (by the EPA), probable human carcinogen based on findings in the urinary bladder, hepatocellular carcinomas, and hepatocellular and bronchioalveolar adenomas. Unrefined petroleum and mineral oils are considered Group 1 carcinogens of the skin and scrotum, by the International Agency for Research on Cancer (IARC). On the other hand, highly refined petroleum and mineral oils are Group 3 (not classifiable). Sulfur, glyphosate, and chloropicrin are considered non-carcinogenic by the EPA while glyphosate was classified as *probably carcinogenic to humans* (Group 2A) by the IARC based on increased risks in non-Hodgkin's lymphoma.[40] The amount of applied chemicals classified as carcinogens by the EPA have increased in poundage over the past decade by

approximately 10%, although the total acreage treated has decreased.[41]

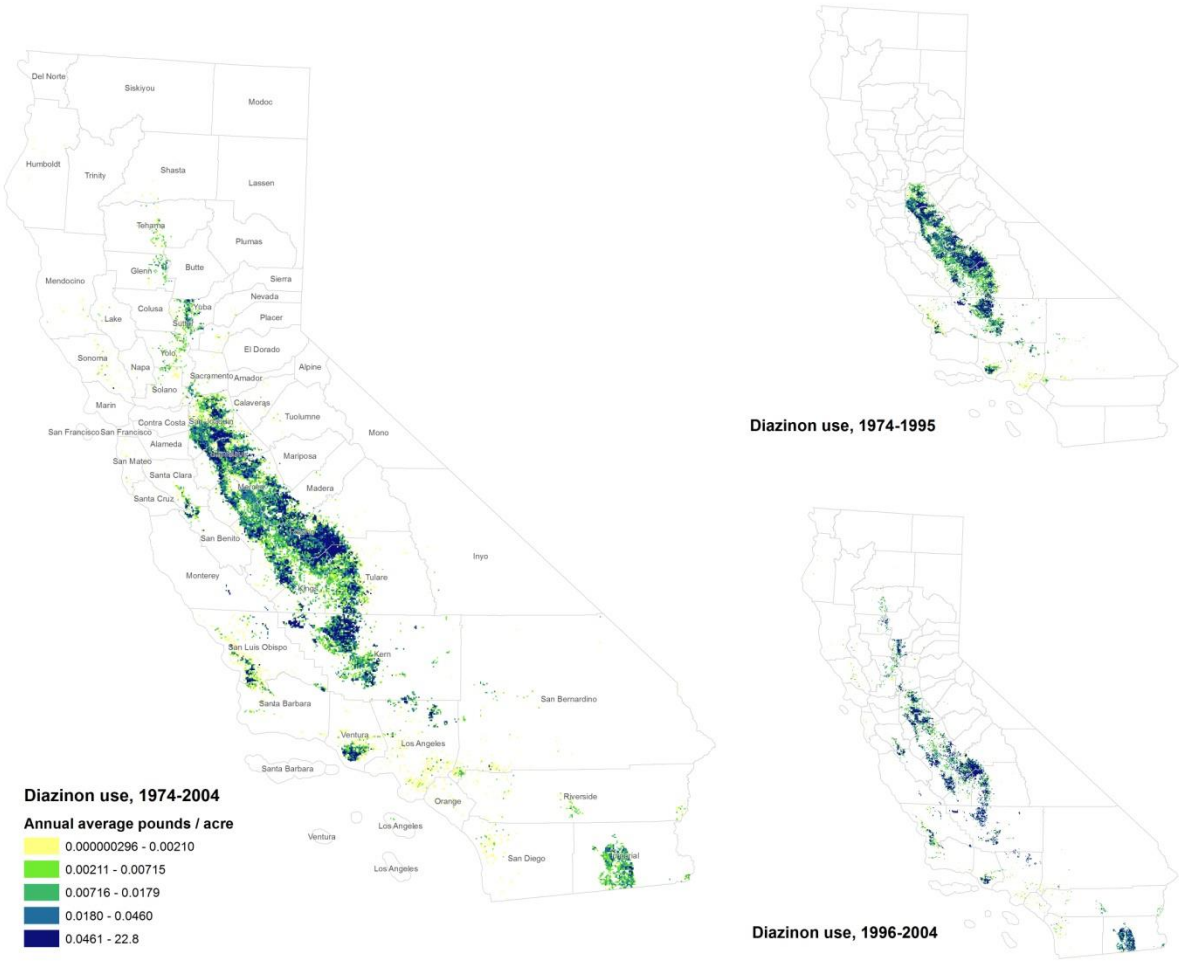

Figure 1.2.1 Maps of Diazinon use in California between 1974-2004

Due to the widespread use of pesticides in rural communities, ambient pesticide exposures in agricultural communities and near pesticide-treated fields are common. As such, "agricultural use" (as defined by California's broad legal definition which includes pesticide applications in agriculture, parks, golf courses, cemeteries, rangeland, pastures, and along roads and railways)[41] during pregnancy and early life are of concern. One study reported median house dust concentrations of dimethyl OP pesticides in agricultural families to be seven times higher than

reference homes and metabolite concentrations in agricultural children to be five times higher than reference.[42] Another study reported mean phosmet concentrations in soil and household dust samples at 2080 ng/g for agricultural families compared to 227 ng/g in non-agriculturally employed families living at least one-quarter mile from a commercial orchard or crop.[42-44] Pesticide drift from agricultural use accounted for approximately 26% of all reported pesticide poisonings between 1997 to 2000 in California. Symptoms include irritation of skin, eye, nose, throat, and respiratory tract, fluid in the lungs, CNS, liver, and kidney damage, headache, chest pain, nausea, convulsions, muscle cramps, dizziness, sweating, shortness of breath, and many more. Some longer term effects that have been documented include damage to the reproductive system, birth defects, neurotoxicity, and carcinogenicity.[43]

Most studies on pesticides and childhood ALL were focused on occupational exposures or residential use of pesticides. A study by Meinert *et al* in Germany observed increase risk of childhood leukemia (OR = 1.5, 95% CI [1.0, 2.2]) among those exposed to pesticide use on farms.[45] In Shanghai, Shu *et al* saw an association with maternal occupational exposure to pesticides during pregnancy and childhood ALL (OR = 3.5, 95% CI [1.1-11.2]).[46] Another study in France found maternal household pesticide use during pregnancy (ever vs. never) to increase childhood ALL (OR = 2.3, 95% CI [1.9-2.8]).[47] A study in Italy observed an increase in childhood leukemia (OR = 2.0, 95% CI [0.5, 8.4]) for those living near arable crops.[48] In Northern California, researchers sampled house dust and found elevated risk of ALL in those exposed to the residential herbicide chlorthal, had an OR of around 1.5.[49] A case-control study by Reynolds *et al* in California examining residential proximity to agricultural fields and childhood cancers found increased risks for metam-sodium ($\geq 50^{th}$ percentile) and dicofol ($\geq 50^{th}$

percentile) for childhood leukemias.[50] A similar case-control study by Rull *et al* in California investigating residential proximity to agricultural pesticide applications found increased risk of childhood ALL with exposure to organophosphates, chlorinated phenols, and triazines, as well as pesticides used as insecticides or fumigants.[51]

A pooled study of 13 case-control studies by the Childhood Leukemia International Consortium found no association between maternal occupational exposure during pregnancy and childhood ALL but found and increase in paternal occupational exposure and childhood ALL (OR = 1.2, 95% CI [1.1, 1.4]).[52] The authors also examined home pesticide use in 12 case-control studies and found an increase of ALL for those with any pesticide exposure before conception (OR = 1.4, 95% CI [1.3, 1.6]), during pregnancy (OR = 1.4, 95% CI [1.3, 1.5]), and after birth (OR = 1.4 95% CI [1.2, 1.5]).[53]

A recent meta-analysis of two cohort and 38 case-control studies conducted in 2011 by Vinson *et al*[54] concluded that maternal prenatal pesticide exposures were linked to an increased risk in leukemias and lymphomas. These studies mainly relied on parental interview to assess in-home pesticide use or professional applications of home pesticide use in a case-control design. This meta-analysis estimated (OR = 1.20, 95%CI [1.14, 1.32]) for leukemia, with higher risks when both parents were exposed during the prenatal period (OR = 1.84, 95%CI [1.39, 2.44]).[54] In 1998, Zahm and Ward[55] published a review of seventeen case-control studies and one retrospective cohort study. Thirteen of these found increased risks for childhood leukemia. Eleven of the seventeen studies reviewed all leukemia types together and did not specify

histological type (ALL, AML, CML). In 2007, Infante-Rivard *et al*[56] updated this review criticizing that the studies either lacked a clear pattern of risk with respect to timing of exposure, the type of leukemia, or which parent's exposure was more important. Infante-Rivard and colleagues subsequently reviewed seven additional recent case-control studies, three cohort studies, and two ecological studies to address these issues. Similar to the Zahm and Ward review[55], five of the seven case-control studies found increased risks in childhood leukemia.

Research into the biological mechanisms behind ALL has continued to progress over the past few decades. Chromosomal translocations resulting in activation of oncogenes and suppression of regulatory protein expression tends to be found in a majority of ALL cases.[57] Researchers are now identifying specific genes that are activated such as the *SCL* and *LMO1* oncogenes in conjunction with active pre-T-cell antigen receptor (TCR) signaling as a possible minimum set in ALL induction.[58] A recent study found that organophosphates are capable of inducing oxidative DNA damage to rat lymphocytes.[59] Another study found DNA damage caused by diuron in exposed oysters and some evidence of vertical transmission of DNA damage.[60] Several other studies have shown other types of damage such as chromosomal aberrations, sister chromatid exchange, and increases in specific biomarkers suggesting the genotoxic effects of pesticide exposures.[61-63] Therefore, it is possible that pesticides may be inducing damage resulting in activation of oncogenes in lymphocytes or in their progenitor cells aiding in their proliferation and survival. In addition, most pesticide exposures do not occur as a single exposure but often with multiple other pesticides that may result in a synergistic effect resulting in ALL.

Dichloromethane and Childhood Cancer

Dichloromethane (or methylene chloride) is a chlorinated hydrocarbon that is used in paint removers, adhesives, aerosols, pharmaceuticals, chemical processes, and metal cleaning. It has also been used in many household products including lubricants, adhesive removers, paint removers, and other automobile related products.[64] Routes of potential human exposure include inhalation, dermal contact, and ingestion.[65] The main route of exposure for the general population is inhalation of ambient dichloromethane, with additional exposures occurring from the use of household products.[64] 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.[66, 67]

The volatile nature of dichloromethane results in it being found mostly in the air. It has a half-life of about 130 days in the air and is broken down through reactions photochemically generated hydroxyl radicals. In addition, dichloromethane vapors are heavier than air (vapor density = 2.93 versus air density = 1) and tend to stay close to the ground. Once inhaled, the body metabolizes dichloromethane fairly rapidly and releases it through exhalation and urine within 48 hours. However, increased amounts of physical activity or body fat can lead to accumulation in body tissue, mainly fat. This accumulated dichloromethane is slowly released back into the blood stream over a longer period of time. In water, it is degraded at very different rates depending on temperature, pH, and aerobic or anaerobic degradation. These values have been found to range

from hundreds of years to several hours. In soil, dichloromethane generally does not absorb readily, resulting in risk for leaching to groundwater, but most likely to be released into the air through volatilization. Therefore, it is most likely that exposure will be due to inhalation of ambient dichloromethane. In adults, it is likely to affect the cardiovascular, hepatic, and neurological systems, but studies have not examined if children are affected similarly to adults.[68]

Dichloromethane has been found to cause liver and lung cancer in rodent experiments.[65] A recent review by Cooper et al. examining cohort and case-control studies found increased risks in lung cancer, and non-Hodgkin lymphoma as well as limited associations with brain, breast, and liver cancers.[69] Most of the studies in this review examined occupational exposures and adult cancers, with one study examining maternal occupational exposure up to 2 years before pregnancy and childhood ALL. The study regarding childhood ALL was conducted in Canada with cases of ALL diagnosed in 1980 to 2000. Occupational histories were taken from the mothers from 18 years of age to the end of pregnancy. Maternal exposures to dichloromethane and childhood leukemia were examined and found elevated odds among those probably/definitely exposed (OR = 3.22, 95%CI [0.88-11.73]).[70]

Several studies have examined the possible mechanistic pathways for dichloromethane and its association with cancer. The two primary pathways involve a *CYP2E1* dependent oxidative pathway that yields carbon monoxide, and a glutathione S-transferase theta 1 (*GSTT1*) pathway that yields carbon dioxide. The *CYP2E1* pathway saturates at fairly low levels and CO levels alone have not been sufficiently linked to genotoxicity. However, at larger concentrations of

dichloromethane, the *GSTT1* pathway creates S-haloalkylglutathione and formaldehyde as intermediates which are both more reactive than the parent compound.[71] These increases, especially in formaldehyde, have been linked to carcinogenic potential.[72]

Maternal Smoking and ALL

The prevalence of smoking in developed countries has decreased in recent decades most likely due to the elucidation of its effects on morbidity and mortality.[73] The rates of smoking in men and women have recently become similar in Europe.[73] In adolescents, the initiation of smoking appears to be increasing at a faster pace and in higher frequency in girls than in boys.[74] This is of particular concern as these young females mature into child-bearing age. In Denmark, the prevalence of smoking during pregnancy has decreased from 30.6% to 12.5% from 1991 to 2010.[75]

Fetal exposure to smoking during pregnancy has been linked to several birth defects including cardiovascular, digestive, musculoskeletal, and face and neck body systems.[76] Additionally, the carcinogenic effects of smoking on adults has been extensively studied. Due to these effects, prenatal exposure to maternal smoking and childhood ALL has been studied by a number of previous researchers. However, results have proven inconsistent with studies showing null and often inverse associations with ORs ranging from 0.78 to 1.90.[77-88] Examinations of dose-response effects tended to show a positive association of maternal smoking and ALL among light smokers (<10 cigarettes per day) (median OR = 1.10, range OR: 0.69-1.63) while heavier smokers ($\geq$30 cigarettes per day) resulted in null or inverse associations.[78, 83, 86, 89-92] Interestingly,

paternal smoking has been linked more consistently to elevated risk of ALL in smoking during preconception and in pregnancy, but it is difficult to determine which time period is more critical due to the overlap in both periods.[79-81, 85, 88, 93-95]

Spontaneous abortion, or miscarriage, is the most common pregnancy complication. Rates of miscarriage have been estimated ranging from 25% upwards of 50% of all conceptions and around 12-15% of clinically recognized pregnancies.[96, 97] The etiology of miscarriage is complex with possible causes ranging from genetic abnormalities, abnormal endocrine levels, anatomical deformities, immunological incompatibilities of mother and fetus, and infections.[98-102] In addition, persistent environmental and occupational chemicals, endocrine disruptors, and industrial pollutants have been implicated as potential risk factors.[101, 103]

The association of maternal smoking and miscarriage has been well-documented over the past several decades. Of the larger cohort studies, a study in the United Kingdom observed a slight increase in miscarriage among mothers who actively smoked during pregnancy (OR: 1.13, 95% CI [1.05, 1.22]).[104] Also, a large Canadian cohort study found a dose-response association of smokers and spontaneous abortion (10-19 cigarettes per day (cpd) OR = 1.22, 95% CI [1.13, 1.32], 20+ cpd, OR = 1.68 [1.57, 1.79]).[105] On the other hand, a Danish cohort study reported no association between maternal smoking and spontaneous abortion and did not find any indication of a dose-response relationship.[106] There has been some debate regarding whether or not maternal smoking truly causes spontaneous abortion, but as more studies are published, the evidence supports a positive association. Some recent case-control studies such as one by Baba

et al in Japan found increased risk of early spontaneous abortion among maternal smokers (OR: 2.39, 95% CI [1.26, 4.25]).[107] Another case-control study in Sweden found similar estimates with OR: 2.11, 95% CI [1.36, 3.27]) for active maternal smoking and miscarriage.[108] A meta-analysis in 2014 by Pineles *et al* estimated a summary relative risk ratio for smoking during pregnancy of 1.32, 95% CI [1.21, 1.44].[109] In their dose-response analysis, the summary relative risks for 1-10 cpd, 11-19 cpd, and 20+ cpd were 1.08, 95% CI [0.96, 1.21], 1.25, 95% CI [1.17, 1.34], and 1.42, 95% CI [1.19, 1.70]. This association was originally documented by Zabriskie *et al* in 1963,[110] and subsequent studies have generally shown consensus and similar magnitude and direction of estimates.

1.3 Specific Aims for This Dissertation

We aimed to test the hypothesis that ambient pesticide exposures during pregnancy and early life may increase the risk of childhood ALL by causing genetic mutations, suppression of regulatory protein expression, and oxidative DNA damage by conducting a population-based case-control study in California (Chapter 2). In the third chapter, utilizing the same study, we examined the association of industrial dichloromethane releases and increasing risks of childhood cancers of pregnant mothers and infants living in proximity to industrial facilities.

In Chapter 4, we delved into a possible explanation for the inconsistent effects of maternal smoking and ALL seen in previous studies. Using priors from the Danish National Registries, we simulated a type of survivor bias previously referred to as a ‘live-birth bias’ and assessed the impact on the magnitude and direction of the association.

Chapter 2. Prenatal Pesticide Exposure and Childhood Leukemia – a California statewide case-control study

2.1 Abstract

Background

A number of epidemiologic studies with a variety of exposure assessment tools implicated pesticides as risk factors for childhood cancers. Here we explore the association of pesticide exposure in pregnancy and early childhood and childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) based on CA state agricultural pesticide records.

Methods

We frequency matched cancer cases less than 6 years of age identified from the California Cancer Registry to 20 cancer-free controls from birth certificates by birth year and restricted to those living in rural areas and born 1998-2011, resulting in 162 cases of childhood leukemia and 9,805 controls. Possible carcinogens were selected from the Environmental Protection Agency's classifications and pesticide use was collected from the California Department of Pesticide Regulation's (CDPR) Pesticide Use Reporting (PUR) system and linked to land-use surveys. Exposures for subjects were assessed using a 4000m buffer around the geocoded residential addresses at birth. Unconditional logistic and hierarchical regression models were used to assess individual pesticide and pesticide class associations.

Results

We observed elevated risks for ALL with exposure to any carcinogenic pesticide (adjusted Odds Ratio (aOR): 2.83, 95% CI: 1.67-4.82), diuron (Single-pesticide model, adjusted (OR): 2.38, 95% CI: 1.57-3.60), phosmet (OR: 2.10, 95% CI: 1.46-3.02), kresoxim-methyl (OR: 1.77, 95% CI: 1.14-2.75), and propanil (OR: 2.58, 95% CI: 1.44-4.63). Analyses based on chemical classes

showed elevated risks for the group of 2,6-dinitroanilines (OR: 2.50, 95% CI: 1.56-3.99), anilides (OR: 2.16, 95% CI: 1.38-3.36), and ureas (OR: 2.18, 95% CI: 1.42-3.34).

Conclusion

Our findings suggest that in rural areas of California exposure to certain pesticides or pesticide classes during pregnancy due to residential proximity to agricultural applications may increase the risk of childhood ALL and AML. Future studies into the mechanisms of carcinogenicity of these pesticides may be beneficial.

2.2 Introduction

Leukemia, which makes up 40% of all childhood cancers, is the most frequent childhood malignancy. The most common subtype, acute lymphocytic leukemia (ALL) alone accounts for 25% of all childhood malignancies in children younger than 15 years of age,[111] and 78% of all childhood leukemia cases. Nevertheless, it is a rare disease with an incidence of 39 cases per million, with diagnoses peaking between ages 2-5 and the highest rates estimated for Hispanics.[112] Acute myeloid leukemia accounts for most of the remaining cases of childhood leukemia (16%). Few risk factors for childhood leukemia are considered established apart from ionizing radiation and specific genetic abnormalities.

In 2010, 173 million pounds of pesticide active ingredients were used in California.[113] Higher concentrations of pesticides have been measured in communities abetting agricultural fields, as measured by urine and hand wipe samples as well as in house dust.[44, 114-116] Previous studies have shown that pesticides and their metabolites (organophosphates, pyrethroids) persist in media such as house dust and clothing in families of farmworkers living near agricultural fields.[117-119] This is of great concern as pesticide residues may build-up in residences located in agricultural communities and expose pregnant women and infants.[119]

A number of previous studies suggested that pesticide exposures are risk factors for childhood ALL.[120-123] A recent meta-analysis conducted by Vinson *et al.*[123] concluded that pregnancy exposure to any pesticide exposure increases the risk of leukemias (48%) and lymphomas (53%) in offspring. However, the contributing studies mainly relied on parental interviews to assess in-home pesticide use or professional applications of residences, and the retrospective assessment

of exposures made these studies vulnerable to recall bias since parents of children with cancer may recall exposures in more detail and may want to explain their child's disease. In 2007, Infante-Rivard *et al.*[120] critiqued the literature as lacking clarity on the most important time period of exposure, the type of leukemia most impacted by pesticide exposures, and which parent's exposure may be more important. This study aims to shed light on the subtypes of leukemia and to determine any differences in risks whether children were exposed during pregnancy or early childhood.

Importantly, most prior studies did not report on risk related to individual pesticides, instead they assessed pesticides by type (insecticides, fungicides, herbicides, fumigants, etc.), chemical class (organophosphates, organochlorines, triazines, azoles, etc.), classifications according to level of carcinogenicity (Group A, B, probable carcinogen, etc.),[124-126] or they targeted specific pesticides but investigated all childhood leukemias together instead of separating ALL and AML.[50] Our study expands upon earlier publications by identifying specific pesticide exposures and by assessing risk of ALL and AML separately. A previous paper examined all leukemias in California (all types combined) in children born 1990-97.[50] Since agricultural pesticide use changes frequently due to improvements in formulations and to address pest adaptation and evolution,[127] updates with more recent exposure data are needed. We are focusing on children born in more recent years (1998-2011) and we are employing a very sophisticated GIS tool we developed that combines land use and pesticide use records for those years; we applied this tool to all rural areas in California that use pesticides agriculturally because urban communities apply pesticides for non-agricultural purposes and therefore are not capture in the PUR. Urban pesticide exposures include home and building fumigations, which are not reported in PUR on

the house-level (only on the county-level). Agricultural pesticide use is rarer in urban areas and urban dwellers experience other exposures which may impact risk,[128, 129] hence we decided to focus on rural populations that also have higher levels of pesticide exposure. This exposure assessment method does not rely on recall and does not suffer the same limitations as many prior studies.

2.3 Methods

Study Population

Cases were collected from records of incident ALL [International Classification of Childhood Cancer, Third Edition (ICCC) code 011] and AML (ICCC code 012) diagnosed in 1986-2012 (born 1983-2011) in the California Cancer Registry, younger than age 6, and born in California. Using a probabilistic linkage program (LinkPlus, CDC), we linked cases to birth certificates using first and last names, date of birth, and social security number when available. With this method, 89% of cases were matched to a California birth certificate. The remaining 11% were likely born out of state and moved to California prior to diagnosis.[130] Controls were selected at random from California birth records for the same time period, frequency-matched by year of birth to all childhood cancers in the study. Controls had no record of a cancer diagnosis in California before age 6. As this was a record-based study, we did not seek informed consent from individual subjects. The study received approvals from the human subject protection boards of the University of California, Los Angeles, the University of Southern California, and the California Committee for the Protection of Human Subjects.

Exposure Assessment

Starting in 1974, California's Department of Pesticide Regulation required farmers to report the use of restricted pesticides, defined as pesticides whose application was restricted by federal law due to potential harm to people, crops, or the environment, to the state via California Pesticide-Use Reports (PUR). In 1990, this California PUR program was expanded to require full reporting of all agricultural pesticide use. In the PUR, detailed information is given regarding the active ingredients, the acreage treated, the amounts used, the crops that are treated, and the location and date of the application. Our group combined data from the PUR with data from land-use surveys from the California's Public Land Survey System (PLSS). The PLSS is a countywide survey conducted every 7-10 years by the California Department of Water Resources recording the extent of land use in terms of crop cover by location. The combination of the PUR and land-use data allowed us to more precisely locate pesticide applications by linking them with their respective crops. We calculated monthly and annual application rates (total pounds applied per acre in a PLSS section, within a given time period) for each pesticide as detailed elsewhere.[131, 132]

Participant data were obtained from California Cancer Registry records, from birth certificates, and additionally from the year 2000 census; including parental demographics such as age, education, race/ethnicity, socioeconomic status, gestational age, and child's sex information were obtained from birth certificates. Neighborhood socioeconomic status was measured with a multi-factorial index that used principal components analysis to develop a single, 5-level measure from seven census-level indicators (education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value).[133] Based on the date of last reported menses we excluded children

with implausibly long (>45 weeks) gestations, likely non-viable births (gestational age <20 weeks or birth weight <500g, n=32), and those with missing data for gestation length (n=12,786). In addition, those with a residential address outside of California (n=632), and controls who had died before age 6 (n=1,202) were excluded from the dataset resulting in 5,112 cases of leukemia and 270,776 controls prior to restriction. We used an urban/rural designation based on rural-urban commuting area codes (RUCA) created by a collaboration of government organizations based on Census Tract information[134] to restrict our sample to rural residents only (RUCA levels 4-10). Our rural study population contained 132 cases of ALL, 30 cases of AML, and 9,805 controls.

Residential addresses as listed on the birth certificate were mapped using Geographic Information System (GIS) tools based on street address (54%), street intersection (38%), city centroid, or ZIP code centroid (7%). We examined several buffer sizes (500m, 2000m, 4000m) around the home. Due to the distances that pesticides can reach from where they are initially applied (pesticide drift),[135] and to improve sample size, we present results at the 4000m distance. We also examined smaller buffers (500m, 2000m) in sensitivity analyses.

We pre-selected 133 pesticides considered possible, likely, or probable carcinogens by the EPA,[123] (See Supplement 1 for more detail on EPA carcinogen classifications).[136] We further categorized pesticides according to physiochemical type and class, based on information from the Pesticide Action Network (PAN) Pesticide Database[137] and we also considered 6 additional pesticides (methyl bromide, diazinon, paraquat, chlorpyrifos, glyphosate, and simazine) because these chemicals are widely used in California and little is known about potential adverse effects

form co-exposures. Of these, we report results for 65 pesticides for which at least 10 cases were exposed during the study years.

Approximately 85% of PUR reports have an exact date of application, while the remaining 15% only have the year. We conducted sensitivity analyses to elucidate whether exposure in a specific trimester was most relevant for ALL risk.

Statistical Analyses

Unconditional logistic regression was utilized to derive ORs and 95% CIs adjusting for the matching factor (birth year) in single and multiple-pesticides models for the 65 selected pesticides. We examined 'ever' exposure during pregnancy for each pesticide as well as for chemical class for ALL and AML outcomes. The single-pesticide models adjusted for any exposure to another carcinogenic pesticide as a binary variable. Multiple-pesticide models, co-adjusted for ever/never exposure to all other pesticides selected via semi-Bayesian hierarchical logistic regression, i.e. assuming that the estimated effects are either 1) drawn from the same distribution for all carcinogenic pesticides or 2) are specific to a pesticide class (2,6-dinitroanilines, azoles, chloroacetanilides, dithiocarbamates, n-methyl carbamates, organochlorines, organophosphates, pyrethroids, substituted benzenes, and triazines). Both assumptions yielded similar results, thus here we present the hierarchical logistic regression model results using the first assumption (same distribution of effects for all carcinogenic pesticides) only. We also conducted sensitivity analyses examining the entire state among those born 1998-2011 and restricted to those exposed to at least one pesticide in the PUR database.

Selection of variables for adjustment was based upon literature review as well as the 10% change in estimate criterion.[4, 138-140] We adjusted for birth year (matching factor), mother's race (White non-Hispanic, Black, and Other race/refused to report), neighborhood socioeconomic index, and the binary indicator for any other carcinogenic pesticide exposure as possible confounders. We considered for inclusion in models neighborhood and individual level socioeconomic indicators: maternal education (years), paternal education (years), and the source of payment for prenatal care, which was defined as private insurance (including Health Maintenance Organizations, Blue Cross-Blue Shield, or any other private insurance) versus other payment methods (including self-pay and government aid programs, such as Medicare, Medi-Cal, worker's compensation, Title V, and CHAMPUS/TRICARE), which we have previously observed to be a reasonable proxy for family income.[141] However, these factors were not included in final models due to not fulfilling the 10% change in estimate criterion.

2.4 Results

In terms of demographic characteristics (Table 2.1) fathers of ALL cases were more likely to be White non-Hispanics and Hispanics than any other race. Mothers of ALL cases were older and more likely to be Hispanic. Families of ALL cases were more likely to have had their prenatal care paid by private insurance. ALL cases were more often male children.

Exposure to any of the 59 carcinogenic pesticides during pregnancy resulted in elevated odds for ALL (OR: 2.83, 95% CI: 1.67-4.82) and AML (OR: 3.75, 95% CI: 0.97-11.57). Table 2.2 and 2.3 provide the exposure distributions of cases and controls based on specific pesticide exposures during pregnancy, presented by pesticide class. We estimated elevated odds for ALL with

exposures to the following classes in our single-pesticide models: 2,6-dinitroanilines (OR: 2.50, 95% CI: 1.56-3.99), anilides (OR: 2.16, 95% CI: 1.38-3.36), and ureas (OR: 2.18, 95% CI: 1.42-3.34). Point estimates for AML were elevated for organophosphates (OR: 1.82, 95% CI: 0.70-4.74) and ureas (OR: 3.38, 95% CI 1.22-9.38) but small sample sizes resulted in wide confidence intervals.

In Table 2.4 we present ORs for individual pesticides. We estimated elevated odds ratios for ALL with exposure to diuron (OR: 2.38, 95% CI: 1.57-3.60), phosmet (OR: 2.10, 95% CI: 1.46-3.02), kresoxim-methyl (OR: 1.77, 95% CI: 1.14-2.75), and propanil (OR: 2.58, 95% CI: 1.44-4.63) in the single-pesticide model. Using hierarchical regression models instead these effects estimates attenuated slightly except for phosmet (OR: 2.10, 95% CI: 1.3-3.39). The addition of all other pesticides in the hierarchical logistic models attenuated the effects of most pesticides, likely due in part to co-adjustment for the other pesticides in the list, along with drawing each pesticide to the overall mean of the carcinogenic pesticides.

In relation to AML (Table 2.5), we saw elevated odds for metam-sodium (OR: 2.56, 95% CI: 1.19, 5.49) and paraquat dichloride (OR: 3.38, 95% CI: 1.23, 9.27) in single-pesticide models.

Effect estimates were similar across trimesters and comparable in size to the estimates for entire pregnancy exposures (Supplemental table 2.1). Exposure correlations between the first and second trimesters, and second and third trimesters were around 0.40-0.55 while the first and third trimesters were not correlated (r^2 = -0.01-0.30). In the sensitivity analysis in which we relied on 2000m buffers to assess exposure, associations with the four pesticides mentioned above were

slightly weaker for ALL but remained elevated with CIs including the null (ORs: 1.41-2.28) except for diuron, which was higher (OR: 2.28, 95% CI: 1.56-3.33). With regards to AML, paraquat dichloride remained elevated (OR: 2.59, 95% CI: 1.08-6.20), and metam-sodium had only 7 exposed cases at 2000m but remained elevated (OR: 2.17, 95% CI: 0.91-5.21). Results of sensitivity analyses statewide and among those exposed to at least one pesticide were similar among the pesticides with elevated effect estimates, although the magnitude of effect was generally closer to the null.

Table 2.1. Demographic characteristics of children in California born in 1998-2011 living in rural areas.

Characteristic	ALL N = 132	AML N = 30	Controls N = 9805
Sex of Child, n (%)			
Male	77 (58.3)	23 (76.7)	5062 (51.6)
Female	55 (41.7)	7 (23.3)	4743 (48.4)
Paternal Race/Ethnicity, n (%)			
White non-Hispanic	38 (28.8)	9 (30.0)	2916 (29.7)
Hispanic	69 (52.3)	15 (50.0)	4657 (47.5)
Other	25 (18.9)	6 (20.0)	2232 (22.8)
Maternal Race/Ethnicity, n (%)			
White non-Hispanic	44 (33.3)	10 (33.3)	4033 (41.1)
Hispanic	80 (60.6)	18 (60.0)	5036 (51.4)
Other	8 (6.1)	2 (6.7)	736 (7.5)
Maternal Age, n (%)			
19 or less	19 (14.4)	4 (13.3)	1251 (12.8)
20-24	37 (28.0)	7 (23.3)	2831 (28.9)
25-29	32 (24.2)	8 (26.7)	2672 (27.3)
30-34	26 (19.7)	4 (13.3)	1856 (18.9)
35 and older	18 (13.6)	7 (23.3)	1186 (12.1)
Missing			9
Maternal Education (years), n (%)			
8 or less	14 (10.7)	4 (13.3)	1134 (11.8)
9-11	28 (21.4)	6 (20.0)	1931 (20.0)
12	45 (34.4)	8 (26.7)	3213 (33.3)
13 to 15	27 (20.6)	8 (26.7)	2179 (22.6)
16 more	17 (13.0)	4 (13.3)	1194 (12.4)
Missing			154
Principal Payment of Prenatal Care, n (%)			
Private/HMO/BCBS	59 (45.4)	12 (40.0)	3435 (35.7)
MediCal/Govt/Self-pay	71 (54.6)	18 (60.0)	6198 (64.3)
Missing	12		172
Census-based SES index level, n (%)			
1 (reference)	33 (25)	13 (43.3)	2924 (29.8)
2	56 (42.4)	8 (26.7)	3158 (32.2)
3	34 (25.8)	6 (20.0)	2980 (30.4)
4	9 (6.8)	3 (10.0)	743 (7.6)

Table 2.2. Associations between ALL and exposure to agricultural pesticide applications within 4000m of the residential address, by pesticide class

Chemical Class	Exposed Cases N=132	Exposed Controls N=9,805	Crude OR[a]	Single-pesticide class model[b]	HLM OR (95% CI)[c]
2,6-Dinitroaniline	108	6,343	2.51	2.50 (1.56, 3.99)	1.76 (0.91, 3.38)
Amide	36	2,134	1.37	1.23 (0.83, 1.83)	1.09 (0.72, 1.66)
Anilide	52	3,204	2.23	2.16 (1.38, 3.36)	1.62 (1.02, 2.56)
Azole	85	5,037	1.73	1.69 (1.16, 2.45)	1.25 (0.76, 2.05)
Chloroacetanilide	55	3,119	1.54	1.47 (1.03, 2.11)	1.27 (0.82, 1.99)
Dicarboximide	77	5,127	1.25	1.15 (0.79, 1.67)	0.54 (0.33, 0.89)
Dithiocarbamate	97	5,799	1.91	1.83 (1.21, 2.75)	1.10 (0.61, 1.97)
N-Methyl Carbamate	69	4,166	1.40	1.30 (0.90, 1.87)	0.93 (0.61, 1.42)
Organochlorine	60	3,435	1.40	1.35 (0.93, 1.97)	0.98 (0.63, 1.52)
Organophosphorus	110	6,753	2.26	2.38 (1.48, 3.83)	1.54 (0.81, 2.93)
Pyrethroid	85	5,228	1.62	1.51 (1.03, 2.23)	0.89 (0.51, 1.54)
Substituted-Benzene	72	4,623	1.35	1.21 (0.84, 1.75)	0.81 (0.51, 1.28)
Sulfonylurea	13	794	1.21	1.07 (0.59, 1.94)	0.99 (0.55, 1.77)
Triazine	83	5,018	1.61	0.96 (0.60, 1.54)	0.77 (0.47, 1.25)
Urea	100	5,741	2.22	2.18 (1.42, 3.34)	1.43 (0.79, 2.58)

[a]Adjusted for matching variable, birth year

[b]Adjusted for birth year, SES-index variable, and mother's race

[c]Adjusted for birth year, mother's race, SES-index variable, and using an overall pesticide effect in the hierarchical model

Table 2.3. Associations between AML and exposure to agricultural pesticide applications within 4000m of the residential address, by pesticide class

Chemical Class	Exposed Cases N=30	Exposed Controls N=9,805	Crude OR[a]	Single-pesticide class model[b]	HLM OR (95% CI)[c]
2,6-Dinitroaniline	26	6,343	3.54	3.31 (1.10, 10.03)	1.63 (0.58, 4.58)
Anilide	14	3,204	2.18	2.00 (0.80, 4.98)	1.15 (0.49, 2.69)
Azole	21	5,037	2.21	1.99 (0.88, 4.53)	1.00 (0.43, 2.33)
Chloroacetanilide	13	3,119	1.64	1.50 (0.71, 3.17)	1.11 (0.52, 2.38)
Dicarboximide	22	5,127	2.52	2.31 (0.97, 5.51)	1.30 (0.51, 3.28)
Dithiocarbamate	23	5,799	2.27	2.08 (0.85, 5.10)	1.03 (0.40, 2.64)
N-Methyl Carbamate	17	4,166	1.82	1.62 (0.75, 3.51)	1.04 (0.49, 2.19)
Organochlorine	10	3,435	0.94	0.76 (0.33, 1.75)	0.50 (0.23, 1.08)
Organophosphorus	28	6,753	6.33	1.82 (0.70, 4.74)	0.76 (0.28, 2.05)
Pyrethroid	20	5,228	1.75	1.50 (0.65, 3.48)	0.75 (0.31, 1.79)
Substituted-Benzene	19	4,623	1.94	1.76 (0.79, 3.92)	1.16 (0.52, 2.61)
Triazine	22	5,018	2.63	1.24 (0.50, 3.10)	1.05 (0.46, 2.39)
Urea	25	5,741	3.54	3.38 (1.22, 9.38)	1.89 (0.70, 5.11)

[a]Adjusted for matching variable, birth year

[b]Adjusted for birth year, SES-index variable, mother's race, and exposure to any other pesticide class

[c]Adjusted for birth year, mother's race, SES-index variable, and using an overall pesticide effect in the hierarchical model

Table 2.4. Associations between ALL and exposure to agricultural pesticide applications within 4000m of the residential address, by individual pesticide

Pesticide Class	Pesticide	Exposed Cases N=132	Exposed Controls N=9,805	Crude OR[a]	Single-pesticide model[b]	HLM OR (95% CI)[c]
2,6-Dinitroaniline						
	Pendimethalin	89	5,223	1.87	1.82 (1.22, 2.71)	1.32 (0.74, 2.33)
	Trifluralin	81	4,931	1.57	1.44 (0.97, 2.13)	1.03 (0.58, 1.83)
	Oryzalin	76	4,602	1.57	1.54 (1.08, 2.21)	0.98 (0.58, 1.65)
	Ethalfluralin	24	1,123	1.66	1.51 (0.96, 2.38)	1.15 (0.66, 1.99)
	Benefin	16	933	1.22	1.05 (0.61, 1.81)	0.99 (0.54, 1.83)
Amide						
	Propyzamide	22	1,177	1.45	1.25 (0.78, 2.01)	2.12 (1.06, 4.23)
	Isoxaben	16	1,044	1.20	1.11 (0.65, 1.89)	1.02 (0.58, 1.78)
Anilide						
	Boscalid	43	2,947	1.89	1.81 (1.10, 2.97)	1.38 (0.78, 2.43)
	Propanil	13	405	2.58	2.58 (1.44, 4.63)	2.21 (1.16, 4.22)
Azole						
	Propiconazole	66	3,818	1.60	1.56 (1.09, 2.24)	1.57 (0.92, 2.66)
	Tebuconazole	55	3,484	1.34	1.24 (0.86, 1.80)	0.80 (0.48, 1.32)
	Fenbuconazole	21	1,273	1.32	1.21 (0.75, 1.96)	1.01 (0.55, 1.84)
	Triadimefon	11	753	0.90	0.86 (0.45, 1.63)	0.79 (0.41, 1.51)
Chloroacetanilide						
	S-Metolachlor	38	2,462	1.37	1.30 (0.87, 1.94)	1.19 (0.70, 2.00)
	Metolachlor	23	1,061	1.49	1.45 (0.89, 2.35)	1.09 (0.62, 1.91)
Dicarboximide						
	Iprodione	75	5,104	1.19	1.08 (0.74, 1.56)	0.50 (0.29, 0.86)
Dithiocarbamate						
	Ziram	60	3,200	1.70	1.68 (1.17, 2.40)	1.09 (0.65, 1.83)
	Maneb	52	3,490	1.16	1.03 (0.71, 1.48)	0.62 (0.38, 1.00)
	Mancozeb	70	4,324	1.41	1.28 (0.89, 1.83)	0.90 (0.58, 1.40)
	Metam-Sodium	39	2,208	1.37	1.21 (0.82, 1.79)	1.07 (0.67, 1.73)
Halogenated organic						
	Methyl Bromide†	54	3,106	1.42	1.33 (0.93, 1.92)	N/A
	1,3-Dichloro-propene	48	2,905	1.39	1.26 (0.86, 1.82)	1.03 (0.62, 1.69)
N-Methyl Carbamate						
	Carbaryl	66	4,044	1.34	1.25 (0.86, 1.79)	0.91 (0.58, 1.42)
	Thiodicarb	19	744	1.76	1.56 (0.93, 2.63)	1.65 (0.88, 3.09)
Organochlorine						
	Dicofol	60	3,345	1.47	1.41 (0.97, 2.06)	1.11 (0.68, 1.82)
Organophosphorus						
	Chlorpyrifos†	97	5,934	1.81	1.71 (1.12, 2.60)	N/A

	Dimethoate	82	4,982	1.56	1.44 (0.98, 2.12)	1.02 (0.61, 1.71)
	Malathion	78	4,515	1.67	1.54 (1.06, 2.22)	1.16 (0.73, 1.85)
	Diazinon†	76	4,731	1.38	1.27 (0.87, 1.83)	N/A
	Phosmet	76	3,757	2.09	2.10 (1.46, 3.02)	2.10 (1.30, 3.39)
	Acephate	48	3,146	1.18	1.06 (0.73, 1.54)	0.82 (0.50, 1.33)
	Methidathion	29	2,053	0.97	0.91 (0.58, 1.41)	0.62 (0.36, 1.07)
	S,S,S-Tributyl Phosphoro-trithioate	27	1,282	1.57	1.47 (0.94, 2.30)	1.59 (0.81, 3.12)
Pyrethroid						
	Permethrin	73	4,765	1.31	1.18 (0.81, 1.72)	0.65 (0.37, 1.14)
	Bifenthrin	56	3,760	1.27	1.18 (0.82, 1.70)	0.82 (0.51, 1.34)
	(S)-Cyper-methrin	40	2,768	1.25	1.13 (0.76, 1.69)	1.05 (0.64, 1.74)
Substituted Benzene						
	Chlorothalonil	67	4,262	1.34	1.19 (0.83, 1.72)	0.99 (0.59, 1.66)
	Dicloran	26	1,632	1.17	1.05 (0.67, 1.63)	0.96 (0.54, 1.68)
Triazine						
	Simazine†	72	4,340	1.50	1.49 (1.04, 2.14)	N/A
	Pymetrozine	14	980	1.17	1.08 (0.61, 1.91)	1.00 (0.52, 1.89)
Urea						
	Diuron	98	5,364	2.38	2.38 (1.57, 3.60)	1.79 (1.02, 3.15)
	Linuron	22	1,209	1.42	1.25 (0.78, 2.00)	1.63 (0.85, 3.12)
Other classes						
	Glyphosate‡	113	7,125	2.28	2.20 (1.33, 3.63)	N/A
	Oxyfluorfen	104	6,247	2.15	2.10 (1.35, 3.27)	1.43 (0.72, 2.81)
	Paraquat Dichloride†	95	5,711	1.83	1.74 (1.16, 2.62)	N/A
	Propargite	68	4,219	1.39	1.32 (0.91, 1.90)	0.76 (0.41, 1.42)
	Norflurazon	58	3,466	1.35	1.27 (0.88, 1.84)	0.84 (0.51, 1.38)
	Thiophanate-Methyl	56	3,127	1.61	1.52 (1.06, 2.17)	1.34 (0.87, 2.05)
	Captan	55	2,893	1.61	1.58 (1.10, 2.28)	1.52 (0.91, 2.56)
	Clofentezine	38	2,173	1.40	1.33 (0.90, 1.96)	1.09 (0.65, 1.83)
	Buprofezin	32	2,181	1.30	1.20 (0.78, 1.85)	1.01 (0.61, 1.67)
	Kresoxim-Methyl	31	1,673	1.86	1.77 (1.14, 2.75)	1.47 (0.83, 2.60)
	Hexythiazox	30	2,219	1.17	1.09 (0.71, 1.69)	0.74 (0.44, 1.26)
	Pyrithiobac-Sodium	24	1,666	1.01	0.94 (0.59, 1.50)	0.61 (0.31, 1.18)
	Metaldehyde	17	984	1.30	1.22 (0.73, 2.05)	1.39 (0.75, 2.56)
	Pyraflufen-Ethyl	16	1,310	1.18	1.11 (0.62, 1.99)	0.97 (0.50, 1.87)
	Chlorthal-Dimethyl	15	1,351	0.80	0.67 (0.39, 1.16)	0.41 (0.18, 0.93)
	Pyrimethanil	15	1,290	1.18	1.11 (0.60, 2.06)	0.85 (0.43, 1.68)

Piperonyl Butoxide	15	911	1.15	1.08 (0.62, 1.87)	0.94 (0.51, 1.72)
Cacodylic Acid	14	647	1.35	1.30 (0.71, 2.36)	1.00 (0.48, 2.08)
Bromacil	13	884	1.09	1.02 (0.57, 1.83)	0.87 (0.44, 1.72)
Thiazopyr	12	546	1.58	1.47 (0.80, 2.70)	1.26 (0.68, 2.34)
Triflusulfuron-Methyl	12	772	1.13	0.97 (0.52, 1.78)	1.05 (0.55, 2.02)
Hydrogen Cyanamide	11	1,192	0.70	0.65 (0.35, 1.22)	0.53 (0.27, 1.02)
Spirodiclofen	10	787	1.36	1.28 (0.62, 2.62)	1.35 (0.63, 2.89)

†Added based on previous literature or high usage in California

‡Glyphosate was defined as the sum of the following chemicals: glyphosate, glyphosate (salt), glyphosate (diammonium salt), glyphosate (isopropylamine salt), glyphosate (potassium salt), and glyphosate (trimesium)

[a]Adjusted for matching variable, birth year

[b]Adjusted for birth year, mother's race, and SES-index variable

[c]Adjusted for birth year, mother's race, SES-index variable, and using an overall pesticide effect in the hierarchical model

Table 2.5. Associations between AML and exposure to agricultural pesticide applications within 4000m of the residential address, by individual pesticide

Pesticide Class	Pesticide	Exposed Cases N=30	Exposed Controls N=9,805	Crude OR[a]	Single-pesticide model[b]	HLM OR (95% CI)[c]
2,6-Dinitroaniline						
	Pendimethalin	22	5,223	2.41	2.19 (0.90, 5.30)	1.31 (0.74, 2.33)
	Oryzalin	21	4,602	2.63	2.39 (1.06, 5.38)	0.99 (0.55, 1.78)
	Trifluralin	19	4,931	1.71	1.46 (0.63, 3.36)	2.23 (1.38, 3.60)
Anilide						
	Boscalid	13	2,947	2.27	2.00 (0.76, 5.30)	0.82 (0.5, 1.34)
Azole						
	Propiconazole	14	3,818	1.37	1.18 (0.56, 2.52)	1.66 (0.97, 2.84)
	Tebuconazole	14	3,484	1.58	1.37 (0.64, 2.94)	1.09 (0.65, 1.83)
Chloroacetanilide						
	S-Metolachlor	11	2,462	1.74	1.58 (0.72, 3.46)	0.78 (0.48, 1.28)
Dicarboximide						
	Iprodione	22	5,104	2.55	2.32 (0.97, 5.52)	1.02 (0.61, 1.71)
Dithiocarbamate						
	Mancozeb	18	4,324	1.91	1.75 (0.82, 3.77)	0.49 (0.28, 0.86)
	Maneb	13	3,490	1.39	1.22 (0.57, 2.61)	1.32 (0.86, 2.04)
	Metam-Sodium	13	2,208	2.69	2.56 (1.19, 5.49)	1.53 (0.91, 2.58)
	Ziram	12	3,200	1.38	1.17 (0.55, 2.52)	0.80 (0.48, 1.33)
N-Methyl Carbamate						
	Carbaryl	17	4,044	1.91	1.71 (0.79, 3.69)	0.91 (0.58, 1.42)
Organochlorine						
	Dicofol	10	3,345	0.98	0.79 (0.34, 1.81)	1.44 (0.81, 2.56)
Organophosphorus						
	Chlorpyrifos†	25	5,934	3.26	3.05 (1.09, 8.52)	N/A
	Dimethoate	20	4,982	1.95	1.72 (0.75, 3.94)	1.12 (0.7, 1.79)
	Diazinon†	18	4,731	1.64	1.43 (0.66, 3.13)	N/A
	Acephate	15	3,146	2.13	1.94 (0.92, 4.12)	0.92 (0.58, 1.44)
	Malathion	15	4,515	1.17	0.99 (0.46, 2.12)	0.79 (0.42, 1.48)
	Phosmet	11	3,757	0.94	0.79 (0.36, 1.71)	1.06 (0.64, 1.76)
Pyrethroid						
	Permethrin	18	4,765	1.59	1.33 (0.60, 2.96)	0.95 (0.56, 1.60)
	Bifenthrin	14	3,760	1.40	1.20 (0.56, 2.58)	1.12 (0.68, 1.84)
	(S)-Cyper-methrin	14	2,768	2.29	2.09 (0.95, 4.59)	0.85 (0.51, 1.40)
Substituted Benzene						
	Chlorothalonil	18	4,262	1.95	1.79 (0.82, 3.89)	0.65 (0.37, 1.14)
Triazine						
	Simazine†	19	4,340	2.18	1.94 (0.89, 4.22)	N/A
Urea						

	Diuron	22	5,364	2.28	2.02 (0.85, 4.84)	1.70 (0.96, 2.99)
Other classes						
	Glyphosate‡	27	7,125	3.38	2.99 (0.88, 10.19)	N/A
	Paraquat Dichloride†	25	5,711	3.59	3.38 (1.23, 9.27)	N/A
	Oxyfluorfen	24	6,247	2.27	1.99 (0.76, 5.17)	1.39 (0.71, 2.75)
	Propargite	15	4,219	1.33	1.07 (0.49, 2.34)	0.97 (0.58, 1.64)
	Norflurazon	12	3,466	1.24	1.02 (0.47, 2.24)	0.60 (0.37, 0.98)
	Thiophanate-Methyl	10	3,127	1.07	0.92 (0.42, 2.01)	1.09 (0.66, 1.80)
	Captan	10	2,893	1.21	1.04 (0.47, 2.31)	1.09 (0.68, 1.77)

†Added based on previous literature or high usage in California

‡Glyphosate was defined as the following chemicals: glyphosate, glyphosate (salt), glyphosate (diammonium salt), glyphosate (isopropylamine salt), glyphosate (potassium salt), and glyphosate (trimesium)

[a]Adjusted for matching variable, birth year

[b]Adjusted for birth year, mother's race, SES-index variable, and exposure to any other pesticide

[c]Adjusted for birth year, mother's race, SES-index variable, and using an overall pesticide effect in the hierarchical model

2.5 Discussion

In this rural population-based study of ALL and AML which was not subject to recall or participation biases, we observed an over two-fold increased odds for ALL and an over four-fold increased odds for AML with exposure to any carcinogenic pesticide. This risk estimate is higher than the estimates from recent meta-analyses for ALL (meta-OR: 1.74, 95% CI:1.37-2.21)[142] and for AML, from a recent meta-analysis (meta-OR: 1.4).[143] The analyses for AML, however, were generally under-powered due to the small number of cases in less densely populated rural areas, which prevented us from estimating risks for one-third of the potentially carcinogenic pesticides. Many pesticides exhibited effect estimates above the null in single pollutant models. Due to the highly correlated nature of agricultural pesticide use and exposure, we employed hierarchical logistic modelling (HLM) in an attempt to identify the pesticides with the strongest effects after adjusting for other carcinogenic pesticide exposures, which however assumes that carcinogenic pesticides have a common effect or mean effect. By comparing our results from the single-pesticide models to the multiple-pesticide adjusted model (with HLM), several specific pesticide associations remained elevated: diuron, phosmet, kresoxim-methyl, and propanil. The effects estimated for the classes of anilides and ureas can be explained by the presence of propanil and diuron in these classes, and these classes only contain two pesticides each for ALL. Additionally, propyzamide had no effect in the single-pesticide model, but showed an association only in the hierarchical regression model.

While pesticides have previously been associated with increased risk of ALL, those results were almost exclusively based on studies that utilized ecological or case-control designs fraught with a potential for biased parental recall of pesticide exposure. Other studies that avoided retrospective

self-reporting of exposures assessed exposures according to census block groups or acreage devoted to farming, exposure assessment methods that are relatively crude.[50, 116, 144, 145] Our study is unique in that it utilizes specific address information and time of pregnancy to assess exposures of subjects in the state of California.

A similar case-control study in California assessing residential proximity to agricultural fields and childhood cancers in 1990-1997 found elevated risks in children of mothers exposed to metam-sodium ($\geq 50^{th}$ percentile) and dicofol ($\geq 50^{th}$ percentile) for all leukemias grouped together.[50] Our results suggest the elevated risk these authors observed with metam-sodium may have been driven by the association we also observed for AML. We were not able to confirm this studies finding of an increased risk of AML for dicofol as our point estimate was OR: 0.79, however, ALL was slightly elevated (OR: 1.41). Paraquat is not considered a carcinogen, yet we detected an increase of AML that could be linked to its potential as an agent that causes oxidative stress and mitochondrial DNA damage.[146] These mechanisms may explain the increase in AML seen here.

Of the pesticides we identified as being associated with ALL, diuron, a substituted phenylurea, is classified as a "known/likely" carcinogen according to the EPA. It is currently approved for use as an herbicide on terrestrial crops, for terrestrial non-crops (highways, pipelines, storage areas, etc.), and aquatic non-crops (irrigation, drainage ditches). Diuron has previously been linked to reproductive toxicity in rats,[147] and shown to harm placental choriocarcinoma cells.[148] Studies of human cell lines (breast adenocarcinoma and placental choriocarcinoma cells) showed that diuron is cytotoxic and potentially genotoxic; generation of reactive oxygen species (ROS) is a

likely mechanism for its toxicity. To the best of our knowledge, no studies have examined the effects of diuron exposure on human cancers.

The second pesticide with strong and consistent associations to ALL, phosmet is an organophosphate (OP) insecticide, which have been shown to be able to cross the placental barrier and OP metabolites have been discovered in meconium and cord blood samples.[149, 150] A study testing phosmet exposures on a human choriocarcinoma cell line reported decreased cell viability, reduced DNA synthesis, and induction of inflammatory cytokines.[151]

Propanil is an anilide classified as a suggestive carcinogen by EPA based upon studies in rats that found an increase in testicular interstitial cell adenomas after exposure.[136] However, there is relatively little previous research in humans. Lastly, the strobilurin class fungicide kresoxim-methyl has been classified as a likely carcinogen by the EPA based on findings that it is highly toxic to several aquatic species such as *daphnia magna* and grass carp.[152, 153] It has also been seen as having neurotoxic effects in a study of cultured cortical neurons.[154] This is the first human study to find a link between kresoxim-methyl and ALL.

Pesticides become airborne during and after applications with 'drift' determined by factors such as application method (aircraft dispersion vs. hydraulic spraying vs. controlled droplet application), wind direction, wind speed and pesticide volatility.[155-157] Validation studies of PUR data, which utilized biomarkers or employed air monitoring to compare pesticide use reported in the PUR system with chemical concentrations, have reported that pesticides have been measured at up to 8,000m from the location where they are applied.[135, 158-160] One validation study

comparing air samples collected by the California EPA Toxic Air Contaminant program and California Department of Pesticide Regulation records showed strong correlations between reported agricultural applications within a 3-mile radius and pesticide air concentrations measured up to 4 days later.[158] In addition to these validations of our exposure assessment, another strength of our study was that we were able to examine individual-level exposures at the residential address at birth.

Our study attempts to identify true confounders and adjust for them accordingly. However, with correlated exposures, it is difficult to identify and adjust for true confounders while avoiding over-adjustment.[161] In order to address this, we presented single-pesticide models which only adjust for likely confounders while excluding other pesticide exposures, while the semi-Bayesian approach accounts for co-exposures among carcinogens. Our results show most pesticides having effects greater than the null in the single-pesticide models while only a few survive the HLM.

This study has some limitations common to studies of pregnancy exposures. Since fetuses would have had to survive to birth and into early childhood, it is possible that those exposed who would have later developed cancers may at the same time have been less likely to survive if high exposures to a pesticide results in miscarriage or spontaneous abortion, which would generate a life birth bias. That is, selection of healthier fetuses with less exposure would result in an attenuation of effects. Another limitation is that residential information was only available at birth and not throughout pregnancy or early childhood. Previous studies have estimated that between 11%-32% of pregnant women move at least once during pregnancy with median move distances ranging from 4.2 to 10 km.[162-164] With an expected low percentage of women moving,

and those who do moving relatively small distances on average, our 4km exposure radius might have captured most residential ambient pesticide exposures from agricultural applications quite well. However, information on maternal occupational addresses and jobs that may also contribute to pesticide exposures in these rural communities were not available importantly we did not have information whether parents were employed in agriculture and incurred occupational exposures possibly leading to a severe underestimation of total exposures. Nevertheless, living on a farm not only generates ambient exposures, which we captured with our GIS tool, but is also associated with occupational exposures, thus our residential exposure estimates for these rural communities may reflect an appropriate exposure ranking for the most heavily exposed subjects.

2.6 Conclusion

In conclusion, our study results suggest that exposure to any carcinogenic pesticide exposure, or 2,6-dinitroanilines, anilides, and ureas classes of pesticides, specifically diuron, phosmet, kresoxim-methyl, and propanil increase the odds of ALL among those children exposed during pregnancy. Furthermore, exposure to metam-sodium and paraquat dichloride may increase the odds of AML. This study adds to the growing body of knowledge regarding prenatal pesticide exposures and childhood leukemias.

2.7 Appendix

Supplement 1

The EPA reclassified pesticides based on guidelines formed in 1986, 1996, 1999, and 2005. The 2005 classification contained five levels: “carcinogenic to humans,” “likely to be carcinogenic to humans,” “suggestive evidence of carcinogenic potential,” “inadequate information to assess carcinogenic potential,” and “not likely to be carcinogenic to humans.” The 1999 classification utilizes similar levels: “carcinogenic to humans,” “likely to be carcinogenic to humans,” “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential,” “data are inadequate for an assessment of human carcinogenic potential,” and “not likely to be carcinogenic to humans.” In 1996, there were three levels in the classification: “known/likely,” “cannot be determined,” and “not likely.” The 1986 classification used terminology similar to that of IARC: “group A – human carcinogen,” “group B – probable human carcinogen,” “group C – possible human carcinogen,” “group D – not classifiable as to human carcinogenicity,” and “group E – evidence of non-carcinogenicity for humans.”[136] We selected pesticides that were Group C and above (1986 classification), "Known/likely" (1996 classification), and "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" and above (1999, 2005 classifications).

Supplemental Table 2.1. Associations between ALL and exposure to agricultural pesticide applications within 4000m of the residential address, by trimesters

	Trimester 1			Trimester 2			Trimester 3		
Chemical	**Exposed Cases** N=132	**Crude OR[a]**	**Single-pesticide model[b]**	**Exposed Cases** N=132	**Crude OR[a]**	**Single-pesticide model[b]**	**Exposed Cases** N=132	**Crude OR[a]**	**Single-pesticide model[b]**
Diuron	61	2	1.96 (1.37, 2.8)	67	1.94	1.87 (1.31, 2.68)	62	1.72	1.65 (1.15, 2.36)
Phosmet	34	1.85	1.80 (1.20, 2.70)	47	1.87	1.82 (1.24, 2.67)	37	1.55	1.48 (1.00, 2.20)
Propanil	2	1.34	1.31 (0.32, 5.39)	5	2.83	2.84 (1.14, 7.09)	5	2.59	2.55 (1.02, 6.34)
Kresoxim-methyl	8	1.5	1.42 (0.68, 2.98)	12	1.63	1.53 (0.83, 2.84)	15	2.09	1.94 (1.10, 3.42)

[a]Adjusted for matching variable, birth year

[b]Adjusted for birth year, mother's race, and SES-index variable

Chapter 3. Exposure to Ambient Dichloromethane in Pregnancy and Infancy from Industrial Sources and Childhood Cancers in California

3.1 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 subjects. 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.

Conclusion

Our findings suggest that exposure to industrial dichloromethane releases might be a risk factor for childhood germ cell tumors, teratomas, and possibly acute lymphoblastic leukemias and AML.

3.2 Introduction

Childhood cancers are the leading cause of death from disease among children less than 14 years of age in the United States.[1] Incidence rates have been increasing and incidence in 2010 was 41% higher than it was in 1975.[165] Still, not much is known about the causes of childhood cancers. 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.[166-168] There is also possible support for a role of environmental exposures including ambient air pollution and pesticides.[129, 169, 170]

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.[171] Potential routes of human exposure to dichloromethane include inhalation, dermal contact, and ingestion.[172] 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.[66] 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.[173] 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.[174, 175] In adults, dichloromethane can affect the respiratory, gastrointestinal, hepatic, and neurological systems, but research on possible health effects in children is scarce.[176]

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.[66, 67] 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.[69] 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) and 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.[66, 177] 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.[178, 179] 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).[180]

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.[181]

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.

3.3 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.[182] 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.[129, 182-188]

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).[189]

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. 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 are classified 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.[66]

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,[190] 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 ($K_{ir} = 1/d_{ir}^2$) to an exposure total summed over multiple sites

denoted by *i* and residences denoted by *r*, where *K* is the total exposure amount. The quadratic decay model uses a modified equation based on equation 1 from Cutter et al.[191] 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.[190]

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

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 those living within 3km of any industrial release of dichloromethane 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.

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.[192]

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.[129] 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.

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 sufficient sample size. Results for the first year of life using the inverse-distance weighting and quadratic decay models are presented in Supplemental Table 3.2.

3.4 Results

Demographics are presented in Tables 3.1 and 3.2. 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 3.1 and 3.2). 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 3.3). The association with teratomas was mostly responsible for the elevated odds ratio for all germ cell tumors. 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).

In sensitivity analyses (Table 3.4) 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). In the inverse-weighted and quadratic decay models, we found similar elevated odds ratios with AML and teratomas (Supplemental Table 3.3) during pregnancy.

Table 3.1. Dichloromethane exposure patterns in relation to demographic characteristics

Characteristics	Ever Exposed[a]	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		
Metropolitan	25,200 (9.7%)	233,856 (90.3%)
Micropolitan/Small Town	0 (0%)	11,987 (100%)
Rural	0 (0%)	13,266 (100%)

[a]Children and pregnant women living within 3km of dichloromethane releases

Table 3.2. Dichloromethane exposures at 3km and childhood cancers

	ICCC/ICD-O-3[b] Codes	Ever Exposed[a]	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, [b]9071	22 (12.2%)	159 (87.9%)
Teratomas	101-105, [b]9080	34 (16.4%)	171 (83.6%)
Controls		23,956 (8.9%)	246,717 (91.1%)

[a]Children and pregnant women living within 3km of dichloromethane releases
[b]ICD-O-3 Code

Table 3.3. 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)**	**Crude OR[a]**	**Adjusted OR[b]**	**Cases (N)**	**Crude OR[a]**	**Adjusted OR[b]**
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)

[a]Adjusted for matching factor only (birth year)

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

Table 3.4. Associations of dichloromethane exposure and childhood cancers within a 3km buffer between residences and releasing facilities for births in CA between 1998-2011 (exact birth addresses only)

	Pregnancy			First year of life		
Cancer	**Cases (N)**	**Crude OR[a]**	**Adjusted OR[b]**	**Cases (N)**	**Crude OR[a]**	**Adjusted OR[b]**
Hematopoietic cancers	112	1.06	1.07 (0.88, 1.29)	97	1.05	1.05 (0.85, 1.29)
Leukemias	102	1.08	1.08 (0.88, 1.32)	91	1.09	1.09 (0.88, 1.34)
ALL	86	1.11	1.12 (0.89, 1.39)	80	1.10	1.11 (0.88, 1.39)
AML	13	1.00	1.01 (0.57, 1.76)	9	1.04	NA
Lymphomas	10	0.92	0.94 (0.50, 1.77)	6	0.68	NA
Non-Hodgkin's Lymphoma	3	1.06	NA	2	0.74	NA
CNS tumors	46	1.13	1.16 (0.86, 1.56)	36	1.05	1.08 (0.77, 1.52)
Ependymoma	7	1.52	NA	3	0.91	NA
Astrocytoma	18	1.01	1.07 (0.66, 1.72)	15	0.95	1.03 (0.61, 1.74)
Neuroblastoma	24	1.09	1.11 (0.74, 1.68)	13	0.97	0.95 (0.54, 1.66)
Retinoblastoma	15	1.20	1.23 (0.73, 2.07)	9	1.31	NA
Unilateral RB	8	0.95	NA	7	1.25	NA
Bilateral RB	7	1.74	NA	2	1.60	NA
Wilms tumor	14	0.77	0.79 (0.46, 1.35)	10	0.65	0.68 (0.36, 1.28)
Hepatoblastoma	4	0.60	NA	4	0.98	NA
Soft tissue sarcomas	12	0.98	0.94 (0.53, 1.68)	6	0.70	NA
Germ Cell tumors	7	0.99	NA	4	1.42	NA
Yolk Sac tumors	2	0.82	NA	1	0.65	NA
Teratomas	5	1.48	NA	3	6.98	NA

[a]Adjusted for matching factor only (birth year)

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

3.5 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;[193] while worldwide background levels in ambient air have been ranging from 0.17 – 43 ug/m^3.[66] 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.[194]

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).[178, 179] 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.[195, 196] 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.[197-200] 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.[201] These increases, especially in formaldehyde, have been linked to carcinogenic potential.[202]
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%) [130, 203]. There is a possibility of differential exposure misclassification if case mothers moved more frequently than control mothers. Some risk factors previously associated with higher mobility are low SES, lower maternal age, unmarried status.[203, 204] 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.

3.6 Conclusion

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 ALL and AML. The findings for leukemias supports the results of previous studies.[178, 179]

Appendix 3.7

Supplemental Table 3.1. Demographic characteristics of childhood cancer cases and controls.

Characteristics	Controls N=270,673 (%)	Hemato-poietic cancers (%)	Leukemias N=5,108 (%)	ALL N=4,127 (%)	AML N=740 (%)	Lymphoma N=621 (%)	Non-Hodgkin's Lymphoma (%)	CNS tumors N=2,380 (%)	Ependy-moma N=286 (%)	Astro-cytoma N=1,001 (%)	Neuro-blastoma N=1,381 (%)
Child's Sex											
Male	51	56	54.8	55.4	51.4	65.9	63.1	55.3	56.6	54	55.8
Female	49	44	45.2	44.6	48.6	34.1	36.9	44.7	43.4	46	44.2
Mother's Age											
<20	10.6	9.2	9.3	9.3	10	8.2	8.3	10	9.8	9.5	9.4
20-25	24.2	22.4	22	22.2	22.2	26.2	25.6	21.9	21.7	22.2	21.3
25-30	27.7	27.6	27.5	28.4	23.8	28.3	26.8	28	25.2	28.3	28.8
30-35	23.3	24.1	24.1	24.1	23.4	24.2	27.4	24.3	25.5	25.2	26.6
>35 years	14.3	16.7	17.1	16.1	20.7	13	11.9	15.9	17.8	14.9	13.9
Mother's Education (1989+)											
<8 years	12.6	13.4	13.4	13.1	13.4	13.1	10	9.4	8.5	8.6	7.9
9-11 years	18.5	17.5	17.2	17.5	15.4	20.3	19.2	17.2	16.3	15	15.1
12 years	28.3	29.7	29.6	29.5	31.6	30.2	31.5	27.8	29.3	29.4	29.6
13-16	20.3	19.2	19.5	19.4	19.6	16.7	23.1	21.2	24.4	23.1	21.5
>16 years	20.3	20.3	20.3	20.5	20.1	19.7	16.2	24.4	21.5	23.8	25.9
SES-Index											
1 (Lowest)	25	24.3	24	23.8	24.7	26.6	21.4	22.2	21	21.8	20
2	24.3	24.8	25	25.1	24.1	23.3	24.4	23.3	25.9	24	24.3
3	22.1	22.2	22.2	22.5	20.8	22.1	17.3	22.8	25.9	21.5	24.1
4	15.8	15.9	15.9	15.8	17.7	15.8	22.6	17.4	12.9	17.1	16.8
5 (Highest)	12.7	12.8	12.8	12.8	12.7	12.2	14.3	14.3	14.3	15.7	14.8
Method of Payment for Prenatal Care (1989+)											
Private	49.9	54	54.2	55	50.9	52.7	59.4	57.6	60.9	59.7	58.4
Public	50.1	46	45.8	45	49.1	47.3	40.6	42.4	39.1	40.3	41.6
Mother's Race											
White Non-Hispanic	35	35.3	35.4	35.7	33.6	34.9	41.7	45.8	38.5	50.9	47.3
Hispanic	45.9	49.1	49.3	49.8	46.6	47	39.9	37.7	42.3	34	35
Black	6.7	3.6	3.4	2.8	6.2	5.2	7.7	6.7	8.4	6.2	6.2
Other	12.5	12	11.9	11.6	13.5	12.9	10.7	9.7	10.8	8.9	11.5
Father's Race											
White Non-Hispanic	30.7	33.4	33.8	35.1	28.2	29.8	35.1	39.4	31.8	44.2	40
Hispanic	43.5	46.6	46.7	47.1	43.9	45.6	39.3	36.6	40.2	33.5	32.9
Black	6.7	4	3.8	3.2	7	5.8	7.7	7.2	8	6.7	6.4
Other	19.1	16	15.7	14.5	20.8	18.8	17.9	16.7	19.9	15.7	20.6
Urban/Rural											
Metropolitan	91.1	91.4	91.4	91.5	91.4	91.3	90.5	90.5	91.3	90.4	92.4
Micropolitan	4.2	4.3	4.3	4.2	4.7	4.5	5.4	4.9	4.5	5.1	3.5
Small town/Rural	4.6	4.2	4.2	4.3	3.9	4.2	4.2	4.5	4.2	4.5	4.1

Supplemental Table 3.2. Demographic characteristics of childhood cancer cases and controls in percentages *cont.*

	Retinoblastoma N=743 (%)	Unilateral Retinoblastoma N=513 (%)	Bilateral Retinoblastoma N=223 (%)	Wilms tumor N=1,057 (%)	Hepatoblastoma N=342 (%)	Soft Tissue sarcomas N=707 (%)	Germ Cell tumors N=451 (%)	Yolk Sac tumors N=181 (%)	Teratomas N=207 (%)
Child's Sex									
Male	55	53.2	57.8	47.2	59.8	58.3	56.8	72.9	44
Female	45	46.8	42.2	52.8	40.2	41.7	43.2	27.1	56
Mother's Age									
<20	9.6	9.4	10.3	9.8	13.5	9.5	11.8	14.9	12.1
20-25	23.7	25.1	21.1	20.9	15.8	21.6	24.2	21	26.1
25-30	30.6	31.8	27.8	28	25.2	29.8	24.8	25.4	25.6
30-35	21.9	20.5	24.2	27.9	24.6	24	23.7	23.2	21.7
>35 years	14.3	13.3	16.6	13.3	20.8	15	15.5	15.5	14.5
Mother's Education (1989+)									
<8 years	10.5	10.2	11.6	9.8	13.4	11.6	14.6	24.5	8.2
9-11 years	19.5	17.7	22.7	15.4	16.9	16.4	18.1	18.5	17
12 years	29.4	31.3	25.1	32.7	29	29.5	29.2	23.8	34
13-16	21.1	22.5	17.9	20.7	14.3	19.9	19.4	19.2	21.6
>16 years	19.5	18.4	22.7	21.3	26.4	22.6	18.6	13.9	19.1
SES-Index									
1 (Lowest)	24.1	24.2	23.3	23.2	23.8	24.8	23.3	24.3	22.2
2	24.9	23.6	28.7	25.7	18.8	23.3	26.8	26.5	30
3	21.7	23.2	17.5	20.9	22.9	23.1	20.4	17.1	21.7
4	17.9	16.6	21.1	16.6	17.3	14.7	15.1	15.5	13.5
5 (Highest)	11.4	12.5	9.4	13.6	17.3	14.1	14.4	16.6	12.6
Method of Payment for Prenatal (1989+)									
Private	51.9	53.2	50.2	55.6	52.7	55.7	51.6	48.1	53.5
Public	48.1	46.8	49.8	44.4	47.3	44.3	48.4	51.9	46.5
Mother's Race									
White Non-Hispanic	31.4	30.8	33.2	42.8	33.4	37.6	31.7	29.8	30
Hispanic	47	46.8	47.1	41.4	50.1	43.1	43	47.5	42.5
Black	8.1	8.8	6.3	7.9	3.2	6.2	5.3	1.7	7.7
Other	13.6	13.6	13.5	7.9	13.2	13	20	21	19.8
Father's Race									
White Non-Hispanic	29.1	28.8	30.5	37.9	29	34.7	26.8	22.7	27.1
Hispanic	45.4	45.2	45.7	39.2	48.1	40.6	40.8	46.4	39.1
Black	6.7	7.4	4.9	8.4	3.8	7.1	4.2	1.7	6.8
Other	18.8	18.5	18.8	14.5	19.1	17.7	28.2	29.3	27.1
Urban/Rural									
Metropolitan	91.9	91.8	92.4	92.1	91.8	91.5	91.8	91.7	91.8
Micropolitan	4.6	4.9	4	4.3	4.4	4.2	4.2	3.9	4.8
Small town/Rural	3.5	3.3	3.6	3.6	3.8	4.2	4	4.4	3.4

Supplemental Table 3.3. 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)**	**Crude OR[a]**	**Adjusted OR[b]**	**Cases (N)**	**Crude OR[a]**	**Adjusted OR[b]**
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)

[a]Adjusted for matching factor only (birth year)

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

Chapter 4. Maternal Smoking and Childhood Acute Lymphoblastic Leukemia: A study of survivor bias

4.1 Abstract

Background

Previous studies on maternal smoking during pregnancy and the risk of childhood acute lymphoblastic leukemia (ALL) have yielded inconsistent and often negative results. This may be due to a special type of survivor bias in pregnancy studies, 'live birth bias,' which may result from miscarriages arising from maternal smoking. In this study, we aimed to examine the likelihood that this bias accounts for the associations found between maternal smoking and ALL.

Methods

Utilizing data from the Danish National Registries, we performed Monte-Carlo techniques to simulate populations reflecting Danish demographic characteristics. Simulations tested a range of possible effects of maternal smoking on ALL (1.0, 1.25, 1.75, 2.0) and on fetal loss.

Results

Assuming a null relationship between maternal smoking and ALL, we observed a weak selection bias across the range of values tested. In the scenario with the strongest assumptions of the effects of the biasing pathway, we found the bias to affect values up to 16%. In other scenarios using a smoking effect of 1.25, 1.75, and 2.0, we saw a similarly weak selection bias.

Conclusion

Based on our findings, the survivor bias, or 'live-birth bias,' does not seem to have a strong enough effect to fully explain the null or sometimes inverse associations seen in previous studies. It is likely that this type of selection bias may partially explain the inconsistent findings, but other possible explanations should be explored.

4.2 Introduction

Despite advances in medical technology and research, miscarriage, also known as pregnancy loss or spontaneous abortion, remains quite common. Miscarriage occurs in at least 25% and upwards of 50% of all conceptions and approximately 12-15% of clinically recognized pregnancies.[96, 97] Most miscarriages occur in the first 12 weeks of gestation.[97] A number of risk factors for miscarriage have been identified, including prior miscarriage, genetic abnormalities, maternal age, imbalanced endocrine levels, uterine abnormalities, and immunological interactions between the maternal immune system and fetal antigens.[94, 95, 205, 206] Exposures to persistent environmental and occupational chemicals, endocrine disruptors, and industrial pollutants have also been suggested as possible risk factors for miscarriage.[95, 101, 103] In addition, alcohol and smoking have also been reported as being associated with miscarriage.[109, 207]

Childhood acute lymphoblastic leukemia (ALL) is the most common cancer among children and accounts for approximately 78% of childhood leukemias, and occurs most commonly among children aged 2 to 5.[208, 209] Tobacco is the largest contributor to cancer worldwide and is an established cause of myeloid leukemia in adults, with evidence for lymphoblastic leukemia still lacking.[210] Prenatal parental smoking is a plausible risk factor for childhood ALL due to its ability to cause DNA damage, and its ability to cross the placenta.[210-212] At least 60 known carcinogens are present in tobacco smoke and their active ingredients are hypothesized to affect the fetus.[213, 214] Measures of cord blood and amniocytes of fetuses of mothers who smoke have been shown to have much higher frequencies of lymphocyte and chromosomal mutations than in those of mothers who did not smoke.[211, 215]

Despite that maternal smoking may plausibly be a cause of ALL, studies on this topic have shown null and often inverse associations.[77-88] Considering only the population-based prospective studies, both negative[78, 216, 217] and null associations have been reported.[218] In the studies that examined dose-response effects, maternal smoking has tended to show a positive association with ALL among light smokers (<10 cigarettes per day) (median OR =1.10, range OR: 0.69-1.63) but null or inverse associations were reported with heavier levels of smoking (≥30 cigarettes per day) reaching effect estimates as low as 0.26.[78, 83, 86, 89-92] In contrast, studies that have examined paternal smoking have more consistently found increases in risk with preconception smoking.[79-81, 85, 88, 93-95]

When measuring exposure-disease relationships in reproductive epidemiology, miscarriages can bias the results of studies due to a type of survivor bias referred to as a 'live-birth' bias.[219] As such, only those strong enough to survive insults during pregnancy are observed at birth and can be counted in a population study. Hence, studies of outcomes such as childhood cancers that are ascertained only among live births are missing the remaining cohort that fail to survive through pregnancy. Because smoking is potentially a reason for miscarriage and may also be a cause of ALL, we examine in this study the possibility of survivor bias as an explanation for the null and inverse associations seen in the literature between maternal smoking during pregnancy and childhood ALL. Here we utilized the Danish national registries[220-222] to obtain prior information on the frequencies of smoking and childhood ALL in the population. We selected this population for its relatively high smoking prevalence and prospectively collected maternal smoking information.

4.3 Methods

We utilized directed acyclic graphs (DAGs) to depict the structural relationships between our exposure, covariates, and outcome of interest. The use of DAGs utilizes a basic set of rules that have been described and used elsewhere.[223] The two largest sources of bias in a DAG can be represented through uncontrolled confounding, with the first being failure to control for a confounder (a common cause, Fig. 1a) and the second resulting from conditioning on a collider (Fig. 1b), thereby opening a previously closed path between the exposure and disease through unknown factors or unmeasured common cause(s) (UF) of ALL and fetal loss. When selecting or conditioning only on those who survive until birth, UF connects the open collider path from smoking to ALL. Selection bias or survivor bias is an example of collider bias resulting from study participants' differential non-response or loss to follow-up.[224, 225]

When we examine outcomes only among live births, we lack important data on non-surviving fetuses (Figures 4.1/4.2). If there exists an association between the exposure of interest and an uncontrolled common cause of fetal loss and the outcome of interest, a form of collider bias is present. In Figures 4.1 and 4.2, [S=1] represents survival or live-birth status.

In our study we examine three possible scenarios based on existing knowledge of maternal smoking and childhood ALL. In the first scenario (Figure 4.3), we assumed that there is no causal association between maternal smoking and childhood ALL, but we assumed that maternal smoking increases the risk of fetal loss.[109] We also included unknown factors (UF) that represent common causes of a fetal loss as well as leukemia. Based on the literature, UF could possibly represent genetic predisposition to childhood ALL, ionizing radiation, or altered exposure to infectious diseases.[226, 227] In addition, we adjusted for known confounding factors (Z) of

childhood ALL and maternal smoking that are also associated with fetal loss, which based on the literature might include paternal smoking or maternal age.[227-230] In the second scenario (Figure 4.4), we employ the same variables and introduce a weak causal relationship between maternal smoking and childhood ALL risk (ORs ranging from 1.25 - 2.0). We tested a range of associations regarding the strength of smoking to survival ($P_{Sm-S=1}$) and the strength of UF to survival and ALL ($OR_{UF-S=1}$ and OR_{UF-ALL}). In the third scenario (Figure 4.5), we examined the effect of uncontrolled confounding in our study. One uncontrolled confounder, UC_1 was created with a prevalence of 20%. We simulated a range of causal effects of the uncontrolled confounder from 0.3 to 1.25 in its effects on maternal smoking and ALL (OR_{UC1-Sm} and $OR_{UC1-ALL}$).

Statistical analyses

We performed Monte-Carlo techniques to simulate populations of 10,000,000 individuals with fixed priors for population characteristics. Using rates from the Danish National Registries, we estimated an incidence rate around 3.8 per 100,000 for childhood ALL.[231] Known and unknown confounders (Z and U1) and smoking status were simulated as binary variables using random draws from Bernoulli distributions. The probabilities for covariates were set as follows: $OR_{Z-Sm} = 1.2$, $OR_{Z-ALL} = 1.2$, $OR_{Z-S=1} = 0.8$. Based on the smoking rates in the Danish Medical Birth Register, smoking prevalence was set at 21%, with a slight decline by birth year. Effects of birth year on maternal smoking and ALL were set to $OR_{BY-SM} = 0.95$ and $OR_{BY-ALL} = 1.11$.

Conditional probabilities for survival or live birth status and childhood ALL were determined using the following formulas:

Scenario 1:

Childhood ALL ~ B(1,(1/(1+exp(-(log(P(ALL=1)/(1-P(ALL=1))) + log($OR_{Z\text{-}ALL}$)*Z + log($OR_{UF\text{-}ALL}$)*UF + log($OR_{BY\text{-}ALL}$)*BY))))

S ~ B(1,(1/(1+exp(-(log(P(S=1)/(1-P(S=1))) + log($OR_{Z\text{-}ALL}$)*Z + log($OR_{Sm\text{-}S=1}$)*Sm + log($OR_{UF\text{-}S=1}$)*UF))))

Scenario 2:

Childhood ALL ~ B(1,(1/(1+exp(-(log(P(ALL=1)/(1-P(ALL=1))) + log($OR_{Z\text{-}ALL}$)*Z + log($OR_{UF\text{-}ALL}$)*UF + log($OR_{BY\text{-}ALL}$)*BY+ log($OR_{SM\text{-}ALL}$)*SM))))

S ~ B(1,(1/(1+exp(-(log(P(S=1)/(1-P(S=1))) + log($OR_{Z\text{-}ALL}$)*Z + log($OR_{Sm\text{-}S=1}$)*Sm + log($OR_{UF\text{-}S}$)*UF))))

Scenario 3:

Childhood ALL ~ B(1,(1/(1+exp(-(log(P(ALL=1)/(1-P(ALL=1))) + log($OR_{Z\text{-}ALL}$)*Z + log($OR_{UF\text{-}ALL}$)*UF + log($OR_{BY\text{-}ALL}$)*BY+ log($OR_{Sm\text{-}ALL}$)*Sm + log($OR_{UC1\text{-}S}$)*UC1))))

Maternal Smoking ~ B(1,(1/(1+exp(-(log(P(Sm)/(1-P(Sm))) + log($OR_{Z\text{-}Sm}$)*Z + log($OR_{BY\text{-}Sm}$)*BY + log($OR_{UC1\text{-}S}$)*UC1))))

S ~ B(1,(1/(1+exp(-(log(P(S=1)/(1-P(S=1))) + log($OR_{Z\text{-}ALL}$)*Z + log($OR_{Sm\text{-}S=1}$)*Sm + log($OR_{UF\text{-}S}$)*UF + log($OR_{UC1\text{-}S}$)*UC1))))

We used SAS 9.3 (SAS Institute Inc., Cary, NC, USA) to perform the simulations and analyses. We used logistic regression on each of the simulated datasets to analyze the association between maternal smoking and childhood ALL for each scenario, which were then repeated across the

range of parameter values in each scenario. We then compared the "biased" or observed OR (OR_{bias}) to the simulated "true" OR (OR_{true}) to determine the extent of bias. For each simulation, the observed ORs and 95% simulation intervals were shown using the 2.5th, 50th, and 97.5th percentiles.

4.4 Results

Table 4.1 presents the results from scenario 1, where smoking is assumed to have no effect on the risk of childhood ALL. The magnitude of the inverse association between smoking and ALL was greatest with more extreme values of the relationships between UF and survival, smoking and survival, and UF and ALL. Of the three parameters, the relationship between smoking and survival had the greatest impact on the magnitude of bias present in the simulation ORs. With all three parameters set to their most extreme values, that is, $OR_{Sm\text{-}S=1} = 0.3$, $OR_{UF\text{-}S=1} = 0.3$, and $OR_{UF\text{-}ALL} = 10$, the simulation OR was 0.88, with simulation interval (0.77, 0.99). Assuming moderate values ($OR_{Sm\text{-}S=1} = 0.5$, $OR_{UF\text{-}S=1} = 0.5$, $OR_{UF\text{-}ALL} = 5$) for the respective parameters resulted in a weak decrease (OR: 0.94, 95% CI: 0.82, 1.08).

In scenario 2, we estimated the magnitude of bias in a model with varying levels of smoking effects on childhood ALL (true OR = 1.25 to 2.0). In table 4.2, we assume the true OR to be 1.25. Here we also limited the table to $OR_{U\text{-}ALL} = 5$. The table shows that bias from survival in this scenario would result in an OR of around 1 or less only in scenarios where the effect of smoking on survival is quite strong (< 0.3), in addition to the effect of UF on survival being equally strong (< 0.3). Although the direction of the bias remained consistent with attenuation of effects, however, none of the ORs were below null.

Table 4.3 depicts that using a true OR of 1.75 for the effect of smoking on ALL and with $OR_{UF-ALL} = 5$, the largest bias results in a simulation OR of 1.64 (7% decrease). Similar to the previous findings, the most extreme values of the effects of smoking on survival affected the ORs the most. In this table, none of the point estimates were below the null, though with increasing values of OR_{UF-ALL} up to 10, the lowest estimate we found was OR = 1.58. Table 4.4 presents the estimates from the true OR of smoking on ALL to be OR = 2.0. Again, results were mildly biased towards the null.

In the third scenario, where we examined the effects of uncontrolled confounding, fixing priors to the following: $OR_{Sm-ALL} = 1.25$, $OR_{UF-ALL} = 5$, $OR_{Sm-S=1} = 0.5$, $OR_{UF-S=1} = 0.5$, we found that, using a range of possible effects for U1, effect estimates ranged from OR = 1.05 to 1.58. Table 4.5 shows the scenario where $OR_{U1-Sm} = 0.3$ and $OR_{U1-ALL} = 4$ (the strongest negative assumption of U1 on smoking) we saw a negative bias to 1.05 from the assumed true estimate of 1.20. On the other hand, using the assumption that $OR_{U1-Sm} = 1.25$ and $OR_{U1-ALL} = 4$, we found an overall positive bias to OR = 1.38.

Table 4.1. Observed effects, bias corrected estimates, and the strength of live-birth bias on the assumed null relationship between maternal smoking and ALL

Set	OR_{UF-ALL}	$OR_{UF-S=1}$	$OR_{Sm-S=1}$	Biased, Confounder Adjusted OR	"True" OR	Bias Factor
Sim 1	3	0.7	0.7	0.94 (0.81, 1.10)	0.94	1
Sim 2	3	0.7	0.5	0.90 (0.77, 1.06)	0.94	1.04
Sim 3	3	0.7	0.3	0.84 (0.71, 1.01)	0.94	1.12
Sim 4	3	0.5	0.7	0.92 (0.78, 1.08)	0.94	1.03
Sim 5	3	0.5	0.5	0.89 (0.76, 1.05)	0.94	1.06
Sim 6	3	0.5	0.3	0.85 (0.71, 1.02)	0.94	1.11
Sim 7	3	0.3	0.7	0.89 (0.75, 1.05)	0.94	1.06
Sim 8	3	0.3	0.5	0.88 (0.74, 1.05)	0.94	1.07
Sim 9	3	0.3	0.3	0.86 (0.72, 1.04)	0.94	1.09
Sim 10	5	0.7	0.7	0.99 (0.87, 1.13)	1.00	1.01
Sim 11	5	0.7	0.5	0.95 (0.83, 1.09)	1.00	1.05
Sim 12	5	0.7	0.3	0.90 (0.77, 1.04)	1.00	1.11
Sim 13	5	0.5	0.7	0.96 (0.84, 1.10)	1.00	1.04
Sim 14	5	0.5	0.5	0.94 (0.82, 1.08)	1.00	1.06
Sim 15	5	0.5	0.3	0.88 (0.76, 1.03)	1.00	1.13
Sim 16	5	0.3	0.7	0.92 (0.80, 1.07)	1.00	1.08
Sim 17	5	0.3	0.5	0.90 (0.78, 1.05)	1.00	1.11
Sim 18	5	0.3	0.3	0.90 (0.76, 1.05)	1.00	1.12
Sim 19	8	0.7	0.7	1.01 (0.91, 1.13)	1.01	1
Sim 20	8	0.7	0.5	0.99 (0.88, 1.11)	1.01	1.03
Sim 21	8	0.7	0.3	0.94 (0.83, 1.07)	1.01	1.08
Sim 22	8	0.5	0.7	0.99 (0.88, 1.11)	1.01	1.02
Sim 23	8	0.5	0.5	0.97 (0.86, 1.09)	1.01	1.05
Sim 24	8	0.5	0.3	0.91 (0.80, 1.03)	1.01	1.12
Sim 25	8	0.3	0.7	0.96 (0.85, 1.08)	1.01	1.06
Sim 26	8	0.3	0.5	0.92 (0.81, 1.04)	1.01	1.1
Sim 27	8	0.3	0.3	0.89 (0.77, 1.02)	1.01	1.14
Sim 28	10	0.7	0.7	1.00 (0.90, 1.10)	1.02	1.02
Sim 29	10	0.7	0.5	0.98 (0.88, 1.08)	1.02	1.04
Sim 30	10	0.7	0.3	0.94 (0.84, 1.05)	1.02	1.09
Sim 31	10	0.5	0.7	0.98 (0.88, 1.09)	1.02	1.04
Sim 32	10	0.5	0.5	0.96 (0.86, 1.07)	1.02	1.06
Sim 33	10	0.5	0.3	0.91 (0.81, 1.02)	1.02	1.12
Sim 34	10	0.3	0.7	0.95 (0.85, 1.06)	1.02	1.08
Sim 35	10	0.3	0.5	0.91 (0.81, 1.03)	1.02	1.11
Sim 36	10	0.3	0.3	0.88 (0.77, 0.99)	1.02	1.16

Table 4.2. Observed effects, bias corrected estimates, and the strength of live-birth bias on the assumed effect of smoking on ALL set at OR = 1.25 setting the UF-ALL relationship at OR = 5.

Set	OR_{UF-ALL}	$OR_{UF-S=1}$	$OR_{Sm-S=1}$	Biased, Confounder Adjusted OR	"True" OR	Bias Factor
Sim 1	5	0.7	0.7	1.26 (1.08, 1.38)	1.27	1.01
Sim 2	5	0.7	0.5	1.22 (1.01, 1.32)	1.27	1.04
Sim 3	5	0.7	0.3	1.16 (1.13, 1.43)	1.27	1.09
Sim 4	5	0.5	0.7	1.24 (1.06, 1.37)	1.27	1.02
Sim 5	5	0.5	0.5	1.21 (0.99, 1.31)	1.27	1.05
Sim 6	5	0.5	0.3	1.14 (1.10, 1.41)	1.27	1.11
Sim 7	5	0.3	0.7	1.20 (1.02, 1.33)	1.27	1.06
Sim 8	5	0.3	0.5	1.16 (0.98, 1.31)	1.27	1.09
Sim 9	5	0.3	0.3	1.14 (0.98, 1.31)	1.27	1.11

Table 4.3. Observed effects, bias corrected estimates, and the strength of live-birth bias on the assumed effect of smoking on ALL set at OR = 1.75 setting the UF-ALL relationship at OR = 5.

Set	OR_{UF-ALL}	$OR_{UF-S=1}$	$OR_{Sm-S=1}$	Biased, Confounder Adjusted OR	"True" OR	Bias Factor
Sim 1	5	0.7	0.7	1.80 (1.62, 2.00)	1.78	0.99
Sim 2	5	0.7	0.5	1.75 (1.57, 1.95)	1.78	1.02
Sim 3	5	0.7	0.3	1.71 (1.52, 1.91)	1.78	1.05
Sim 4	5	0.5	0.7	1.77 (1.59, 1.97)	1.78	1.01
Sim 5	5	0.5	0.5	1.74 (1.56, 1.94)	1.78	1.02
Sim 6	5	0.5	0.3	1.67 (1.49, 1.88)	1.78	1.07
Sim 7	5	0.3	0.7	1.73 (1.55, 1.94)	1.78	1.03
Sim 8	5	0.3	0.5	1.68 (1.50, 1.88)	1.78	1.06
Sim 9	5	0.3	0.3	1.64 (1.45, 1.86)	1.78	1.09

Table 4.4. Observed effects, bias corrected estimates, and the strength of live-birth bias on the assumed effect of smoking on ALL set at OR = 2.0 setting the UF-ALL relationship at OR = 5.

Set	$OR_{UF\text{-}ALL}$	$OR_{UF\text{-}S=1}$	$OR_{Sm\text{-}S=1}$	Biased, Confounder Adjusted OR	"True" OR	Bias Factor
Sim 1	5	0.7	0.7	2.04 (1.85, 2.25)	2.04	1
Sim 2	5	0.7	0.5	2.00 (1.80, 2.21)	2.04	1.02
Sim 3	5	0.7	0.3	1.96 (1.76, 2.18)	2.04	1.04
Sim 4	5	0.5	0.7	2.02 (1.82, 2.23)	2.04	1.01
Sim 5	5	0.5	0.5	1.98 (1.78, 2.20)	2.04	1.03
Sim 6	5	0.5	0.3	1.92 (1.72, 2.15)	2.04	1.06
Sim 7	5	0.3	0.7	1.97 (1.77, 2.19)	2.04	1.04
Sim 8	5	0.3	0.5	1.91 (1.72, 2.14)	2.04	1.07
Sim 9	5	0.3	0.3	1.89 (1.68, 2.12)	2.04	1.08

Table 4.5. Results from simulation of scenario 3, the presence of uncontrolled confounding, among live-born subjects and uncontrolled confounding

$OR_{U1\text{-}Sm}$	$OR_{U1\text{-}ALL}$	Adjusted OR[b]
0.3	2	0.97 (0.85, 1.12)
0.3	4	0.84 (0.74, 0.96)
0.7	2	1.14 (1.01, 1.30)
0.7	4	1.11 (1.00, 1.24)
1.25	2	1.29 (1.15, 1.45)
1.25	4	1.38 (1.25, 1.52)

[a]Priors were fixed as follows: $OR_{Sm\text{-}ALL} = 1.25$, $OR_{UF\text{-}ALL} = 5$, $OR_{U2\text{-}ALL} = 2$, $OR_{Sm\text{-}S=1} = 0.5$, $OR_{UF\text{-}S=1} = 0.5$

[b]Adjusted for known confounders (Z)

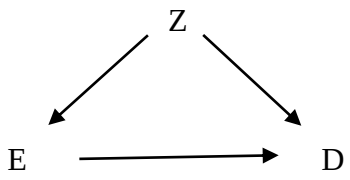

Figure 4.1. Uncontrolled confounding by Z on the relationship of E on D.

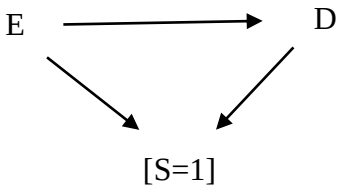

Figure 4.2. Collider bias resulting from conditioning on the child of both E and D.

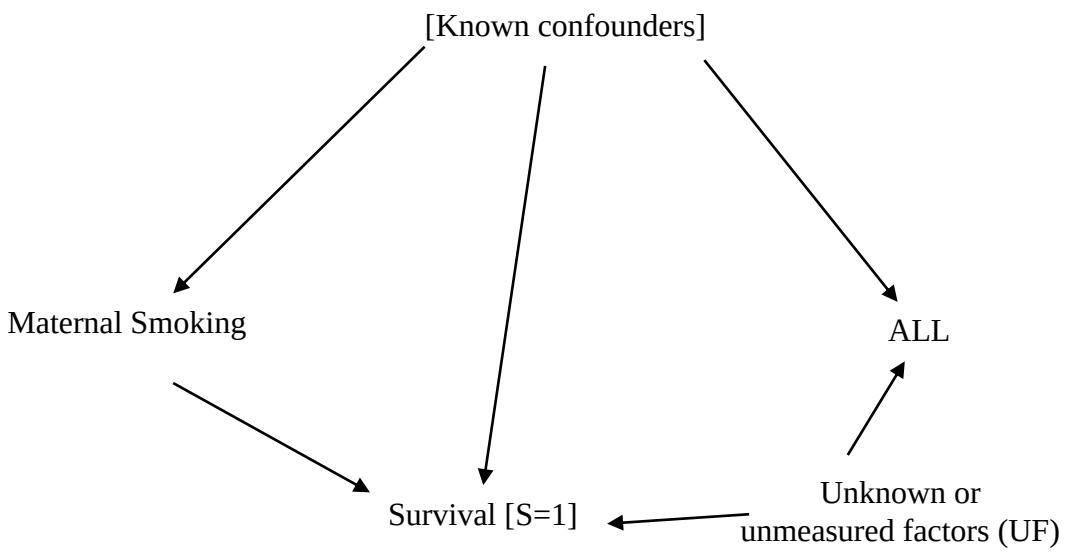

Figure 4.3. "Live-birth" bias represented as "[S=1]" with an assumed null relationship between maternal smoking and ALL

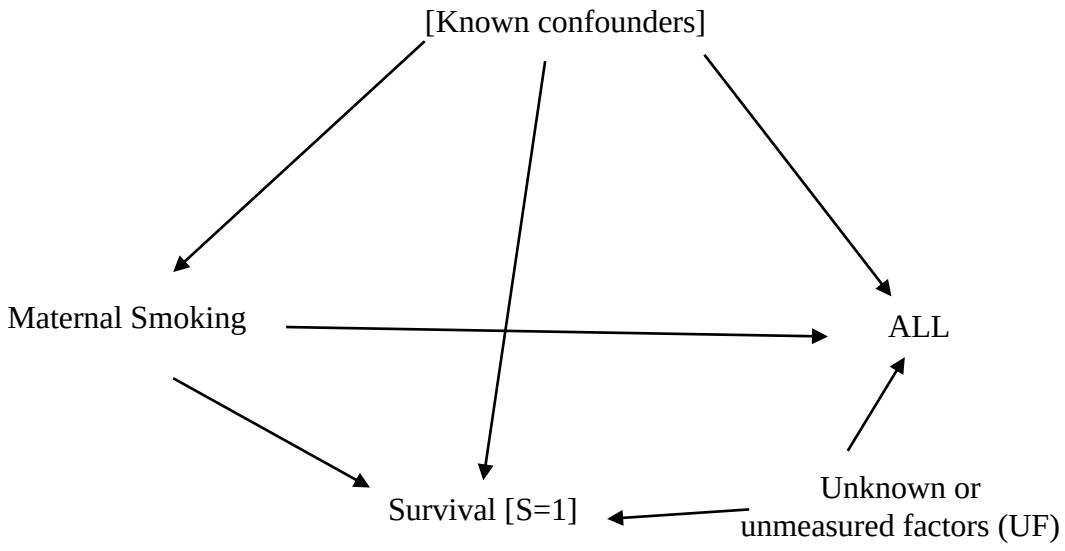

Figure 4.4. "Live-birth" bias represented as "[S=1]" with an assumed positive relationship between maternal smoking and ALL

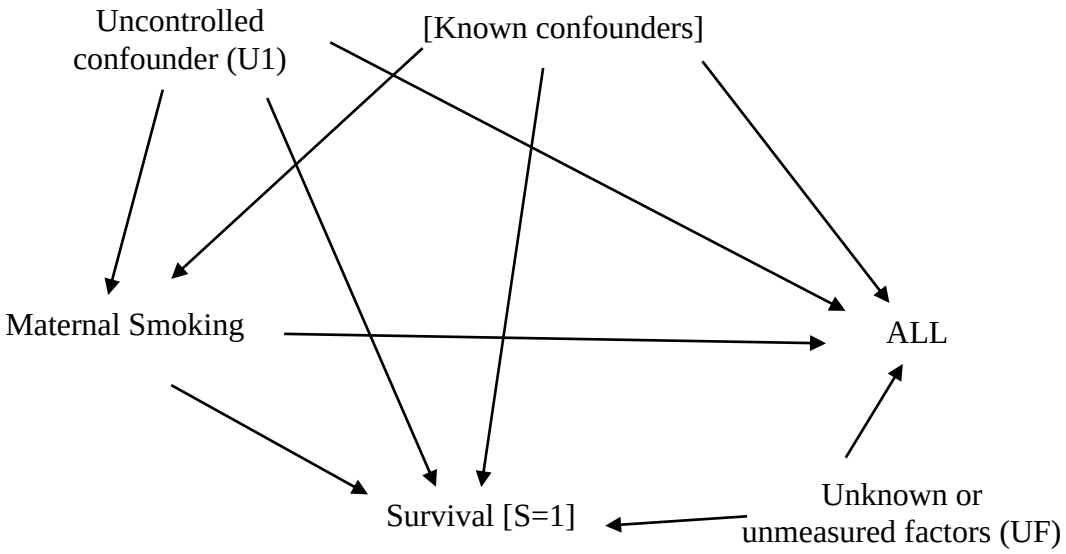

Figure 4.5. "Live-birth" bias represented as "[S=1]" with an assumed positive relationship between maternal smoking and ALL with uncontrolled confounding

4.7 Discussion

Our aim was to demonstrate an example of survivor bias, previously referred to as 'live-birth bias,' in prenatal and perinatal epidemiology.[219] Since only those that survive to birth are able to be studied, each factor influencing survival which is also connected to the exposure or outcome, on the same path in our DAG, will result in a "collider" bias. Maternal smoking may have a strong inverse association to fetal survival, and is potentially a common risk factor of survival and ALL, thus it is on the biasing pathway. When each relationship is strong, a larger number of those that would have become ALL cases no longer survive. This is an example of conditioning on survival, which opens the biasing "collider" pathway. The negative bias produced by this open pathway results in an underestimation of the effect of maternal smoking on ALL. The null and sometimes negative associations found with maternal smoking and ALL may be due, in part, to the aforementioned bias, however, the magnitude of the bias was fairly weak with bias factors ranging from 0.98 to 1.16 for the most extreme parameter values. This bias resulted in a maximum 15% decreased OR. Thus, in published studies, even assuming the strongest relationships between our variables, smoking explains only a small portion of the reported negative associations.

Smoking during pregnancy has been linked to a number of negative birth outcomes including stillbirths.[232] Even though rates of pregnancy smoking have decreased over the past several decades from a peak of around 31.6% in 1991 to 12.5% in 2010[75], it is estimated that the decreases seen in smoking during pregnancy are more likely due to a decrease of smoking initiation rather than mothers quitting during pregnancy. Successful quit rates in pregnancy are estimated to be only between 20%-40%.[233] In another study, social norms and pressures to stop

smoking during pregnancy often hindered by the women's dependence on tobacco resulted in relapse in a majority of women.[234] This likely underestimation in properly categorizing or assessing women's true smoking status could offer an additional explanation for the lack of association seen in previous studies.

Although some earlier studies found no association between maternal smoking and miscarriage, recent evidence on both active maternal smoking and secondhand smoke exposure have been linked to an increased risk of miscarriage.[109] A recent meta-analysis (2014) reported a 23% increase in miscarriage for any active smoking, and an overall 1% increased risk of miscarriage per cigarette smoked per day.[212] Interestingly, two studies found an increased risk of ALL among those born after a prior miscarriage,[227, 235] results which would seem to support a possible link in fetal survivorship and ALL risk as modeled in our simulation.

In a recent meta-analysis of the effect of maternal smoking on ALL, ever smoking in pregnancy was related to a 10% increase in ALL (Meta-OR=1.10), an estimate which was not found to be influenced by publication bias.[236] This provides us with an estimate against which we can compare our simulation results. Utilizing the strongest assumptions in our simulation of the effects of known and unknown risk factors, a biased OR of 1.10 would be seen if the true effect of smoking on ALL is OR = 1.25 (14% decrease). If our assumptions of the effects of known and unknown risk factors are more moderate, a biased OR of 1.10 would indicate a true OR of 1.15-1.20 (6% decrease).

In considering the findings of our study, it is important to note that specific assumptions were made with regards to the associations between the major variables in our model. To account for the range of strengths of associations in the most important relationships, we utilized a variety of effect estimates to explore how strongly these factors affected survival. These are simulated data based on information taken from the Danish registers, but relationships are simplified and, therefore, do not represent a population directly comparable to that of the actual data. Other assumptions include no other uncontrolled confounding or bias from other sources. As we observed in our Table 4.5 when there was an uncontrolled confounding factor, odds ratios ranged from 0.84 to 1.38 (bias factors U1 = 0.3 to 1.25), assuming an OR of 1.20 of maternal smoking on ALL, resulting in biases with unpredictable direction and magnitude. However, with the selection of an uncontrolled confounder that negatively affects smoking and is a risk factor for ALL, this results in a strong downward bias. According to this analysis, in the presence of a true effect of 1.20, the combination of uncontrolled confounding, in combination with survivor bias, could demonstrate the findings that were seen in the meta-analysis. Assuming relatively weak associations between U1 and smoking and U1 and ALL, the biased OR reaches 1.14 and 1.11. This highlights the need to account for known confounders in analyses; at present, well-recognized and suspected risk factors for ALL include ionizing radiation, genetic abnormalities, race (Hispanics), paternal smoking, topoisomerase inhibitors, benzene metabolites, low folic acid levels, pesticides, and low exposure to infectious diseases.[30, 123, 228, 237-239]

4.6 Conclusion

In conclusion, based on our simulations, we did not find that the 'live-birth bias' previously examined was sufficient to completely explain the inverse associations reported between

maternal smoking and ALL. It is possible that it contributes a negative bias to the overall observed estimates found in the literature and should be considered when considering inverse associations seen in previous studies.

Chapter 5. Public Health Relevance

Childhood cancers remain the leading cause of death from disease among children in the US. Since the 1970's, the incidence of childhood cancers has increased by over 40%.[165] In addition, there is still a gap in knowledge of the preventable causes of childhood cancer. Due to advances in medical technologies to diagnose and treat cancer patients, we have fortunately seen an increase in survivorship upwards of 80%.[240] However, this comes at great financial, societal, and psychological cost. Studies on survivors of childhood cancer have found marked increases in subsequent primary neoplasms and other late effects that arise from the treatment of the first childhood cancer.[241] These late effects include physical effects such as increases in cardiovascular disease, endocrine complications, particularly thyroid disorders, obesity, mortality, and pulmonary dysfunction.[242] Uncovering the etiology of childhood cancers can lead to prevention and decreasing the incidence of childhood cancer and the late effects associated with survival. The early age at diagnosis in many of the childhood cancers have suggested prenatal and early life exposures as targets for further research. The state-wide case-control study in California allowed us to examine these rare cancers and added evidence toward the association of pesticide and possibly dichloromethane exposures and childhood cancers. Specifically, increases in childhood ALL for ambient maternal pesticide exposures and increased risk of germ cell tumors and possibly leukemias with exposure to dichloromethane. These findings shed light on the importance of minimizing, where possible, exposures to environmental toxins, through interventions at the individual level, to interventions at the population level through education and, where necessary, legislation.

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