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Agricultural Pesticide Exposure, Adverse Birth Outcomes and Childhood Cancers in California

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Agricultural Pesticide Exposure, Adverse Birth Outcomes and Childhood Cancers in California

A dissertation submitted in partial satisfaction of the

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in Epidemiology

by

Chenxiao Ling

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ABSTRACT OF THE DISSERTATION

Agricultural Pesticide Exposure, Adverse Birth Outcomes and Childhood Cancers in California

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Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2018

Professor Beate R. Ritz, Chair

Pesticides are a group of chemicals that are used to control harmful insects, weeds, fungi, and other forms of plant or animal life. Individuals may be exposed to pesticides from residues in food or home/garden use or in occupational settings, as well as spray drift from agricultural applications on the fields. Exposure to pesticides can cause a series of chronic adverse effects in humans including reproductive toxicity, neurotoxicity, and carcinogenicity.

In a large population-based sample, we examined whether prenatal exposure to agricultural pesticides contributes to risk of preterm birth or term low birthweight in California. Subjects were children born between 1998 and 2010 had been randomly selected from CA birth records as controls to study autism or childhood cancers. We employed a Geographic Information System (GIS)-based system to estimate residential exposures to agriculturally

applied pesticides within 2km of birth addresses for 17 individual pesticides and 3 chemical classes. First or second trimester exposures to selected individual pesticides (e.g., glyphosates OR=1.05, 95% CI: 1.02-1.08; paraquat OR=1.07, 95% CI: 1.03-1.11; imidacloprid OR=1.06, 95% CI: 1.03-1.10) and the classes of organophosphates, carbamates, and pyrethroids were associated with small increases (3-7%) in risk for preterm birth, with stronger estimated effects in females. We did not find enough evidence to support associations between exposures to pesticides and term low birthweight. Future studies that assess and integrate maternal pregnancy exposures at both workplaces and residences are needed.

Record-linkage studies of residential proximity to agricultural pesticides and childhood cancers often only use maternal address at birth or address at cancer diagnosis to assess exposures in early childhood, possibly leading to exposure misclassification. We examined patterns of and identify factors that may predict residential mobility in early childhood, and assessed the impact of mobility on early childhood exposure measures. We found that older age at diagnosis, younger maternal age, lower maternal education, non-Hispanic ethnic background, and other proxies for lower socioeconomic status were predictors of higher residential mobility. There was moderate to strong agreement (kappa=0.7-0.8) between the first year of life exposures assessed at birth address and diagnosis address or LexisNexis addresses, but agreement decreased as the distance increased. These findings suggest that birth residence or diagnosis residence should be used with caution when estimating environmental exposures in early life of children. Future research should consider factors that help correct for the exposure misclassification introduced by residential mobility.

To extend the previous study, we further assessed the effect estimates for early life exposure to pesticide based on registry-acquired addresses, and compared the effect estimates

with those using reconstructed address history based on LexisNexis records, using childhood brain tumors as an example. Additionally, we also examined whether selection bias may occur when restricting our study population to children with available LexisNexis records. In the subset of children with all three types of addresses, we found no associations between children's lifetime exposures to agricultural pesticides of interest and brain tumors. Among these children, effect estimates were generally attenuated when exposures were estimated based on LexisNexis addresses. Interestingly, among the children whose LexisNexis addresses were not available, we observed the largest increased risks for brain tumors and several pesticides based on birth and diagnosis addresses alone. We concluded that using a single source of address to assess children's early life environmental exposure to pesticides does not account for residential mobility and may cause exposure misclassification that leads to bias in effect estimates. Future research should also be cautious about the potential for selection bias introduced by the limitations of database containing public records.

The dissertation of Chenxiao Ling is approved.

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University of California, Los Angeles

2018

DEDICATION

This dissertation is dedicated to my dear parents and grandparents.

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ABBREVIATIONS

PTB	Preterm Birth
LBW	Low Birthweight
TLBW	Term Low Birthweight
EPA	Environmental Protection Agency
PECA	Pesticide Exposure and Childhood Autism
BMI	Body Mass Index
ORs	Odds Ratios
CIs	Confidence Intervals
PUR	Pesticide Use Reports
CALINE4	CAlifornia LINE source dispersion model
APCC	Air Pollution and Childhood Cancers
RUCA	Rural-Urban Commuting Area
CCR	California Cancer Registry
GIS	Geographic Information System
PAN	Pesticide Action Network
IARC	International Agency for Research on Cancer
EPA	U.S. Environmental Protection Agency
NIH	U.S. National Institutes of Health
TRI	U.S. EPA Toxics Release Inventory
CA Prop65	California Proposition 65

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After almost five years' hard work, today is the day: writing this note of thanks is the finishing touch on my dissertation. It has been a period of intensive learning for me, not only in the scientific arena, but also on a personal level. I would like to reflect on the people who have supported and helped me greatly throughout this period.

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CONFERENCE PRESENTATIONS

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1. Introduction

1.1 Adverse Birth Outcomes

Epidemiology and risk factors. It is now well recognized that adverse birth outcomes are related to impaired health status later in life. Gestational age and birth weights are the two most commonly used measures for perinatal health (Urquia and Ray, 2012). The normal gestational age typically ranges from 38 to 42 weeks. The World Health Organization (WHO) has defined *preterm birth* (PTB) as delivery before 37 complete weeks (or 259 days) of gestation. The PTB rate in the US rose by more than one-third from the early 1980s through 2006 with peak of 12.8% in 2006 (Martin et al., 2009) and has slightly decreased in recent years (Martin et al., 2015). Though survival of infants born preterm has been improved in the last decades due to advancement in prenatal and neonatal care (Behrman et al., 2007), the survivors of preterm births are at a higher risk of a number of adverse health outcomes later in life such as neurodevelopmental impairments, respiratory and gastrointestinal complications (Paneth et al., 2006; Saigal and Doyle, 2008), and consequently a greater public health burden.

However, risk factors for preterm birth remain largely unexplained. Possible factors associated with preterm birth have included race/ethnicity, maternal age, marital status, maternal behavioral factors (smoking and alcohol use), other socioeconomic status measures, psychosocial stress, infections, genetics, and environmental toxicants including environmental tobacco smoke, air pollutants, and pesticides (Behrman and Butler, 2007; Goldenberg et al., 2008). These factors have explained only a small fraction of preterm birth and many others remain unexplored. Therefore, further studies on the modifiable risk factors for PTB will help improve the understanding of the etiology of PTB and develop prevention strategies accordingly.

Low birth weight (LBW) includes infants born preterm, or too small for gestational age (Goldenberg and Culhane, 2007). Birth weights vary by infant's race and ethnicity but the normal range is considered 2,500 grams to 4,000 or 4500 grams. A 2013 U.S. report estimated that about 8% of infants are born LBW (defined as birth weight under 2,500 grams) (USDHHS, 2013). Infants born LBW were reported to have elevated risks for adverse health outcomes in both short and long terms. For example, the mortality rates in infancy are up to 40 times higher for LBW infants compared with normal weight infants (Goldenberg and Culhane, 2007). LBW children are at increased risk for asthma (Mu et al., 2014) and a range of other chronic disease outcomes, such as obesity (Yu et al., 2011), hypertension (Mu et al., 2012), and kidney disease (Luyckx and Brenner, 2015). The main risk factors for LBW are mostly similar to those for PTB (Nkwabong et al., 2015); however, some factors are different for these two birth outcomes. For example, males are at higher risk for preterm birth (Peelen et al., 2016) but lower risk for term low birth weight (Wilhelm et al., 2012).

Pesticides and adverse birth outcomes. Pesticides have been found in indoor residential dust in residences near agricultural fields, and may persist for years (Curwin et al., 2007; Harnly et al., 2009; Holland et al., 2006; Trunnelle et al., 2013; Whitehead et al., 2015a, 2015b). Earlier epidemiologic studies using ecological and cross-sectional designs typically reported positive associations for pesticide use in agriculture assessed based on residence and PTB and LBW (Acosta-Maldonado et al., 2009; De Siqueira et al., 2010; Rezende Chrisman et al., 2016). However, results from studies assessing self-reported or occupational use of pesticides were inconsistent (Figà-Talamanca, 2006; Sathyanarayana et al., 2010; Snijder et al., 2012; Zhu et al., 2006). Some indicated an increased risk of PTB, LBW, or impaired fetal growth in pregnant women with occupational exposure to pesticides (Figà-Talamanca, 2006; Snijder et al., 2012);

while findings from the Danish National Birth Cohort (Zhu et al., 2006) and the Agricultural Health Study (Sathyanarayana et al., 2010) suggested little effect of occupational exposures to pesticides on preterm birth and low birthweight.

The approaches for studying pesticides in relation to adverse birth outcomes have been improved using Geographic Information System (GIS) in the last a few decades. A systematic review of 25 early studies examining agriculture-related exposures from residential proximity to pesticide applications suggested weak or no effects on preterm birth and low birth weight, possibly due to the methodological limitations such as poor exposure measurement and potentially inadequate control of confounding (Shirangi et al., 2011). Recent residential proximity studies using simple or aggregate-level exposure assessments provided some evidence for pesticide influencing birth outcomes (Rezende Chrisman et al., 2016; Winchester et al., 2016).

A northern California cohort study employed a Geographic Information System (GIS) to estimate methyl bromide use within 5 km of mother's home (n=442) during pregnancy using Pesticide Use Reporting (PUR) records from the California Department of Pesticide Regulation and reported that high methyl bromide use (vs. no use) in the second trimester was associated with reduced birth weight (β = –113.1 g, 95% CI: –218.1, –8.1) (Gemmill et al., 2013) in 1999-2000. Two recent GIS-PUR based studies restricted to the San Joaquin Valley of California (an agriculturally dominated area) both improved the spatial resolution of pesticide estimates through overlay of matched land use survey maps provided by the California Department of Water Resources, but reported conflicting results. One study assessed pesticides labeled with EPA signal word toxicity by summing up their active ingredients applied in the 2.6 km^2 section surrounding maternal residences for more than 500,000 births between 1997–2011 and reported high exposure to pesticides increased risks of preterm birth and low birthweight by 5-9% overall

(Larsen et al., 2017). The other study examined exposure to 543 commonly used specific chemicals (any vs. none) or 69 chemical groups by gestational month in 1998-2011 and reported mostly negative associations between spontaneous preterm deliveries and pesticide exposure (Shaw et al., 2018). The difference can be partly explained by the pregnancy period of interest in these two studies, of which the second largely focused on late pregnancy rather than early or mid-pregnancy, which is believed to be the critical period for exposures causing preterm birth (Chang et al., 2015; Sadler, 1995).

1.2 Childhood Cancers

Epidemiology. Overall about 14 per 100,000 children (0-14 years of age) are diagnosed with cancer in the United States (Pallapies, 2006). Although cancer in children is rare, it is the leading disease-related cause of death among children aged 1 to 14 years. In 2018, the estimated incidence of childhood cancers (diagnosed from birth to 14 years) is 10,590, among whom about 1,180 will die from this disease (Siegel et al., 2018). Among children (age 0-14) in the United States, acute lymphocytic leukemia (ALL) is the most common type of cancer (26%), followed by brain and central nervous system (CNS) tumors (21%), neuroblastoma (7%), and non-Hodgkin lymphoma (NHL) (6%) (Ward et al. 2014). A modest rise in age-adjusted incidence was observed for leukemia, brain tumors, and neuroblastoma in the mid-1980s, likely reflecting diagnostic improvements or reporting changes, while dramatic declines in mortality represent improved survival rate due to advancement in treatment (Linet et al., 1999).

Risk factors. Little is known about the etiology of childhood cancers. The established risk factors including therapeutic doses of ionizing radiation and inherited genetic conditions, together only account for 5- 10% of childhood cancers (Bunin, 2004). Childhood cancer incidence has long been linked to demographic characteristics such age, sex, and race/ethnicity (Spector et al.,

2005). Other commonly examined potential risk factors include maternal and paternal age, socioeconomic status (SES), and living environment. Advanced maternal and paternal age seems to represent risk factors for several types of childhood cancers including leukemia or brain tumors (Crump et al., 2015; Hemminki et al., 1999; Sergentanis et al., 2015) but the conclusions are inconsistent and vary by cancers. High SES has previously been linked to higher risks for childhood brain tumors (Pallapies, 2006), yet a review showed that connections of SES measures to childhood leukemia are likely to vary with place, time, and study design (Poole et al., 2006). Living environment (urban vs rural) could reflex a matrix of factors including housing conditions/types (Amoon et al., 2018), farm residence (Cordier et al., 1994), proximity to traffic-related or industrial air pollution and air toxics (Cordier et al., 2004; von Ehrenstein et al., 2016), and infections (particularly in the occurrence of leukemia) (Kinlen, 1988), which pointed to childhood cancers to some extent.

It has been reported that some predisposing or initiating events such as parental occupational exposures to solvents, pesticides, metals, paints, or plastics, and exposures to air pollutants and air toxics, non-ionizing radiation (e.g., magnetic fields), and home use or agricultural use of pesticide that occur before pregnancy, during fetal life or in infancy may be associated with childhood cancers (Buffler et al., 2005).

Pesticides and childhood cancers (interview-based studies). Many interview-based, case-control studies published have found an increased risk of childhood cancer with household pesticide use. Overall, these studies reported positive associations with home use of insecticides, mostly before the child's birth, while findings for herbicides are mixed (Metayer and Buffler, 2008). Other than household use of pesticides, studies generally supported positive associations between parental occupational pesticide exposures and brain tumors (Van Maele-Fabry et al., 2013). The

association between childhood leukemia and prenatal maternal occupational pesticide exposure was also reported in most studies but evidence is not as strong as that for paternal pesticide exposure (Wigle et al., 2009). These abovementioned studies assessed pesticide exposure primarily based on parental occupational history or household use, possibly reflecting exposure to a higher dose of exposure to chemical agents, whereas agricultural pesticides near individuals' residences that drift during application may represent exposures occurring at lower doses.

Pesticides and childhood cancers (residential studies). Earlier residence-based ecologic studies linked agricultural pesticide use or agricultural activity to childhood cancers. A California ecologic study that analyzed high vs low agricultural pesticide use at the block group level using California's pesticide use reporting (PUR) database in relation to childhood cancer incidence rates among children diagnosed under 15 years of age between 1988 and 1994 generally found no association between pesticide use density and childhood cancer incidence, except for elevated leukemia rates (RR=1.48, 95% CI: 1.03–2.13) in block groups with the highest use of propargite (Reynolds et al., 2002). Another US-wide ecologic study explored the association between county-level measures of agricultural activity estimated using the 1997 US agricultural census data and risk of cancer in children (diagnosed < 15 years of age between 1995-2001) and showed statistically significant increased risk estimates for many types of childhood cancers (e.g., leukemia and childhood central nervous system cancer) associated with residence at diagnosis in counties having a moderate to high level of agricultural activity (Carozza et al., 2008). For example, children living in counties with high agricultural activity (≥60% of the total county acreage devoted to farming) have increased risks for leukemia (OR=1.2, 95% CI: 1.1–1.3) and central nervous system cancer (OR=1.3, 95% CI: 1.1–1.4) (Carozza et al., 2008). Since most pesticide applications are spatially explicit (i.e., applied on a targeted area) and the usage may

vary over years, these studies face challenges of lacking high spatial and temporal resolution for exposure assessment, on top of the known ecological fallacy.

On the other hand, individual level GIS-based studies that assessed exposure to agricultural pesticides in proximity to residences, have shown inconsistent findings. A recent Spanish study explored the possible association between childhood renal tumors and residential proximity to environmental pollution sources (including industrial and urban areas, and agricultural crops) by calculating the percentage of total crop surface within a 1-km buffer around each individual's last known residence and discovered that children living in the proximity of agricultural crops (≥24.35% in crop surface) have higher risk (OR=3.16, 95% CI: 1.54-8.89) of developing renal cancer (García-Pérez et al., 2016).

However, US studies of individual measures of agricultural pesticides in proximity to residences, mostly suggested no association with childhood cancers, or at best modest associations for certain types of cancers and chemicals or chemical groups. A Texas study measured crop field density within a 1-km buffer of residence at birth for both cases (age at diagnosis <15) and controls born in 1990-1998 to study the risk for childhood cancers by subtypes and found no evidence of elevated risk associated with residential proximity to cropland for most childhood cancers, except for modestly positive associations with non-Hodgkin lymphoma (NHL; OR=1.5, 95% CI: 0.6, 3.7), Burkitt lymphoma (OR = 1.5, 95% CI: 0.4, 5.5), and other gliomas (OR=1.6, 95% CI: 0.7, 3.2) (Carozza et al., 2009). A California population-based case-control study of early childhood cancer (age 0–4 years) used mothers' residential addresses at the time of birth to evaluate risks associated with residential proximity to agricultural applications of pesticides during pregnancy and also found no associations with most specific chemicals and chemicals groups, except for modestly elevated ORs for leukemia associated with probable and possible

carcinogen use and with nearby agricultural applications of organochlorines and organophosphates. They suggested that the few elevated risk associations for specific chemicals including metam sodium (OR=2.05, 95% CI: 1.01–4.17) and dicofol (OR=1.83, 95% CI: 1.05–3.22) in this study are likely due to chance from multiple comparisons (Reynolds et al., 2005). Another Northern California study assessed residential proximity within a half-mile of pesticide applications by linking address histories with reports of agricultural pesticide use and examined the association of the first year of life or early childhood pesticide exposures and childhood acute lymphoblastic leukemia (ALL) and suggested elevated ALL risk was associated with lifetime moderate exposure to certain physicochemical groups of pesticides, including organophosphates (OR=1.6, 95% CI: 1.0-2.7), cholorinated phenols (OR=2.0, 95% CI: 1.0-3.8), and triazines (OR=1.9, 95% CI: 1.0-3.7), and with pesticides classified as insecticides (OR=1.5; 95% CI: 0.9-2.4) or fumigants (OR=1.7, 95% CI: 1.0-3.1) (Rull et al., 2009).

These results vary by chemicals or chemical groups examined, and methods of exposure assessment, and therefore produced inconsistent results. In addition, many of the above studies found no or week associations between all cancer types grouped together and proximity to crop fields, agricultural activities, specific agents, or groups of chemicals. It may problematic because the etiologies of most childhood cancer subtypes remain largely unknown and may not share the same causal pathway mediated by pesticides.

1.3 Exposure Misclassification due to Residential Mobility

As mentioned before, these studies of ambient pesticide exposures in pregnancy or early childhood, often assign exposures based upon the child's or mother's residence. While large-scale record-linkage studies can avoid selection and recall biases that often impact smaller studies with active subject recruitment, previous record-based studies often relied solely on

maternal residential address at birth, which is readily available on many birth certificates (Carozza et al., 2009; Reynolds et al., 2005) and/or residential address at diagnosis, as was done in some childhood cancer studies (Carozza et al., 2008; García-Pérez et al., 2016).

Previous evidence suggested that exposure to pesticides before or during pregnancy may harm the developing fetus. Nevertheless, increased risks were seen for postnatal period as well. For instance, a study of childhood leukemia tried to distinguish between pre-pregnancy, pregnancy and postnatal (to 3 years after birth) exposures as critical windows for household pesticide exposure, and insecticide exposures early in life appear to be significant, though the effect is not as strong as prenatal exposures (Ma et al., 2002a). After birth, children may also be more susceptible to the harmful effects of pesticides than adults, as they have more actively dividing cells (Greenop et al., 2013), providing the rationale to studies of childhood cancers not only focus on prenatal but also early life exposures.

The reliance on one address for assessment of exposures in the first year of life or early childhood implicitly makes the assumption that a child's residence remained the same throughout the entire period of interest, or if they moved, that the exposure levels remained the same. Even if some studies assessed exposures as the children's residential proximity to agricultural fields or pesticide applications at the time of birth, these exposure indicators at birth are assumed to reflect exposures in prenatal and/or postnatal period, which are believed to be critical windows of exposures for childhood cancers. Consequently, the "one-address" approach may lead to exposure misclassification for those who moved in early childhood especially for exposures with high spatial heterogeneity.

In a 2003-2007 California statewide representative survey, only 14% of all women moved in the 2-7 months post-partum (Margerison-Zilko et al., 2016), but with increasing age of the child, the

frequency of residential moves also increased. For more than 50% of childhood cancer cases under age 5 diagnosed in California between 1988 and 2005, address at birth differed from the address at cancer diagnosis (Reynolds et al., 2004; Urayama et al., 2009), which raises concerns about using residence at birth to assess exposures in early childhood. Exposure misclassification due to moving is a ubiquitous problem encountered by nearly all record-based studies that lack a complete residential history for each child. Previous studies suggested that residential mobility may be associated with certain risk factors for childhood cancers such as maternal age, marital status, parity, family income, and other socioeconomic status metrics (Bell and Belanger, 2012; Tønnessen et al., 2016), resulting in nondifferential or even differential misclassification of exposures.

1.4 LexisNexis: an innovative resource of residential addresses

Currently, in the US, the privilege of having an accurate complete residential history still only belongs to interview-based environmental epidemiological studies, which are often quite small with hundreds of subjects because of high time and monetary costs of such interviews and likely underpowered.

Small case-control studies typically asked for individuals' lifetime residential histories (Camille et al., 2017; Choi et al., 2006; Rull et al., 2009), including the beginning and end dates for each address. Large cohort studies follow participants over for a long time and often update their addresses periodically from follow-up questionnaires, so they may not know the exact moving dates. Sometimes these studies additionally collect information from the US Postal Service change-of-address forms or major credit reporting agencies, but the date associated with each address does not necessarily capture an accurate "move-in" date, but rather reflects the first known date (Hurley et al., 2017).

While it is not feasible to acquire complete residential histories from interviews for all subjects in large record-based studies as a gold standard to compare against the recorded birth or diagnosis address, databases containing public records of individuals collected by commercial companies have become available in recent years, allowing us to trace individuals without a self-reported residential history. For example, LexisNexis Public Records, Inc. (https://www.lexisnexis.com/en-us/products/public-records.page, hereinafter referred to as LexisNexis), a commercial credit reporting company, provides all known addresses for a set of individuals upon request. If the commercial residential history data has relatively high accuracy, their low cost and broad coverage would provide valuable information to all studies requiring residential history data (Jacquez et al., 2011). The basic service provided by LexisNexis returns the latest three known addresses while the enhanced service, with a higher cost, returns all known addresses from at least 1995. This database was maintained primarily for the purpose of contacting study participants but not for scientific research use, and therefore may not be as accurate as residential history obtained from interviews or self-administrated questionnaires. Several earlier studies have attempted to compare reconstructed residential history based on LexisNexis records with interview-based residential history for enrolled subjects and validate its use for research purposes.

A Michigan case-control study of bladder cancer first compared lifetime residential histories collected through written surveys and 3 residential addresses (as part of the basic search with lower cost) available in LexisNexis and reported 71.5% match rate (i.e., percentage of lifetime history years reported by participants, as accounted for by matched LexisNexis data). Their bladder cancer cases were less than 80 years of age (average 65 years) upon diagnosis, and controls were selected from similar age groups. Both cases and controls (n=946) had lived in 1 of

the 11 counties in Michigan for more than 5 years before recruitment in 2008-2009(Jacquez et al., 2011).

Another US-wide study selected a random sample of 1000 subjects originally enrolled in the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, with AARP members aged 50–69 years and living in one of six US states or two metropolitan areas at the time of enrollment. Authors found 72% and 87% detailed address match rates with the basic and enhanced services provided by LexisNexis, respectively (Wheeler and Wang, 2015).

The most recent LexisNexis validation study looked into participants in California Teachers Study, a prospective cohort study initiated in 1995-1996 and originally designed to study breast cancer. These women aged between 22 to 104 years at enrollment (median is 53 years), and lived throughout California. The study pointed out that though the overall match rate between the two sources of addresses was good (85%), it was diminished among black women and younger women (< age of 40 years) (Hurley et al., 2017).

In summary, such residential information from LexisNexis, if of high quality, could potentially augment existing address information and help us reconstruct residential histories for subjects in large record-linkage studies and provide more accurate exposure estimates. However, researchers should be aware that residential mobility of young children or their mothers may be different from that of mid-aged or older population, who were the majority in all three validation studies discussed above and believed to have a more stable residence. In addition, differences in distributions of race/ethnicity, socioeconomic status, and geographic regions may influence residential mobility in various study populations as well.

2. Prenatal Exposure to Agricultural Pesticides and Adverse Birth Outcomes in Agricultural Regions of California

2.1 Abstract

Background: Preterm birth and low birthweight increases risks of mortality and morbidity in infancy and later in life. Prenatal exposure to pesticides have been linked to adverse birth outcomes inconsistently, possibly due to limitations in exposure assessment.

Objective: To examine whether prenatal exposure to agricultural pesticides contributes to risk of preterm birth or term low birthweight in California.

Methods: Subjects in this study were children born between 1998 and 2010 had been randomly selected from CA birth records as controls to study autism or childhood cancers. We employed a Geographic Information System (GIS)-based system to estimate residential exposures to agriculturally applied pesticides within 2km of birth addresses by month of pregnancy for 17 individual pesticides and 3 chemical classes (organophosphates, pyrethroids, and carbamates). Among children living within 2 km of any agricultural pesticide application during gestation we identified 24,693 preterm and 220,297 term births, and 4,412 with term low birthweight and 194,732 with term normal birthweight. Using logistic regression models we obtained odds ratios (ORs) with 95% confidence intervals (CIs) adjusting for maternal and infant covariates.

Results: First or second trimester exposures to selected individual pesticides (e.g., glyphosates OR: 1.04~1.05; paraquat OR: 1.06~1.07; imidacloprid OR: 1.04~1.06) and the classes of organophosphates ($OR_{\geq 2}$: 1.04), carbamates ($OR_{\geq 2}$: 1.02~1.03), and pyrethroids ($OR_{\geq 2}$: 1.05~1.06) were associated with small increases (3-7%) in risk for preterm birth, with stronger estimated effects in females. We did not find associations between exposures to pesticides other

than myclobutanil (OR: 1.11; 95% CI: 1.04-1.20) and maybe pyrethroids as a class and term low birthweight.

Conclusions: First and second trimester exposures to pesticides were associated with preterm delivery but evidence for term low birthweight was little. Future studies that assess and integrate maternal pregnancy exposures at both workplaces and residences are needed.

2.2 Background

During the 1st decade of the 21st century, the estimated rates of *preterm birth* (PTB, defined as gestational age less than 37 weeks) and *low birth weight* (LBW, defined as birth weight under 2,500 grams) peaked at 11%-13% and 7%-8% in the US, respectively (United Health Foundation, 2015). Though survival of infants born preterm and/or low birthweight has improved in the last decades due to advancements in prenatal and neonatal care, they are more susceptible to adverse health outcomes such as neurodevelopmental impairment, respiratory and gastrointestinal complications (Mu et al., 2014; Saigal and Doyle, 2008), obesity, diabetes mellitus, hypertension, and kidney disease (Barker et al., 1993; Luyckx and Brenner, 2015; Mu et al., 2012; Valsamakis et al., 2006; Yu et al., 2011); they also result in substantially higher infant and childhood mortality rates (Goldenberg and Culhane, 2007).

California is the largest agricultural state in the United States, with more than 150 million pesticide active ingredients applied every year (California Department of Pesticide Regulation, 2015). Previous experimental studies show that various pesticides, including organophosphates and pyrethroids, can influence prenatal development related to adverse birth outcomes (Bechi et al., 2013; Beuret et al., 2005; Dallegrave et al., 2007; Farag et al., 2006; Park et al., 2014).

Proposed mechanisms include disturbance of placental functions (Milczarek et al., 2016), endocrine disruption (Bretveld et al., 2006; Park et al., 2014; Tyagi et al., 2015), immune regulation and inflammatory mechanisms (Neta et al., 2011, 2010; Tyagi et al., 2016).

Pesticides have been found in indoor residential dust in residences near agricultural fields, and may persist for years (Curwin et al., 2007; Harnly et al., 2009; Holland et al., 2006; Trunnelle et al., 2013; Whitehead et al., 2015a, 2015b). However, epidemiologic studies yielded inconsistent results, specifically while ecological and cross-sectional studies reported positive associations for PTB and LBW and pesticide use in agriculture (Acosta-Maldonado et al., 2009; De Siqueira et al., 2010; Rezende Chrisman et al., 2016), results from studies assessing self-reported or occupational use of pesticides were inconsistent (Figà-Talamanca, 2006; Mayhoub et al., 2014; Sathyanarayana et al., 2010; Snijder et al., 2012; Zhu et al., 2006). A systematic review of 25 studies examining agriculture-related exposures from residential proximity to pesticide applications suggested weak or no effects on preterm birth and low birth weight, possibly due to the methodological difficulties of exposure assessment (Shirangi et al., 2011). More recent residential proximity studies using simple or aggregate-level exposure assessments provided some evidence for pesticide influencing birth outcomes (Gemmill et al., 2013; Rezende Chrisman et al., 2016; Winchester et al., 2016). Two recent Geographic Information System (GIS)-based studies restricted to the San Joaquin Valley of California reported conflicting results – one found pesticide exposures to increase preterm birth and low birthweight by 5-9% in those highly exposed to chemicals with acute toxicity as based on the US EPA Signal Word (Larsen et al., 2017), while the other assessed 543 individual chemicals and 69 physicochemical groupings found negative associations for spontaneous preterm birth (Shaw et al., 2018). Nevertheless, various small pesticide biomarker-based studies with measured organochlorines,

organophosphates, or pyrethroids and their metabolic breakdown products in maternal blood or urine or umbilical cord blood suggested positive associations with preterm birth or with lower birthweight but results varied by chemicals and outcomes assessed (Guo et al., 2014; Kadhel et al., 2014; Pathak et al., 2010, 2009; Torres-Arreola et al., 2003; Tyagi et al., 2015; Wang et al., 2012; Wolff et al., 2007).

Here, we assessed GIS-derived exposures during pregnancy to selected agricultural pesticides applied near maternal residences and risks of preterm birth and term low birthweight, considering trimester-specific exposure windows in a large sample of births in agricultural regions of California.

2.3 Material and Methods

Study Population

We pooled two sets of randomly selected births from all California Birth Certificates born between 1998 and 2010 who were: 1) controls matched to children with autism or cerebral palsy at a 1:10 ratio by sex and birth year (n=339,210) as described previously (von Ehrenstein OS, 2017) (manuscript in preparation) and, 2) controls matched to children diagnosed with cancers at a 1:20 ratio by birth year (n=143,595) (Julia E. Heck et al., 2013). We excluded children with missing data for gestational length based on the date of last reported menses (n= 20,124), with extreme or implausible gestational ages (<20 weeks or >45 weeks) or birth weights (<500g or >6,800g) (n=6,390), with missing sex (n=2), with home addresses outside of California (n=1,433), and multiple births (n=13,251) and also removed duplicate subjects. The remaining births included 41,089 preterm births (PTB) and 358,256 term births (not low birth weight). For the analysis of low birthweight, we used 7,407 term births that were low birthweight (TLBW),

indicating intrauterine growth restriction (IUGR), and compared them with 317,710 term normal weight infants. Restricting our study population to those born near fields on which agricultural use pesticides were applied (details in the next section), we included 24,693 preterm and 220,297 term births, among them were 4,412 term low birthweight and 194,732 term normal birthweight infants.

Exposure Assessment

We geocoded maternal residential addresses listed on the birth certificates using an automated approach (Goldberg et al., 2008). Birth addresses with a low geocode quality (i.e., at the USPS Zip Code Area centroid level or coarser) due to missing or non-geocodeable fields on the birth certificates accounted for ~12% of all addresses geocoded. We then calculated measures of residential ambient pesticide exposures using a GIS-based Residential Ambient Pesticide Estimation System, as previously described (Rull and Ritz, 2003). In brief, since 1974 agricultural pesticide applications for commercial use are recorded in Pesticide Use Reports (PUR) mandated by the CA Department of Pesticide Regulation (CDPR). Each PUR record includes the name of the pesticide's active ingredient, the poundage applied, the crop type, and the location and the date of application. The California Department of Water Resources (CDWR) performs countywide, large-scale surveys of land use and crop cover every 7–10 years. Land use maps increase spatial resolution because they provide more detailed land use geography that allows us to refine the pesticide applications (Rull and Ritz, 2003). We then combined PUR records, land use maps, and geocoded birth addresses to produce estimates of pesticide exposure during pregnancy. Monthly exposure estimates (pounds per acre) were calculated by adding the poundage of pesticide applied in a 2-kilometer buffer surrounding each address and weighting the total poundage by the proportion of acreage treated within the buffer. Previous pesticide

studies relied on different buffer sizes from 500m (Carmichael et al., 2016; Costello et al., 2009; Wang et al., 2014, 2011), half a mile (804.5m) (Rull et al., 2009), 1000m (Ritz and Costello, 2006), 1250m (Gunier et al., 2011), 1600m (Bell et al., 2001a), 5000m (Gemmill et al., 2013), to up to 8000m distances (Wofford et al., 2013), depending on the pesticide of interest, landscape, and weather conditions. In light of previous research, the buffer of 2-km we chose, will provide a reasonable distance for assessing pesticide applications around residential addresses.

For each calendar month, our integrated GIS-system returned continuous measures (pounds per acre) for each specific chemical applied within 2-km of individuals' residences. We defined the first, second, and third trimesters as 0-12 weeks, 13-25 weeks, and ≥26 weeks of pregnancy, respectively. For preterm birth, the length of gestation and hence exposure period are shorter than term birth by design; to account for that, we assessed the third trimester exposures using 27-32 weeks of gestation only since more than 88% of all preterm births had a gestational length longer than 32 weeks. For each pesticide, daily poundage for each gestational day of pregnancy was calculated based on monthly values, and then averaged across all days in each trimester. We then categorized prenatal exposure as ever/never exposed to a specific chemical in each trimester.

We selected 17 individual chemicals previously observed to have reproductive toxicity (Acosta-Maldonado et al., 2009; Arbuckle et al., 2001; Eskenazi et al., 2004; Gemmill et al., 2013; Guiñazú et al., 2012; Halwachs et al., 2016; Levin et al., 2014; Milczarek et al., 2016; Mink et al., 2012; Ochoa-Acuña et al., 2009; Sathyanarayana et al., 2010; Whyatt et al., 2004, 2002; Yang et al., 2014). Additionally, we also considered all pesticides from three widely used chemical classes that have been linked to reproductive toxicity (Bell et al., 2001b; Ding et al., 2014; Eskenazi et al., 2004; Harley et al., 2016; Wang et al., 2012) based on the Pesticide Action

Network (PAN) pesticide database (http://www.pesticideinfo.org/), i.e. 24 n-methyl carbamate/dithiocarbamates, 50 organophosphates, and 29 pyrethroid pesticides to which one or more study subjects were exposed according to our 2km buffer criterion (Supplementary Table 2.1). For each class, we used the sum of the total number of individual chemicals that each subject was ever exposed to in each time period of interest. We divided subjects into high (exposed ≥2 pesticides), low (exposed to 1 pesticide), and no exposure to the respective pesticide, and compared high and low with the no exposure group as the reference.

Since information about the specific location of non-agricultural pesticide applications (structural pest control, rights of way, and landscape maintenance in urban communities) are not provided by the PUR and because some individuals in urban areas are highly exposed to traffic-related air pollution or hazardous air toxics that are known risk factors for adverse birth outcomes (Wilhelm et al., 2011; J. Wu et al., 2011), we restricted our analyses to individuals born in agricultural regions, defining those as residences within 2km buffer of any type of agricultural pesticide application during pregnancy (Figure 2.1).

Statistical Analysis

We conducted unconditional logistic regression analyses adjusting for matching factors (i.e., sex and year of birth) and the source of control subjects (autism vs cancer study) and estimated odds ratios (ORs) and 95% confidence intervals (CIs). To account for the unbalanced gender ratio (~4:1 male: female among the autism controls) and birth year distribution in this combined sample, we included the inverse of the sampling fraction (calculated as the sample size divided by total births in California by gender and birth year) as a stabilized weighting factor to reflect the sex and birth year distribution of all California births. Statistical analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC). We additionally adjusted for

covariates as potential confounders and effect measure modifiers based on the literature (Bashore et al., 2014; Goldenberg et al., 2008; Ritz et al., 2007; Valero De Bernabé et al., 2004): including maternal age at delivery (≤19, 20-24, 25-29, 30-34, ≥35), maternal race/ethnicity (non-Hispanic White, Hispanic, Black, Asian/Pacific islander, others), maternal birthplace (US vs. foreign), maternal education (<12 years, 12 years, 13-15 years, ≥16 years), parity (1, 2, ≥3), payment source for prenatal care as a proxy for family income (private/HMO/BCBS vs. MediCal/government/self-pay), prenatal care in the first trimester (yes vs. no), and a previously-developed neighborhood-level SES metric (Yost et al., 2001). Furthermore, we conducted stratified analyses by maternal race/ethnicity (non-Hispanic Whites, US born Hispanics, and foreign born Hispanics) since exposures may be higher among Hispanics, especially recent immigrants, who may live close to agricultural fields and have poor housing conditions (Trunnelle et al., 2013); by infant sex because males are more likely to be born preterm (American College of Obstetricians and Gynecologists, 2013; Challis et al., 2013; Ingemarsson, 2003); as well as by season of conception (Jan-Mar, Apr-Jun, Jul-Sep, and Oct-Dec), estimated from the last menstrual period and length of gestation, because of seasonal variations in pesticide applications (Figure 2.2).

Sensitivity Analyses

In sensitivity analyses, we compared effect estimates with and without adjusting for two risk factors for adverse birth outcomes, maternal cigarette smoking during pregnancy and pre-pregnancy Body Mass Index (BMI), calculated as maternal pre-pregnancy weight (kilograms) divided by maternal height (meters squared) (Goldenberg et al., 2008; Valero De Bernabé et al., 2004) for births in 2007-2010 only, since these variables are only available on the birth certificate from 2007 onward. We also investigated the potential confounding effects from

outdoor air pollution that can impact fetal growth during critical periods (Ghosh et al., 2012; Ritz and Wilhelm, 2008; Wilhelm et al., 2011) among the autism controls only due to data availability. We estimated trimester-specific exposures to local, traffic-derived NOx, $PM_{2.5}$, and CO, including roadways within 1.5 km of subjects' birth addresses (see (Ritz et al., 2014; J. Wu et al., 2011)), i.e. inter-quartile range (IQR)-scaled measure of NOx as a local traffic marker derived from the CAlifornia LINE source dispersion model (CALINE4) model (Benson, 1989; Chen et al., 2009). Additionally, we adjusted for co-exposure to at least one of other individual chemicals as a single variable (yes/ no) when assessing each individual chemical, and estimated mutually adjusted ORs for the three chemical class exposures during the same exposure window. When evaluating later trimester exposures we adjusted for exposure during prior pregnancy periods, because these effect estimates may be altered by earlier exposures (Lewis et al., 2011). Since a low geocode quality is likely to introduce spatial exposure misclassification, we excluded those with a geocode quality at the USPS Zip Code Area centroid level or coarser. Lastly, we examined spontaneous vaginal deliveries only, excluding medically indicated preterm deliveries (about 35% of all preterm deliveries in our study population) more likely to be due to severe maternal pregnancy complications including pre-eclampsia (American College of Obstetricians and Gynecologists, 2013) and gestational diabetes (Sendag et al., 2001; Xiong et al., 2001) that might or might not be in the causal pathway for pesticide exposures and the outcome.

2.4 Results

Infants born preterm or born term with low birthweight were more likely to have mothers of younger age, less education, lower neighborhood SES, starting prenatal care after the first trimester, and using Medi-Cal or other government programs instead of private insurance. In addition, infants born preterm were more likely to be a third or later born child, and have

mothers with Hispanic or Black race/ethnic background; infants born term but with low birthweight were more likely to be female and a first born child, and born to Black and Asian mothers (Table 2.1).

First- and second trimester exposures to some pesticides we have selected were associated with a small increase in risk for preterm birth. Specifically, in multivariate adjusted models, first trimester exposures to glyphosate compounds, paraquat dichloride, chlorpyrifos, imidacloprid, permethrin, dimethoate, and methyl bromide, and second trimester exposures to chlorothalonil, glyphosate compounds, paraquat dichloride, simazine, and imidacloprid, yielded adjusted ORs between 1.03 and 1.07 with 95% CIs excluding the null value (Table 2.2). Maternal education changed the OR estimates the most among all covariates. Exposures to pesticides in the third trimester (27-32 weeks of gestation) did not increase risk for preterm birth. Effect estimates were generally slightly stronger in female infants, except for simazine, which shows stronger effect in males with an OR of 1.06~1.07 (Supplementary Table 2.2). Stratified analysis by season of conception suggested that effect estimates were generally stronger when the peak season of pesticide application concurred with the first or second trimester of pregnancy (data not shown).

When examining chemical classes, first trimester exposures to carbamates (OR_{1st}: 1.04; 95% CI: 1.00-1.08), or pyrethroids (OR_{1st}: 1.06; 95% CI: 1.02-1.09) increased ORs for preterm birth in the high (ever exposed to ≥2 pesticides) exposure group, compared with the no exposure group, while second trimester exposures to carbamates, organophosphates, or pyrethroids were all associated with small increases (3-6%) in ORs for preterm birth (Table 2.3). We generally did not observe elevated ORs for preterm birth among male infants, but observed a stronger 7–11% increase with exposure during the first or second trimester among female infants (Table 2.4).

Exposure prevalence and effect estimates were generally stronger in infants born to the foreign-born or US-born Hispanic mothers than White mothers (Supplementary Table 2.3).

Associations between the selected individual pesticides or chemical classes and term low birthweight for each trimester in pregnancy were mostly null. In multivariate adjusted models, we only saw increased ORs for second or third-trimester exposures to myclobutanil (OR_{2nd}: 1.11; 95% CI: 1.03-1.19; OR_{3rd}: 1.11; 95% CI: 1.04-1.20 (Supplementary Table 2.4); similarly, exposures to the three chemical classes were not associated with term low birthweight in general, except for marginally elevated odds (OR_{1st}: 1.05; 95% CI: 0.98, 1.13; OR_{2nd}: 1.06; 95% CI: 0.99, 1.13) in infants exposed to 2 or more pyrethroids (Supplementary Table 2.5).

Results were similar in our sensitivity analyses, with additional adjustment for maternal pre-pregnancy BMI and maternal smoking in the years 2007-2010, for NOx as traffic-related air pollution, or restricting to those with a high geocode quality only. For each individual pesticide, adjusting for co-exposure to other pesticides resulted in attenuation of odds by 2-3%; ORs mutually adjusted of three chemical classes or adjusted for prior exposures were mostly similar to or slightly decreased; the mutually adjusted OR for pyrethroids was most stable, suggesting a more robust association with pyrethroids, which were used more in recent years (Table 2.3). ORs were generally stronger when we restricted to spontaneous preterm births only for both individual chemicals and chemical classes.

2.5 Discussion

In this large California study of women living within 2km distance from agricultural fields on which pesticides were applied, we found that early and mid-pregnancy exposure to selected pesticides known or suspected to be reproductive toxicants and chemicals in the classes of

pyrethroids and possibly also carbamates or organophosphates, are associated with a small to moderate size increase in risk of preterm birth between 1998 and 2010. We found little evidence for pesticides being related to term low birthweight, except for exposures to pyrethroids as a class further corroborating their adverse influence on pregnancy observed for preterm birth and possibly one single pesticide myclobutanil - however, this might have been a chance observation given that we tested 17 individual chemicals. Yet, term low birth weight is a much rarer event than preterm birth and we had less statistical power to estimate small effects accurately.

Our positive findings for preterm birth are consistent with biomarker-based studies with measured organophosphates, or pyrethroids and their metabolic breakdown products in maternal blood or urine or umbilical cord blood (Kadhel et al., 2014; Wang et al., 2012), though most of the literature assessing environmental exposures to pesticide found inadequate evidence for associations with preterm birth (Shirangi et al., 2011). Less than a handful of studies conducted in the US examined associations for environmental exposures to pesticides from agricultural applications and preterm birth and/or low birthweight and provided month- or trimester-specific estimates (Gemmill et al., 2013; Larsen et al., 2017; Shaw et al., 2018). These studies were almost exclusively conducted using California's unique PUR system, nevertheless they differed in terms of how they assessed exposures and pregnancy outcomes. Our study was in line with an earlier study in the San Joaquin Valley that assessed pesticides labeled with EPA signal word toxicity by summing up their active ingredients applied in the 2.6 km^2 section surrounding maternal residences and reported high exposure to pesticides increased risks of preterm birth and low birthweight by 5-9% overall (Larsen et al., 2017). In contrast, one study reported mostly negative associations between spontaneous preterm deliveries and exposure to 69 chemical groups or 543 specific chemicals (any vs. none) in 1998-2011 in the San Joaquin Valley (Shaw

et al., 2018), perhaps because this study focused on late pregnancy instead of early or mid-pregnancy, which is believed to be the critical period for exposures causing preterm birth (Chang et al., 2015; Sadler, 1995), and in addition a 'live-birth selection bias' (Liew et al., 2015) could in part explain the negative effect. The other study in northern California reported methyl bromide use within 5 km of mother's home was also positively associated with gestational age in the first trimester; yet their results were sensitive to buffer size and could potentially be confounded by chloropicrin or diazinon, often used conjunctively with methyl bromide (Gemmill et al., 2013).

Maternal, placental, and fetal factors are thought to determine risk of preterm birth and may be affected by prenatal exposure to environmental chemicals (Bechi et al., 2013; Beuret et al., 2005; Dallegrave et al., 2007; Farag et al., 2006; Park et al., 2014). For example, it is known that chlorpyrifos can cross the placenta and enter the fetus, possibly altering the growth and development of the fetus (Saulsbury et al., 2008). Mechanisms by which pesticides may affect risks of preterm birth include interference with immune pathways and inflammation (Mustafa et al., 2015), or with metabolic and endocrine regulatory pathways (Bechi et al., 2013; Bhaskar and Mohanty, 2014; Dallegrave et al., 2007) as well as oxidative stress (Beuret et al., 2005). For example, *in-vitro* study results suggested that phosmet and chlorpyrifos alter cell viability and induce an inflammatory cytokine profile, indicating that organophosphates may adversely affect trophoblast cells (Guiñazú et al., 2012). However, the mechanisms underlying environmental impacts on preterm delivery are still insufficiently understood and further experimental research is warranted.

Pesticide exposures affected preterm birth in our study mostly in female children and to a lesser extent if at all males, similar to a Chinese study that found high levels of non-specific

metabolites of organophosphate pesticides in maternal urine to have adversely affected duration of gestation only in girls (Wang et al., 2012). It has been suggested that exposures to pesticides in early pregnancy trigger more spontaneous abortions of male fetuses (Bell et al., 2001a; Settimi et al., 2008), or stillbirth in late pregnancy (White et al., 1988), outcomes not captured in our study. It is well known that the male fetus is more vulnerable in utero and is at greater risk of fetal death with the male-to-female ratio falling from around 120 male conceptions to 105 boys per 100 girls at birth (Kraemer, 2000; Mizuno, 2000). Some pesticides are endocrine disruptors such as those in the organophosphate family that mimic sex steroidal action and resemble estrogenic more than androgenic action in fish models (Senthilkumaran, 2015).

In general, we observed stronger ORs among infants born to Hispanic mothers partly because Hispanic mothers had higher exposure prevalence during pregnancy. According to a recent agricultural survey, about 90% of female farm workers in California were Mexico-born Hispanics (Villarejo et al., 2010; Villarejo and McCurdy, 2008); thus, the foreign-born Hispanic mothers may live near fields where they work, making them more likely to be exposed to ambient pesticides when at home. Unfortunately, information of specific occupations and occupational addresses of the mothers was not collected on birth certificates and therefore we could not determine exposures at workplaces.

Fetal growth restriction, the main reason for low birthweight other than preterm birth, has been associated with transplacental oxygen and nutrient transport, hypoxia, oxidative stress, placental inflammation, and inhibition of placental growth hormone (Vinikoor-Imler et al., 2014); these possible mechanisms may be influenced by toxic exposure to organophosphate and carbamate pesticides (Gupta, 2006). We did not find much evidence for associations between term low birthweight and many specific pesticide exposures, in line with some previous studies. Others

however, reported associations for low birthweight (including preterm births) or a decrease in birthweight (continuous outcome) for some pesticides, including chlorpyrifos and/or diazinon, carbaryl, methyl bromide, as well as with organophosphate and pyrethroid metabolites measured in maternal urine (Ding et al., 2014; Gemmill et al., 2013; Rauch et al., 2012; Sathyanarayana et al., 2010; Whyatt et al., 2004). However, it also has been reported that when adjusting for gestational age associations with low birthweight were attenuated (Rauch et al., 2012). Our results for pyrethroids are consistent with these previous observations for both preterm birth and low birthweight. Our term low birthweight results may have been underpowered but still seem to corroborate a previous report that found residential proximity to methyl bromide use to reduce birthweight overall (Gemmill et al., 2013).

Most previous pesticide and birth outcome studies examined exposures from home/garden or professional use of pesticides and relied on parental interviews after birth; these studies have been criticized for their potential selection or recall bias (Dabrowski et al., 2003; Mayhoub et al., 2014). Other studies using job exposure matrices (JEM) may have been prone to non-differential exposure measurement errors, and often could not distinguish between types of chemicals. Smaller studies were able to employ biomarkers such as maternal blood or urine collected in pregnancy, or umbilical cord blood samples to measure prenatal chemical concentrations (mostly persistent organochlorines and non-persistent organophosphate metabolites) (Guo et al., 2014; Kadhel et al., 2014; Pathak et al., 2010, 2009; Perera et al., 2005; Torres-Arreola et al., 2003; Tyagi et al., 2015; Wang et al., 2012; Windham and Fenster, 2008; Wolff et al., 2007). The necessarily small size of such pregnancy cohorts limits the number of outcomes and hence study power considerably, and they also have to assume that chemical concentrations measure in bio-samples reflect exposures during multiple gestational windows accurately when many pesticides

have relatively short half-lives, e.g., hours to a few days for organophosphates (Huen et al., 2012), and few studies have multiple bio-samples available throughout pregnancy.

Recently, several studies have examined the associations of ambient pesticide exposures and adverse birth outcomes in large populations based on proximity to applications modeling (Gemmill et al., 2013; Larsen et al., 2017; Shaw et al., 2018). These GIS-PUR based approaches applied to birth records avoids selection bias due to non-response and recall bias that threatens studies relying on interviews after births, in which mothers who had babies with adverse outcomes may be more likely to participate or recall their pesticide exposures. Similar to ours, these Californian studies were exclusively based on California's PUR records and land use surveys. Particularly, two studies focused on the agriculturally dominated San Joaquin Valley; one assessed exposures by comparing high exposure (>95th percentile of summed poundage of active ingredients) to low exposure to pesticides with acute toxicity based on EPA signal word, while the other that reported negative associations with spontaneous preterm birth focused on exposures to frequently used chemicals and physicochemical groupings yet they mainly reported results by month in late pregnancy. Our sensitivity analysis stratified by season of conception supported our hypothesis that early but not late pregnancy is the critical period. Besides, different from previous studies, our method employed a four-tier mechanism to improve the match rate of PUR and land use maps (Rull and Ritz, 2003), successfully reducing potential nondifferential misclassification of exposure. We also expanded the study area to the California statewide to include more agricultural regions that might also be populous outside of the Central Valley while providing us with a large sample size and thus high statistical power in this record linkage-based design.

Our study has some limitations. The ambiguous location, only at county level, of those non-agricultural pesticide applications in pesticide reporting, made it difficult to properly assess exposures for mothers living in urban areas at birth, whom were excluded to avoid substantial underestimation of exposure. However, our restriction to women living within 2km of fields might partially and indirectly 'matched on' location and generated a more homogeneous population in terms of potential geographically-specific confounders such as air pollution. Similarly, since our study question is whether proximity to fields with agricultural pesticide applications increases risks of adverse birth outcomes, despite that other unassessed sources of pesticide exposure including occupational, home and garden use, or dietary exposures to pesticides could potentially confound our results, our 'matching' through restriction to women living within 2km of fields might have accounted for such factors. For example, the SUPERB study in northern California suggested that those who live near fields are more similar in their use of pesticides for other purposes, than residents in urban areas (X. Wu et al., 2011). Residents in the San Francisco metropolitan area, had a lower percentage of using outdoor pesticides (59.4%) than two inland areas in northern California they studied (80.7%) (Slough et al., 2003). Another assumption was that addresses at birth reflected the location of mothers over the entirety of pregnancy. A review of research on residential mobility during pregnancy showed that on average 24% (range 14%-32%) of mothers move during pregnancy in the US (Bell and Belanger, 2012); although most moving distances were short (median <10 km), it may result in exposure misclassification in our GIS-based estimates based on a 2km buffer. Particularly, Hispanic mothers are more mobile than White mothers (Bell and Belanger, 2012), increasing their chances of living close to the fields and receiving pesticide exposures during pregnancy. Similar to all other studies of live birth outcomes ours may also be subject to live birth bias, i.e., the fact that

early exposures could lead to fetal loss. While data on the potential confounders maternal smoking and pre-pregnancy BMI, was only available for 4 out of 13 years of our study period, additional adjustment for these variables did not change our results more than minimally and suggests that they may not be confounders.

In summary, this study found that first and second trimester exposures to most selected pesticides known or suspected to be reproductive toxicants were associated with preterm delivery but only one pesticide (myclobutanil) and perhaps pyrethroids as a class and were related to term low birthweight in California among women living near agricultural fields in California. These associations seemed stronger for female infants suggesting possible sex specificity for some of these agents.

Table 2.1 Demographic characteristics of the study population in agricultural regions, 1998-2010.

	Preterm Birth		Term Birth		Term LBW		Term Normal BW	
	N=24,693	**%**	**N=220,297**	**%**	**N=4,412**	**%**	**N=194,732**	**%**
Sex								
Males	18,586	75.3	161,076	73.1	2,972	67.4	140,308	72.1
Females	6,107	24.7	59,221	26.9	1,440	32.6	54,424	27.9
Year of Birth								
1998	1,393	5.6	12,327	5.6	262	5.9	10,728	5.5
1999	1,483	6.0	12,599	5.7	228	5.2	10,944	5.6
2000	1,504	6.1	14,190	6.4	293	6.6	12,381	6.4
2001	1,661	6.7	14,759	6.7	279	6.3	12,856	6.6
2002	1,808	7.3	15,882	7.2	319	7.2	13,846	7.1
2003	2,043	8.3	17,993	8.2	365	8.3	15,684	8.1
2004	2,127	8.6	18,030	8.2	385	8.7	15,924	8.2
2005	2,127	8.6	18,860	8.6	361	8.2	16,824	8.6
2006	2,200	8.9	19,797	9.0	409	9.3	17,680	9.1
2007	2,440	9.9	20,616	9.4	448	10.2	18,412	9.5
2008	2,359	9.6	21,950	10.0	445	10.1	19,696	10.1
2009	2,063	8.4	19,155	8.7	349	7.9	17,160	8.8
2010	1,485	6.0	14,139	6.4	269	6.1	12,597	6.5
Maternal Age								
19 or less	2,976	12.1	21,126	9.6	593	13.4	19,711	10.1
20-24	5,772	23.4	50,362	22.9	1,045	23.7	45,392	23.3
25-29	5,922	24.0	59,782	27.1	1,139	25.8	52,667	27.0
30-34	5,590	22.6	53,719	24.4	938	21.3	46,661	24.0
35 and older	4,432	17.9	35,306	16.0	696	15.8	30,299	15.6
Missing	1	0.0	2	0.0	1	0.0	2	0.0
Maternal Education								
<12 years	8,238	33.4	62,459	28.4	1,351	30.6	55,856	28.7
12 years	6,955	28.2	58,683	26.6	1,249	28.3	51,883	26.6
13-15 years	4,949	20.0	45,809	20.8	866	19.6	40,122	20.6
16+ years	3,984	16.1	48,252	21.9	827	18.7	42,367	21.8
Missing	567	2.3	5,094	2.3	119	2.7	4,504	2.3

Maternal Race/Ethnicity								
White, non-Hispanic	5,919	24.0	64,600	29.3	928	21.0	55,036	28.3
Hispanic, any race	13,801	55.9	116,509	52.9	2,278	51.6	103,428	53.1
Black	1,691	6.8	9,639	4.4	392	8.9	8,843	4.5
Asian/PI	2,437	9.9	21,570	9.8	587	13.3	20,193	10.4
Other/Refused	845	3.4	7,979	3.6	227	5.1	7,232	3.7
Parity								
1	9,319	37.7	84,535	38.4	2,238	50.7	76,877	39.5
2	7,060	28.6	70,977	32.2	1,087	24.6	62,329	32.0
3 or more	8,306	33.6	64,736	29.4	1,084	24.6	55,484	28.5
Missing	8	0.0	49	0.0	3	0.1	42	0.0
Prenatal care in first trimester								
Yes	19821	80.3	186741	84.8	3533	80.1	164640	84.5
No	4580	18.5	32233	14.6	834	18.9	28891	14.8
Missing	292	1.2	1323	0.6	45	1.0	1201	0.6
Payment type of prenantal care								
Private/HMO/BCBS	10731	43.5	110816	50.3	1961	44.4	96650	49.6
MediCal/Govt/self-pay	13591	55.0	108385	49.2	2401	54.4	97085	49.9
Missing	371	1.5	1096	0.5	50	1.1	997	0.5
Maternal birthplace								
US	13585	55.0	119055	54.0	2337	53.0	104048	53.4
Foreign countries	11093	44.9	101169	45.9	2072	47.0	90618	46.5
Missing	15	0.1	73	0.0	3	0.1	66	0.0
Quintiles of neighborhood SES								
1 (Lowest)	7157	29.0	55746	25.3	1254	28.4	49635	25.5
2	6403	25.9	55227	25.1	1174	26.6	48916	25.1
3	5143	20.8	45378	20.6	883	20.0	39879	20.5
4	3451	14.0	35467	16.1	627	14.2	31215	16.0
5 (Highest)	2525	10.2	28364	12.9	474	10.7	24980	12.8
Missing	14	0.1	115	0.1	.	.	107	0.1

Table 2.2 Odds ratios (95% confidence intervals) for trimester exposures to individual pesticides (ever vs never) and preterm birth.

	First trimester				Second trimester			
Pesticide	PTB*	TB*	OR[1]	OR[2]	PTB*	TB*	OR[1]	OR[2]
Fungicide								
Myclobutanil	5307 (22.0%)	47755 (21.6%)	1.02 (0.99, 1.05)	1.02 (0.99, 1.06)	5366 (22.2%)	48337 (21.9%)	1.02 (0.98, 1.05)	1.02 (0.99, 1.06)
Chlorothalonil	5511 (22.8%)	49183 (22.3%)	1.03 (1.00, 1.06)	1.02 (0.99, 1.05)	5585 (23.1%)	49070 (22.2%)	1.05 (1.02, 1.08)	1.04 (1.01, 1.08)
Mancozeb	3600 (14.9%)	32779 (14.8%)	1.00 (0.96, 1.04)	0.98 (0.95, 1.02)	3588 (14.8%)	33038 (15.0%)	0.99 (0.95, 1.02)	0.97 (0.94, 1.01)
Herbicide								
Glyphosate compounds	14346 (59.3%)	127703 (57.8%)	1.07 (1.04, 1.10)	1.05 (1.02, 1.08)	14295 (59.1%)	127672 (57.8%)	1.06 (1.03, 1.09)	1.04 (1.01, 1.07)
Paraquat dichloride	3850 (15.9%)	32073 (14.5%)	1.11 (1.07, 1.16)	1.07 (1.03, 1.11)	3823 (15.8%)	32009 (14.5%)	1.11 (1.07, 1.15)	1.06 (1.02, 1.10)
Simazine	2613 (10.8%)	23310 (10.6%)	1.02 (0.98, 1.07)	1.02 (0.97, 1.06)	2684 (11.1%)	22978 (10.4%)	1.07 (1.03, 1.12)	1.06 (1.02, 1.11)
Insecticide								
Chlorpyrifos	8511 (35.2%)	74414 (33.7%)	1.06 (1.04, 1.10)	1.03 (1.00, 1.06)	8390 (34.7%)	74037 (33.5%)	1.05 (1.02, 1.08)	1.02 (0.99, 1.05)
Abamectin	7715 (31.9%)	68819 (31.2%)	1.04 (1.01, 1.07)	1.02 (0.99, 1.05)	7736 (32.0%)	69606 (31.5%)	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)
Malathion	5696 (23.6%)	51530 (23.3%)	1.01 (0.98, 1.04)	0.99 (0.96, 1.03)	5715 (23.6%)	51429 (23.3%)	1.02 (0.99, 1.05)	1.00 (0.97, 1.03)
Imidacloprid	6107 (25.3%)	53105 (24.0%)	1.07 (1.04, 1.10)	1.06 (1.03, 1.10)	6139 (25.4%)	54444 (24.6%)	1.04 (1.01, 1.08)	1.04 (1.00, 1.07)

Diazinon	5319 (22.0%)	46514 (21.1%)	1.05 (1.01, 1.08)	1.02 (0.99, 1.06)	5185 (21.4%)	45430 (20.6%)	1.05 (1.01, 1.08)	1.02 (0.99, 1.06)
Permethrin	4597 (19.0%)	40300 (18.2%)	1.05 (1.02, 1.09)	1.03 (1.00, 1.07)	4465 (18.5%)	40533 (18.3%)	1.01 (0.97, 1.04)	0.99 (0.95, 1.02)
Dimethoate	3223 (13.3%)	27905 (12.6%)	1.06 (1.02, 1.10)	1.04 (1.00, 1.08)	3216 (13.3%)	27874 (12.6%)	1.06 (1.02, 1.10)	1.03 (0.99, 1.07)
Methyl bromide	2448 (10.1%)	21398 (9.7%)	1.04 (1.00, 1.09)	1.05 (1.00, 1.10)	2337 (9.7%)	20851 (9.4%)	1.02 (0.98, 1.07)	1.01 (0.96, 1.06)
Carbaryl	2241 (9.3%)	20285 (9.2%)	1.00 (0.96, 1.05)	1.00 (0.96, 1.05)	2150 (8.9%)	20160 (9.1%)	0.97 (0.92, 1.01)	0.96 (0.92, 1.01)
Phosmet	1154 (4.8%)	9995 (4.5%)	1.05 (0.99, 1.12)	1.01 (0.95, 1.08)	1099 (4.5%)	9875 (4.5%)	1.01 (0.95, 1.08)	0.97 (0.91, 1.04)
Methyl parathion	448 (1.9%)	3660 (1.7%)	1.11 (1.01, 1.23)	1.05 (0.95, 1.17)	402 (1.7%)	3715 (1.7%)	0.98 (0.88, 1.08)	0.91 (0.82, 1.01)

[1] Adjusted for year of birth, sex

[2] Adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Table 2.3 Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and preterm birth.

	First trimester					Second trimester				
Chemical Class	PTB*	TB*	OR[1]	OR[2]	OR[3]	PTB*	TB*	OR[1]	OR[2]	OR[3]
No. of carbamates ever exposed to										
0 (ref.)	15419 (63.8%)	143956 (65.2%)				15343 (63.5%)	143806 (65.1%)			
1	4519 (18.7%)	40328 (18.3%)	1.04 (1.01, 1.08)	1.03 (0.99, 1.07)	1.01 (0.98, 1.05)	4604 (19.0%)	40390 (18.3%)	1.07 (1.03, 1.10)	1.04 (1.01, 1.08)	1.03 (0.99, 1.07)
2+	4237 (17.5%)	36613 (16.6%)	1.08 (1.04, 1.11)	1.04 (1.00, 1.08)	1.01 (0.97, 1.06)	4227 (17.5%)	36702 (16.6%)	1.07 (1.04, 1.11)	1.04 (1.00, 1.08)	1.03 (0.98, 1.08)
No. of organophosphates ever exposed to										
0 (ref.)	9523 (39.4%)	90246 (40.9%)				9469 (39.2%)	90715 (41.1%)			
1	5105 (21.1%)	46306 (21.0%)	1.04 (1.01, 1.08)	1.01 (0.98, 1.05)	1.00 (0.96, 1.04)	5263 (21.8%)	46494 (21.0%)	1.08 (1.04, 1.12)	1.06 (1.02, 1.10)	1.04 (1.00, 1.08)
2+	9546 (39.5%)	84346 (38.2%)	1.07 (1.03, 1.10)	1.02 (0.99, 1.06)	0.98 (0.94, 1.02)	9442 (39.1%)	83688 (37.9%)	1.07 (1.04, 1.11)	1.03 (1.00, 1.06)	0.99 (0.95, 1.03)
No. of pyrethroids ever exposed to										
0 (ref.)	11938 (49.4%)	112936 (51.1%)				11906 (49.3%)	112617 (51.0%)			
1	4965 (20.5%)	44681 (20.2%)	1.05 (1.01, 1.09)	1.03 (0.99, 1.06)	1.03 (0.99, 1.07)	4977 (20.6%)	44247 (20.0%)	1.06 (1.02, 1.10)	1.04 (1.00, 1.08)	1.03 (0.99, 1.07)
2+	7272 (30.1%)	63281 (28.6%)	1.09 (1.05, 1.12)	1.06 (1.02, 1.09)	1.06 (1.01, 1.11)	7291 (30.2%)	64034 (29.0%)	1.08 (1.04, 1.11)	1.05 (1.01, 1.08)	1.04 (0.99, 1.08)

[1] Adjusted for year of birth, sex

[2] Adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

[3] Adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, neighborhood SES, and co-exposures to other two chemical classes

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Table 2.4 Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and preterm birth, stratified by infant sex.

	First trimester				Second trimester			
Chemical Class	PTB*	TB*	OR[1]	OR[2]	PTB*	TB*	OR[1]	OR[2]
	Males							
No. of carbamates ever exposed to								
0 (ref.)	11978 (64.4%)	104716 (64.9%)			11937 (64.2%)	104618 (64.8%)		
1	3408 (18.3%)	29803 (18.5%)	1.00 (0.96, 1.04)	0.99 (0.95, 1.03)	3466 (18.6%)	29761 (18.4%)	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)
2+	3215 (17.3%)	26835 (16.6%)	1.05 (1.00, 1.09)	1.01 (0.97, 1.06)	3198 (17.2%)	26974 (16.7%)	1.04 (1.00, 1.08)	1.00 (0.96, 1.05)
No. of organophosphates ever exposed to								
0 (ref.)	7352 (39.5%)	65519 (40.6%)			7320 (39.4%)	65953 (40.9%)		
1	3973 (21.4%)	33934 (21.0%)	1.04 (1.00, 1.09)	1.02 (0.97, 1.06)	4055 (21.8%)	34148 (21.2%)	1.07 (1.03, 1.11)	1.05 (1.01, 1.09)
2+	7276 (39.1%)	61901 (38.4%)	1.05 (1.01, 1.08)	1.01 (0.97, 1.04)	7226 (38.8%)	61253 (38.0%)	1.06 (1.02, 1.10)	1.02 (0.98, 1.06)
No. of pyrethroids ever exposed to								
0 (ref.)	9239 (49.7%)	82215 (51.0%)			9281 (49.9%)	82055 (50.9%)		
1	3902 (21.0%)	32699 (20.3%)	1.06 (1.02, 1.10)	1.03 (0.99, 1.08)	3822 (20.5%)	32618 (20.2%)	1.03 (0.99, 1.08)	1.01 (0.97, 1.06)
2+	5460 (29.4%)	46440 (28.8%)	1.04 (1.01, 1.08)	1.01 (0.98, 1.05)	5498 (29.6%)	46681 (28.9%)	1.04 (1.00, 1.08)	1.01 (0.97, 1.05)

	Females							
No. of carbamates ever exposed to								
0 (ref.)	3861 (63.1%)	38769 (65.5%)			3835 (62.6%)	38723 (65.4%)		
1	1171 (19.1%)	10682 (18.0%)	1.09 (1.02, 1.17)	1.08 (1.00, 1.15)	1195 (19.5%)	10731 (18.1%)	1.12 (1.05, 1.20)	1.09 (1.01, 1.17)
2+	1090 (17.8%)	9783 (16.5%)	1.11 (1.03, 1.19)	1.07 (1.00, 1.15)	1091 (17.8%)	9778 (16.5%)	1.12 (1.04, 1.20)	1.08 (1.01, 1.17)
No. of organophosphates ever exposed to								
0 (ref.)	2402 (39.2%)	24352 (41.1%)			2385 (39.0%)	24443 (41.3%)		
1	1276 (20.8%)	12375 (20.9%)	1.04 (0.97, 1.12)	1.01 (0.94, 1.09)	1331 (21.7%)	12396 (20.9%)	1.10 (1.02, 1.18)	1.07 (1.00, 1.15)
2+	2444 (39.9%)	22506 (38.0%)	1.09 (1.03, 1.16)	1.04 (0.98, 1.11)	2406 (39.3%)	22394 (37.8%)	1.09 (1.03, 1.16)	1.04 (0.98, 1.11)
No. of pyrethroids ever exposed to								
0 (ref.)	3003 (49.0%)	30390 (51.3%)			2969 (48.5%)	30277 (51.1%)		
1	1226 (20.0%)	11958 (20.2%)	1.04 (0.97, 1.11)	1.02 (0.95, 1.09)	1263 (20.6%)	11751 (19.8%)	1.09 (1.02, 1.17)	1.08 (1.00, 1.16)
2+	1893 (30.9%)	16886 (28.5%)	1.14 (1.07, 1.21)	1.11 (1.04, 1.18)	1889 (30.9%)	17206 (29.0%)	1.12 (1.05, 1.19)	1.09 (1.02, 1.16)

[1] Adjusted for year of birth

[2] Adjusted for year of birth, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

2.6 Appendices

Supplementary Table 2.1 Individual pesticides included in chemical classes.

ChemCode	Chemical	Use Type PAN
Dithiocarbamates/N-Methyl Carbamates (n=24)		
369	Maneb	Fungicide
616	Metam-Sodium	Fumigant, Herbicide, Fungicide, Microbiocide, Algaecide
589	Thiram	Fungicide
970	Potassium N-Methyldithiocarbamate	Fumigant, Fungicide, Microbiocide, Algaecide, Nematicide
288	Ferbam	Fungicide
417	Nabam	Fungicide, Herbicide
548	Sodium Dimethyl Dithio Carbamate	Fungicide
211	Mancozeb	Fungicide
629	Ziram	Fungicide, Microbiocide, Dog and Cat Repellent
627	Zineb	Fungicide
493	Metiram	Fungicide
383	Methomyl	Insecticide
105	Carbaryl	Insecticide, Plant Growth Regulator, Nematicide
375	Methiocarb	Insecticide, Molluscicide
1910	Oxamyl	Insecticide, Nematicide
575	Aldicarb	Insecticide, Nematicide
111	Formetanate Hydrochloride	Insecticide
106	Carbofuran	Insecticide, Nematicide
2202	Thiodicarb	Molluscicide, Insecticide
1924	Bendiocarb	Insecticide
62	Propoxur	Insecticide
623	Mexacarbate	Insecticide
1875	Pirimicarb	Insecticide
2201	Butoxycarboxim	Insecticide
Organophosphates (n=50)		
253	Chlorpyrifos	Insecticide, Nematicide
1685	Acephate	Insecticide
367	Malathion	Insecticide
198	Diazinon	Insecticide
216	Dimethoate	Insecticide
1626	Ethephon	Plant Growth Regulator
418	Naled	Insecticide
335	Phosmet	Insecticide
70	Bensulide	Herbicide

382	Oxydemeton-Methyl	Insecticide
1689	Methidathion	Insecticide
314	Azinphos-Methyl	Insecticide
394	Methyl Parathion	Insecticide, Nematicide
230	Disulfoton	Insecticide, Nematicide
90394	Methyl Parathion, Other Related	Insecticide, Nematicide
92739	Nonanoic Acid, Other Related	Insecticide, Nematicide
1857	Fenamiphos	Insecticide, Nematicide
1697	Methamidophos	Insecticide, Breakdown product
478	Phorate	Insecticide, Nematicide
558	Sulfotep	Insecticide
404	Ethoprop	Insecticide, Nematicide
254	Fonofos	Insecticide
190	S,S,S-Tributyl Phosphorotrithioate	Defoliant, Plant Growth Regulator
459	Parathion	Insecticide
90480	Mevinphos, Other Related	Insecticide
480	Mevinphos	Insecticide
2042	Profenofos	Insecticide
165	Coumaphos	Insecticide
90459	Parathion, Other Related	Insecticide, Nematicide
187	Ddvp	Insecticide, Breakdown product, Impurity
90187	Ddvp, Other Related	Insecticide
90482	Phosphamidon, Other Related	Insecticide
482	Phosphamidon	Insecticide
88	Trichlorfon	Insecticide
566	Demeton	Insecticide, Nematicide
268	Ethion	Insecticide
110	Carbophenothion	Insecticide
305	Tetrachlorvinphos	Insecticide
192	Dioxathion	Insecticide
90192	Dioxathion, Other Related	Insecticide
479	Phosalone	Insecticide
1523	Phosacetin	Rodenticide
263	Epn	Insecticide
72	Dicrotophos	Insecticide
90293	Merphos, Other Related	Defoliant, Plant Growth Regulator
293	Merphos	Defoliant, Plant Growth Regulator
2006	Sulprofos	Insecticide
577	Tepp	Insecticide
90577	Tepp, Other Related	Insecticide

517	Ronnel	Insecticide
Pyrethroids (n=29)		
2300	Bifenthrin	Insecticide
2008	Permethrin	Insecticide
2321	Esfenvalerate	Insecticide
2195	Tau-Fluvalinate	Insecticide
2223	Cyfluthrin	Insecticide
2297	Lambda-Cyhalothrin	Insecticide
2234	Fenpropathrin	Insecticide
3866	(S)-Cypermethrin	Insecticide
3010	Deltamethrin	Insecticide
2171	Cypermethrin	Insecticide
3956	Beta-Cyfluthrin	Insecticide
5877	Gamma-Cyhalothrin	Insecticide
2119	Resmethrin	Insecticide
2329	Tralomethrin	Insecticide
92119	Resmethrin, Other Related	Insecticide
5327	Imiprothrin	Insecticide
4038	D-Trans Allethrin	Insecticide
2093	Phenothrin	Insecticide
12	Allethrin	Insecticide
1963	Fenvalerate	Insecticide
1695	Tetramethrin	Insecticide
92093	Phenothrin, Other Related	Insecticide
90012	Allethrin, Other Related	Insecticide
92008	Permethrin, Other Related	Insecticide
2293	D-Allethrin	Insecticide
3985	Prallethrin	Insecticide
92293	D-Allethrin, Other Related	Insecticide
91695	Tetramethrin, Other Related	Insecticide
4039	S-Bioallethrin	Insecticide

Supplementary Table 2.2 Odds ratios (95% confidence intervals) for trimester exposures to individual pesticides (ever vs never) and preterm birth, by sex.

	First trimester				Second trimester			
Pesticide	PTB*	TB*	OR[1]	OR[2]	PTB*	TB*	OR[1]	OR[2]
	Males							
Fungicide								
Myclobutanil	3968 (21.3%)	35111 (21.8%)	0.97 (0.94, 1.01)	0.97 (0.93, 1.01)	4072 (21.9%)	35700 (22.1%)	0.99 (0.95, 1.02)	0.99 (0.95, 1.02)
Chlorothalonil	4147 (22.3%)	35912 (22.3%)	1.00 (0.97, 1.04)	0.99 (0.95, 1.03)	4231 (22.7%)	35845 (22.2%)	1.03 (0.99, 1.07)	1.02 (0.99, 1.06)
Mancozeb	2702 (14.5%)	24012 (14.9%)	0.97 (0.93, 1.01)	0.96 (0.92, 1.00)	2735 (14.7%)	24217 (15.0%)	0.98 (0.93, 1.02)	0.97 (0.93, 1.01)
Herbicide								
Glyphosate compounds	11006 (59.2%)	93459 (57.9%)	1.05 (1.02, 1.09)	1.04 (1.01, 1.07)	11018 (59.2%)	93553 (58.0%)	1.05 (1.02, 1.09)	1.04 (1.01, 1.07)
Paraquat dichloride	2964 (15.9%)	23751 (14.7%)	1.10 (1.05, 1.14)	1.06 (1.01, 1.10)	2954 (15.9%)	23577 (14.6%)	1.10 (1.06, 1.15)	1.07 (1.02, 1.11)
Simazine	2093 (11.2%)	17086 (10.6%)	1.07 (1.02, 1.12)	1.06 (1.01, 1.12)	2075 (11.2%)	16938 (10.5%)	1.07 (1.02, 1.12)	1.07 (1.02, 1.13)
Insecticide								
Chlorpyrifos	6496 (34.9%)	54491 (33.8%)	1.05 (1.02, 1.08)	1.02 (0.98, 1.05)	6432 (34.6%)	54201 (33.6%)	1.04 (1.01, 1.08)	1.01 (0.98, 1.05)
Abamectin	5812 (31.2%)	50314 (31.2%)	1.00 (0.97, 1.04)	0.99 (0.95, 1.02)	5911 (31.8%)	50950 (31.6%)	1.01 (0.98, 1.04)	0.99 (0.96, 1.03)
Malathion	4431 (23.8%)	37826 (23.4%)	1.02 (0.99, 1.06)	1.00 (0.96, 1.04)	4410 (23.7%)	37965 (23.5%)	1.01 (0.97, 1.05)	0.99 (0.96, 1.03)
Imidacloprid	4608 (24.8%)	38937 (24.1%)	1.04 (1.00, 1.07)	1.03 (0.99, 1.06)	4632 (24.9%)	39660 (24.6%)	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)
Diazinon	3949 (21.2%)	34395 (21.3%)	0.99 (0.96, 1.03)	0.97 (0.93, 1.00)	3910 (21.0%)	33315 (20.6%)	1.02 (0.98, 1.06)	0.99 (0.96, 1.03)

Permethrin	3479 (18.7%)	29333 (18.2%)	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)	3415 (18.4%)	29546 (18.3%)	1.00 (0.96, 1.04)	0.98 (0.94, 1.02)
Dimethoate	2432 (13.1%)	20514 (12.7%)	1.03 (0.99, 1.08)	1.01 (0.96, 1.06)	2430 (13.1%)	20431 (12.7%)	1.03 (0.99, 1.08)	1.01 (0.96, 1.05)
Methyl bromide	1876 (10.1%)	15659 (9.7%)	1.04 (0.99, 1.10)	1.04 (0.98, 1.09)	1786 (9.6%)	15162 (9.4%)	1.02 (0.97, 1.08)	1.00 (0.95, 1.06)
Carbaryl	1753 (9.4%)	14966 (9.3%)	1.02 (0.97, 1.07)	1.01 (0.95, 1.06)	1651 (8.9%)	14846 (9.2%)	0.96 (0.91, 1.01)	0.95 (0.90, 1.00)
Phosmet	863 (4.6%)	7197 (4.5%)	1.04 (0.97, 1.12)	1.01 (0.94, 1.09)	840 (4.5%)	7200 (4.5%)	1.01 (0.94, 1.09)	0.98 (0.91, 1.06)
Methyl parathion	331 (1.8%)	2688 (1.7%)	1.06 (0.95, 1.19)	1.02 (0.90, 1.15)	301 (1.6%)	2717 (1.7%)	0.95 (0.84, 1.07)	0.91 (0.80, 1.03)

	Females							
Fungicide								
Myclobutanil	1388 (22.7%)	12718 (21.5%)	1.07 (1.00, 1.14)	1.08 (1.01, 1.15)	1381 (22.6%)	12811 (21.6%)	1.05 (0.99, 1.12)	1.06 (1.00, 1.14)
Chlorothalonil	1431 (23.4%)	13193 (22.3%)	1.06 (1.00, 1.13)	1.06 (0.99, 1.13)	1440 (23.5%)	13157 (22.2%)	1.07 (1.01, 1.14)	1.06 (1.00, 1.14)
Mancozeb	938 (15.3%)	8763 (14.8%)	1.03 (0.96, 1.11)	1.01 (0.93, 1.09)	918 (15.0%)	8827 (14.9%)	1.00 (0.93, 1.08)	0.98 (0.91, 1.06)
Herbicide								
Glyphosate compounds	3646 (59.6%)	34175 (57.7%)	1.08 (1.03, 1.14)	1.07 (1.01, 1.13)	3613 (59.0%)	34122 (57.6%)	1.06 (1.01, 1.12)	1.05 (0.99, 1.10)
Paraquat dichloride	975 (15.9%)	8477 (14.3%)	1.13 (1.05, 1.22)	1.09 (1.01, 1.17)	963 (15.7%)	8509 (14.4%)	1.11 (1.03, 1.20)	1.05 (0.98, 1.14)
Simazine	630 (10.3%)	6228 (10.5%)	0.97 (0.89, 1.06)	0.96 (0.88, 1.05)	676 (11.0%)	6103 (10.3%)	1.07 (0.98, 1.16)	1.05 (0.96, 1.15)
Insecticide								
Chlorpyrifos	2175 (35.5%)	19902 (33.6%)	1.08 (1.02, 1.14)	1.05 (0.99, 1.11)	2134 (34.9%)	19807 (33.4%)	1.06 (1.00, 1.12)	1.02 (0.96, 1.08)
Abamectin	2002 (32.7%)	18436 (31.1%)	1.07 (1.02, 1.14)	1.06 (1.00, 1.12)	1975 (32.3%)	18624 (31.4%)	1.04 (0.98, 1.10)	1.02 (0.96, 1.08)

Malathion	1424 (23.3%)	13746 (23.2%)	1.00 (0.94, 1.06)	0.99 (0.93, 1.05)	1442 (23.6%)	13638 (23.0%)	1.03 (0.97, 1.09)	1.01 (0.95, 1.08)
Imidacloprid	1581 (25.8%)	14184 (23.9%)	1.11 (1.05, 1.18)	1.11 (1.04, 1.18)	1590 (26.0%)	14641 (24.7%)	1.07 (1.01, 1.14)	1.07 (1.01, 1.14)
Diazinon	1402 (22.9%)	12313 (20.8%)	1.12 (1.05, 1.19)	1.10 (1.03, 1.17)	1344 (21.9%)	12132 (20.5%)	1.08 (1.01, 1.15)	1.05 (0.98, 1.12)
Permethrin	1186 (19.4%)	10846 (18.3%)	1.07 (1.00, 1.14)	1.05 (0.98, 1.13)	1139 (18.6%)	10892 (18.4%)	1.01 (0.95, 1.08)	0.99 (0.93, 1.07)
Dimethoate	834 (13.6%)	7433 (12.5%)	1.09 (1.01, 1.18)	1.08 (1.00, 1.17)	832 (13.6%)	7447 (12.6%)	1.08 (1.00, 1.17)	1.06 (0.98, 1.15)
Methyl bromide	623 (10.2%)	5727 (9.7%)	1.05 (0.96, 1.14)	1.06 (0.97, 1.16)	596 (9.7%)	5617 (9.5%)	1.02 (0.93, 1.11)	1.02 (0.93, 1.12)
Carbaryl	557 (9.1%)	5383 (9.1%)	0.99 (0.90, 1.08)	1.00 (0.91, 1.10)	545 (8.9%)	5360 (9.0%)	0.97 (0.89, 1.07)	0.98 (0.90, 1.08)
Phosmet	302 (4.9%)	2720 (4.6%)	1.07 (0.95, 1.21)	1.01 (0.89, 1.15)	281 (4.6%)	2653 (4.5%)	1.01 (0.89, 1.15)	0.96 (0.84, 1.09)
Methyl parathion	119 (1.9%)	976 (1.6%)	1.17 (0.96, 1.41)	1.09 (0.90, 1.33)	105 (1.7%)	995 (1.7%)	1.01 (0.82, 1.23)	0.91 (0.73, 1.12)

[1] Adjusted for year of birth

[2] Adjusted for year of birth, maternal age, maternal education, maternal race/ethnicity, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Supplementary Table 2.3 Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and preterm birth, stratified by maternal race/ethnicity.

	First trimester				Second trimester			
Chemical Class	PTB*	TB*	OR[1]	OR[2]	PTB*	TB*	OR[1]	OR[2]
	Whites							
No. of carbamates ever exposed to								
0 (ref.)	3871 (66.0%)	43919 (66.9%)			3854 (65.7%)	43848 (66.8%)		
1	1042 (17.8%)	11555 (17.6%)	1.02 (0.95, 1.10)	1.01 (0.94, 1.09)	1081 (18.4%)	11720 (17.9%)	1.05 (0.98, 1.12)	1.02 (0.95, 1.10)
2+	952 (16.2%)	10173 (15.5%)	1.06 (0.98, 1.14)	1.00 (0.93, 1.08)	929 (15.8%)	10078 (15.4%)	1.04 (0.97, 1.13)	1.00 (0.92, 1.08)
No. of organophosphates ever exposed to								
0 (ref.)	2591 (44.2%)	29817 (45.4%)			2628 (44.8%)	29916 (45.6%)		
1	1173 (20.0%)	12932 (19.7%)	1.04 (0.97, 1.12)	1.04 (0.96, 1.12)	1188 (20.3%)	13221 (20.1%)	1.02 (0.95, 1.10)	1.01 (0.94, 1.09)
2+	2100 (35.8%)	22897 (34.9%)	1.05 (0.99, 1.11)	1.04 (0.98, 1.10)	2049 (34.9%)	22510 (34.3%)	1.03 (0.97, 1.09)	1.00 (0.94, 1.07)
No. of pyrethroids ever exposed to								
0 (ref.)	3164 (54.0%)	36432 (55.5%)			3214 (54.8%)	36350 (55.4%)		
1	1140 (19.4%)	12607 (19.2%)	1.04 (0.97, 1.12)	1.03 (0.96, 1.11)	1131 (19.3%)	12502 (19.0%)	1.02 (0.95, 1.10)	1.02 (0.95, 1.09)
2+	1560 (26.6%)	16608 (25.3%)	1.08 (1.01, 1.15)	1.07 (1.00, 1.14)	1519 (25.9%)	16795 (25.6%)	1.02 (0.96, 1.09)	1.00 (0.94, 1.07)

	US born Hispanics							
No. of carbamates ever exposed to								
0 (ref.)	3354 (61.7%)	28286 (63.6%)			3345 (61.5%)	28205 (63.4%)		
1	1024 (18.8%)	8154 (18.3%)	1.05 (0.98, 1.13)	1.03 (0.95, 1.11)	1053 (19.4%)	8143 (18.3%)	1.09 (1.01, 1.17)	1.07 (0.99, 1.15)
2+	1057 (19.5%)	8016 (18.0%)	1.11 (1.03, 1.19)	1.07 (0.99, 1.15)	1038 (19.1%)	8109 (18.2%)	1.07 (1.00, 1.16)	1.04 (0.96, 1.12)
No. of organophosphates ever exposed to								
0 (ref.)	2010 (37.0%)	16590 (37.3%)			2006 (36.9%)	16693 (37.5%)		
1	1233 (22.7%)	9856 (22.2%)	1.03 (0.96, 1.11)	1.03 (0.95, 1.11)	1264 (23.3%)	9760 (22.0%)	1.07 (1.00, 1.16)	1.08 (1.00, 1.16)
2+	2193 (40.3%)	18011 (40.5%)	1.00 (0.93, 1.06)	0.97 (0.91, 1.04)	2166 (39.8%)	18004 (40.5%)	0.99 (0.93, 1.06)	0.97 (0.91, 1.04)
No. of pyrethroids ever exposed to								
0 (ref.)	2543 (46.8%)	21748 (48.9%)			2543 (46.8%)	21581 (48.5%)		
1	1192 (21.9%)	9362 (21.1%)	1.09 (1.01, 1.17)	1.08 (1.00, 1.16)	1194 (22.0%)	9349 (21.0%)	1.08 (1.01, 1.16)	1.10 (1.02, 1.18)
2+	1701 (31.3%)	13347 (30.0%)	1.09 (1.02, 1.16)	1.07 (1.00, 1.14)	1699 (31.2%)	13526 (30.4%)	1.07 (1.00, 1.14)	1.05 (0.98, 1.12)
	Foreign born Hispanics							
No. of carbamates ever exposed to								
0 (ref.)	4818 (60.5%)	44109 (61.4%)			4787 (60.1%)	44163 (61.4%)		
1	1501 (18.8%)	13571 (18.9%)	1.01 (0.95, 1.07)	1.02 (0.96, 1.09)	1500 (18.8%)	13421 (18.7%)	1.03 (0.96, 1.09)	1.04 (0.97, 1.10)

2+	1649 (20.7%)	14192 (19.7%)	1.06 (1.00, 1.12)	1.05 (0.98, 1.11)	1681 (21.1%)	14287 (19.9%)	1.08 (1.02, 1.15)	1.06 (1.00, 1.13)
No. of organophosphates ever exposed to								
0 (ref.)	2705 (33.9%)	25441 (35.4%)			2674 (33.6%)	25491 (35.5%)		
1	1682 (21.1%)	15476 (21.5%)	1.02 (0.96, 1.09)	1.00 (0.94, 1.07)	1748 (21.9%)	15523 (21.6%)	1.07 (1.01, 1.14)	1.07 (1.00, 1.14)
2+	3582 (45.0%)	30953 (43.1%)	1.08 (1.03, 1.14)	1.05 (0.99, 1.11)	3546 (44.5%)	30858 (42.9%)	1.09 (1.03, 1.15)	1.05 (1.00, 1.11)
No. of pyrethroids ever exposed to								
0 (ref.)	3579 (44.9%)	33219 (46.2%)			3537 (44.4%)	33010 (45.9%)		
1	1667 (20.9%)	15094 (21.0%)	1.02 (0.96, 1.09)	1.01 (0.94, 1.07)	1650 (20.7%)	14976 (20.8%)	1.02 (0.96, 1.09)	1.01 (0.95, 1.07)
2+	2723 (34.2%)	23558 (32.8%)	1.07 (1.02, 1.13)	1.06 (1.00, 1.12)	2781 (34.9%)	23885 (33.2%)	1.09 (1.03, 1.14)	1.07 (1.02, 1.13)

[1] Adjusted for year of birth, sex

[2] Adjusted for year of birth, sex, maternal age, maternal education, parity, prenatal care in first trimester, payment type of prenatal care, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Supplementary Table 2.4 Odds ratios (95% confidence intervals) for trimester exposures to individual pesticides (ever vs never) and term low birthweight.

	First trimester				Second trimester				Third trimester			
Pesticide	TLBW*	Normal BW*	OR[1]	OR[2]	TLBW*	Normal BW*	OR[1]	OR[2]	TLBW*	Normal BW*	OR[1]	OR[2]
Fungicides												
Myclobutanil	1019 (21.7%)	42545 (21.6%)	1.01 (0.94, 1.08)	1.03 (0.96, 1.11)	1093 (23.2%)	43089 (21.8%)	1.08 (1.01, 1.16)	1.11 (1.03, 1.19)	1106 (23.5%)	43578 (22.1%)	1.09 (1.01, 1.16)	1.11 (1.04, 1.20)
Chlorothalonil	1054 (22.4%)	43972 (22.3%)	1.01 (0.94, 1.08)	1.00 (0.93, 1.08)	1089 (23.2%)	43838 (22.2%)	1.06 (0.99, 1.13)	1.06 (0.98, 1.13)	1058 (22.5%)	43593 (22.1%)	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)
Mancozeb	698 (14.8%)	29225 (14.8%)	1.01 (0.93, 1.09)	0.99 (0.91, 1.08)	661 (14.1%)	29420 (14.9%)	0.93 (0.86, 1.02)	0.93 (0.85, 1.01)	675 (14.4%)	29243 (14.8%)	0.97 (0.89, 1.05)	0.95 (0.88, 1.04)
Herbicides												
Glyphosate compounds	2685 (57.1%)	114047 (57.8%)	0.97 (0.91, 1.03)	0.98 (0.92, 1.04)	2701 (57.4%)	114105 (57.8%)	0.98 (0.93, 1.04)	1.00 (0.94, 1.06)	2683 (57.0%)	114236 (57.9%)	0.97 (0.91, 1.02)	0.98 (0.93, 1.05)
Paraquat dichloride	665 (14.1%)	28421 (14.4%)	0.98 (0.90, 1.06)	1.00 (0.92, 1.09)	680 (14.5%)	28358 (14.4%)	1.01 (0.93, 1.09)	1.03 (0.95, 1.13)	687 (14.6%)	28126 (14.3%)	1.03 (0.95, 1.12)	1.07 (0.98, 1.17)
Simazine	479 (10.2%)	20661 (10.5%)	0.97 (0.88, 1.07)	1.01 (0.91, 1.11)	453 (9.6%)	20332 (10.3%)	0.93 (0.84, 1.02)	0.96 (0.87, 1.07)	467 (9.9%)	19897 (10.1%)	0.98 (0.89, 1.08)	1.04 (0.94, 1.15)
Insecticides												
Chlorpyrifos	1550 (32.9%)	66359 (33.6%)	0.97 (0.91, 1.03)	0.98 (0.92, 1.05)	1486 (31.6%)	65983 (33.4%)	0.92 (0.86, 0.98)	0.93 (0.87, 0.99)	1488 (31.6%)	66319 (33.6%)	0.91 (0.86, 0.97)	0.92 (0.87, 0.99)
Abamectin	1497 (31.8%)	61500 (31.2%)	1.03 (0.97, 1.10)	1.02 (0.96, 1.09)	1457 (31.0%)	62299 (31.6%)	0.97 (0.91, 1.04)	0.96 (0.90, 1.02)	1452 (30.9%)	62605 (31.7%)	0.96 (0.90, 1.02)	0.96 (0.90, 1.02)
Malathion	1080 (23.0%)	46146 (23.4%)	0.98 (0.91, 1.05)	0.97 (0.90, 1.04)	1087 (23.1%)	45963 (23.3%)	0.99 (0.93, 1.06)	0.98 (0.91, 1.05)	1106 (23.5%)	46551 (23.6%)	1.00 (0.93, 1.07)	1.00 (0.93, 1.07)

Imidacloprid	1128 (24.0%)	47471 (24.1%)	1.00 (0.93, 1.07)	1.02 (0.95, 1.09)	1146 (24.4%)	48701 (24.7%)	0.98 (0.92, 1.05)	1.01 (0.94, 1.08)	1131 (24.1%)	49673 (25.2%)	0.94 (0.88, 1.01)	0.94 (0.88, 1.01)
Diazinon	1011 (21.5%)	41379 (21.0%)	1.04 (0.97, 1.12)	1.03 (0.96, 1.11)	974 (20.7%)	40383 (20.5%)	1.02 (0.95, 1.10)	1.03 (0.95, 1.11)	892 (19.0%)	39846 (20.2%)	0.93 (0.86, 1.00)	0.92 (0.85, 0.99)
Permethrin	890 (18.9%)	35906 (18.2%)	1.05 (0.97, 1.13)	1.07 (0.99, 1.15)	878 (18.7%)	36100 (18.3%)	1.02 (0.95, 1.10)	1.04 (0.96, 1.12)	850 (18.1%)	36228 (18.4%)	0.98 (0.91, 1.05)	0.99 (0.92, 1.07)
Dimethoate	608 (12.9%)	24722 (12.5%)	1.04 (0.95, 1.13)	1.06 (0.97, 1.16)	585 (12.4%)	24747 (12.5%)	0.99 (0.91, 1.08)	1.00 (0.92, 1.10)	545 (11.6%)	24803 (12.6%)	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)
Methyl bromide	444 (9.4%)	18934 (9.6%)	0.98 (0.89, 1.08)	1.01 (0.91, 1.12)	450 (9.6%)	18423 (9.3%)	1.03 (0.93, 1.14)	1.05 (0.95, 1.17)	465 (9.9%)	18349 (9.3%)	1.07 (0.97, 1.18)	1.07 (0.96, 1.18)
Carbaryl	441 (9.4%)	17919 (9.1%)	1.04 (0.94, 1.15)	1.07 (0.96, 1.18)	421 (8.9%)	17871 (9.1%)	0.99 (0.89, 1.10)	0.99 (0.89, 1.11)	403 (8.6%)	17936 (9.1%)	0.94 (0.85, 1.04)	0.97 (0.87, 1.08)
Phosmet	216 (4.6%)	8863 (4.5%)	1.02 (0.89, 1.18)	1.04 (0.90, 1.20)	205 (4.4%)	8721 (4.4%)	0.99 (0.86, 1.14)	1.01 (0.87, 1.17)	214 (4.6%)	8980 (4.6%)	1.00 (0.87, 1.15)	1.07 (0.93, 1.23)
Methyl parathion	71 (1.5%)	3239 (1.6%)	0.92 (0.73, 1.17)	0.89 (0.70, 1.14)	70 (1.5%)	3279 (1.7%)	0.90 (0.71, 1.14)	0.86 (0.67, 1.11)	62 (1.3%)	3297 (1.7%)	0.79 (0.62, 1.02)	0.74 (0.57, 0.97)

[1] Adjusted for year of birth, sex

[2] Adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Supplementary Table 2.5. Odds ratios (95% confidence intervals) for trimester exposures to chemical classes and term low birthweight.

	First trimester				Second trimester				Third trimester			
Chemical Class	TLBW *	Normal BW*	OR[1]	OR[2]	TLBW *	Normal BW*	OR[1]	OR[2]	TLBW *	Normal BW*	OR[1]	OR[2]
No. of carbamates ever exposed to												
0 (ref.)	3073 (65.3%)	128830 (65.3%)			3083 (65.6%)	128657 (65.2%)			3129 (66.5%)	128964 (65.4%)		
1	863 (18.3%)	35943 (18.2%)	1.01 (0.93, 1.09)	1.00 (0.93, 1.09)	861 (18.3%)	36045 (18.3%)	1.00 (0.92, 1.08)	0.99 (0.91, 1.07)	819 (17.4%)	35834 (18.2%)	0.94 (0.87, 1.02)	0.93 (0.86, 1.01)
2+	768 (16.3%)	32547 (16.5%)	0.99 (0.91, 1.07)	1.01 (0.93, 1.09)	759 (16.1%)	32618 (16.5%)	0.97 (0.90, 1.05)	0.99 (0.91, 1.07)	755 (16.1%)	32523 (16.5%)	0.96 (0.89, 1.04)	0.98 (0.90, 1.07)
No. of organophosphates ever exposed to												
0 (ref.)	1931 (41.1%)	80625 (40.9%)			1948 (41.4%)	81166 (41.1%)			1985 (42.2%)	81408 (41.3%)		
1	972 (20.7%)	41534 (21.0%)	0.98 (0.91, 1.06)	0.98 (0.90, 1.06)	962 (20.5%)	41543 (21.1%)	0.97 (0.89, 1.05)	0.96 (0.88, 1.04)	933 (19.8%)	41134 (20.8%)	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)
2+	1800 (38.3%)	75160 (38.1%)	1.00 (0.94, 1.07)	0.99 (0.93, 1.06)	1793 (38.1%)	74612 (37.8%)	1.00 (0.94, 1.07)	1.00 (0.93, 1.07)	1785 (38.0%)	74778 (37.9%)	0.98 (0.92, 1.05)	0.98 (0.91, 1.05)
No. of pyrethroids ever exposed to												
0 (ref.)	2354 (50.1%)	100915 (51.1%)			2356 (50.1%)	100575 (51.0%)			2402 (51.1%)	100240 (50.8%)		
1	951 (20.2%)	39843 (20.2%)	1.02 (0.95, 1.10)	1.00 (0.92, 1.08)	922 (19.6%)	39417 (20.0%)	1.00 (0.92, 1.08)	0.98 (0.91, 1.06)	913 (19.4%)	39210 (19.9%)	0.97 (0.90, 1.05)	0.97 (0.89, 1.05)
2+	1398 (29.7%)	56563 (28.7%)	1.06 (0.99, 1.13)	1.05 (0.98, 1.13)	1425 (30.3%)	57328 (29.1%)	1.06 (0.99, 1.13)	1.06 (0.99, 1.13)	1388 (29.5%)	57869 (29.3%)	1.00 (0.94, 1.07)	1.00 (0.93, 1.07)

[1] Adjusted for year of birth, sex

[2] Adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity, paternal race, parity, prenatal care in first trimester, payment type of prenatal care, maternal birthplace, and neighborhood SES

* Numbers of exposed cases/controls and the percentages in the parenthesis; numbers used in each model may vary depending on missing values

Figure 2.1 Study subjects in agricultural and non-agricultural regions.

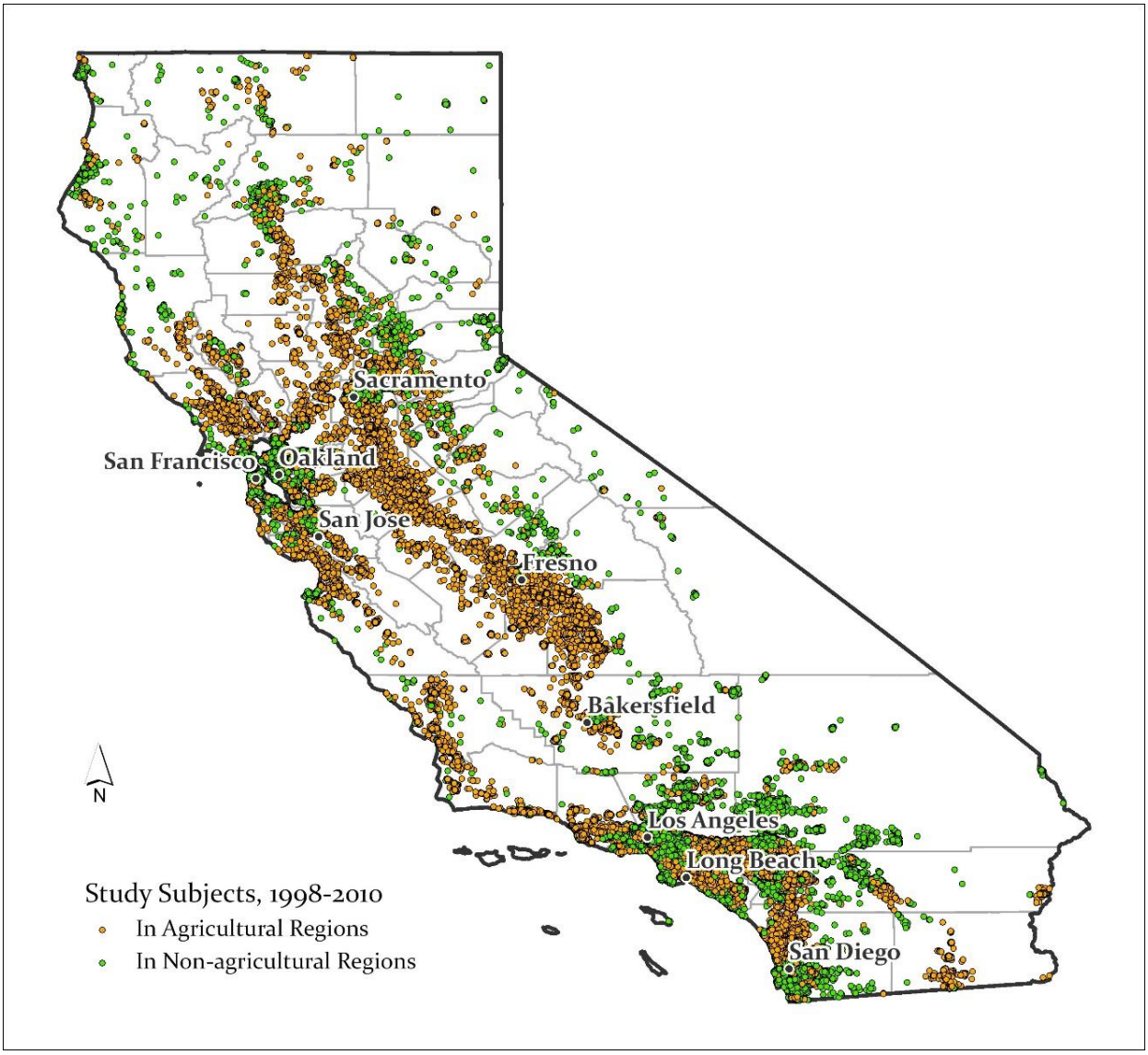
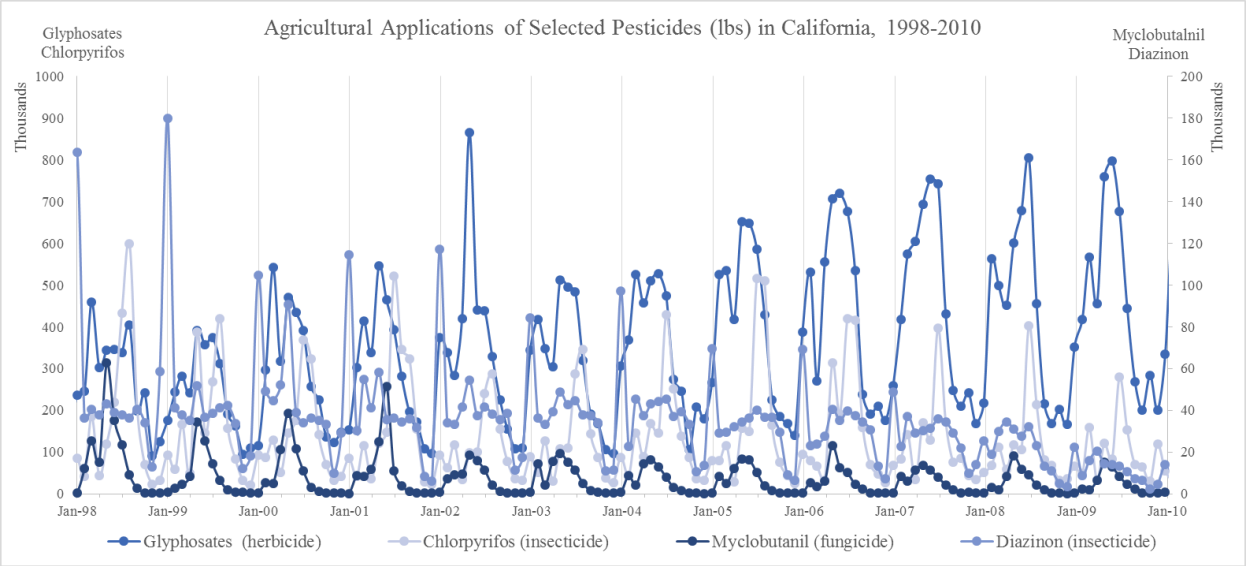


Figure 2.2 Seasonal variation of selected pesticide applications.



3. Residential Mobility and the Impact on Misclassification in Pesticide Exposures, in a Childhood Cancer Study

3.1 Abstract

Background: Studies of environmental exposures and childhood cancers that rely on records only often use maternal address at birth obtained from the birth certificate or address at cancer diagnosis to assess exposures in early childhood, possibly leading to exposure misclassification and questionable validity due to residential mobility during early childhood.

Objective: To assess patterns of and identify factors that may predict residential mobility in early childhood, and examine the impact of mobility on early childhood exposure measures for agriculturally applied pesticides and childhood cancers in California.

Methods: We obtained the residence at diagnosis of all childhood cancer cases born in 1998-2011 and diagnosed at 0-5 years of age from the California Cancer Registry (CCR), and their birth addresses from the birth certificate. Controls were randomly selected from CA birth records and frequency matched (20:1) to all cases by year of birth. We obtained public records of residential history from LexisNexis for both cases and controls. Logistic regression analyses were conducted to assess the socio-demographic factors in relation to residential mobility in early childhood. We calculated the distance moved and timing of a move after birth for both cases and controls. We employed a Geographic Information System (GIS)-based system to estimate children's first year of life exposures to agriculturally applied pesticides based on birth vs diagnosis or LexisNexis-based residential histories and assessed agreement between exposure measures using Spearman correlations and kappa statistics.

Results: Overall, 55% of children with childhood cancer moved between birth and diagnosis, and > 20% of case and control mothers moved in the child's first year of life. Older age at diagnosis, younger maternal age, lower maternal education, non-Hispanic ethnic background, public health insurance, non-metropolitan residence at birth, and exposure to pesticides were predictors of higher residential mobility. In all cases who moved between birth and diagnosis, the median distance between the residences was 5 km, and distance moved increased with age at diagnosis. There was moderate to strong correlation (Spearman correlation=0.76-0.83) and good agreement (kappa=0.75-0.81) between the first year of life exposures to agricultural pesticides within 2 km of a residence at birth and a residence at diagnosis or LexisNexis addresses, but agreement decreased as the distance increased.

Conclusions: These findings suggest that birth residence or diagnosis residence should be used with caution when estimating environmental exposures in the first year of life. Future research should consider factors that help correct for the exposure misclassification introduced by residential mobility. LexisNexis data may be useful for augmenting existing address information and constructing residential histories when estimating environmental exposure measures for large record linkage studies.

3.2 Background

Epidemiologic studies of environmental exposures (e.g., air pollution, pesticides, magnetic fields) in early childhood, often assign exposures based upon the child's or mother's residence. While large-scale record-linkage based studies can avoid selection and recall bias that often impacts smaller studies with active subject recruitment, previous record-based studies often relied solely on maternal residential address at birth, which is readily available on many birth

certificates (Carozza et al., 2009; Heck et al., 2014; Lavigne et al., 2017; Reynolds et al., 2005; von Ehrenstein et al., 2016) and/or residential address at diagnosis, as done in some childhood cancer studies (Carozza et al., 2008; García-Pérez et al., 2016, 2015). The reliance on one address implicitly makes the assumption that a child's residence remains the same throughout early childhood, or if they moved, that the exposure levels remained the same. Consequently, this may lead to exposure misclassification for those who move in early childhood especially for exposures with high spatial heterogeneity.

In a 2003-2007 California statewide representative survey, only 14% of all women moved in the 2-7 months post-partum (Margerison-Zilko et al., 2016), but with increasing age the frequency of residential moves also increased. For more than 50% of childhood cancer cases under age 5 diagnosed in California between 1988 and 2005, address at birth differed from the address at cancer diagnosis (Reynolds et al., 2004; Urayama et al., 2009), which raises concerns about using residence at birth to assess exposures in early childhood. Exposure misclassification due to moving is a ubiquitous problem encountered by nearly all record-based studies that lack a complete residential history for each child. Previous studies suggested that residential mobility may be associated with certain risk factors for childhood cancers such as maternal age, marital status, parity, family income, and other socioeconomic status metrics (Bell and Belanger, 2012; Tønnessen et al., 2016), resulting in differential misclassification of exposures. While previous studies that examined residential proximity to exposure have mentioned the potential bias resulting from residential mobility during pregnancy (Fell et al., 2004; Hodgson et al., 2015; Ochoa-Acuña et al., 2009; Pennington et al., 2016; Schulman et al., 1993), they rarely investigated the impact of residential mobility in early childhood on exposure measures or effect estimates.

While it is not feasible to acquire complete residential histories from interviews for subjects in large record-based studies as a gold standard to compare against the recorded birth or diagnosis address, databases containing public records of individuals collected by commercial companies have become available in recent years, allowing us to trace individuals without a self-reported residential history. For example, LexisNexis® Public Records (https://www.lexisnexis.com/en-us/products/public-records.page, hereinafter referred to as LexisNexis), a commercial credit reporting company, provides all known addresses for a set of individuals upon request. Earlier validation studies have proven addresses acquired from LexisNexis to be useful for reconstructing residential histories for subjects in epidemiological studies with an overall match rate of ~70-85% with detailed address history obtained from interviews (Hurley et al., 2017; Jacquez et al., 2011; Wheeler and Wang, 2015); however, these subjects mostly consisted of mid-aged or older individuals, whose residential mobility may differ from that of women at child-bearing age. Such information, if of high quality, could potentially augment existing address information and help us to reconstruct residential histories for subjects in large record-based studies and provide more accurate exposure estimates.

The degree of exposure misclassification due to mobility depends on the distance moved, the spatial heterogeneity of the exposure (Bell and Belanger, 2012), and the method of exposure assessment each study employed. For example, one study used ecological measures of agricultural activity at the county level (Carozza et al., 2008), thus moving within a county would not alter exposure estimates. Other studies have assessed agricultural land use and crop coverage within a 1-km buffer of a child's residence as proxies of pesticide applications (Gómez‐barroso et al., 2016) or exposures to pesticides within a ½ mile (804.5 m) buffer of child's residence (Rull et al., 2009) in relation to childhood cancers; such individual-level

measures might be more sensitive to changes in location. Compared with these methods to estimate agricultural pesticide exposures near residences, our GIS-based system that integrates California's unique Pesticide Use Reporting (PUR) database and land use maps in California (Rull and Ritz, 2003) estimates children's early life exposures at a finer resolution, but may be subject to more misclassification due to residential mobility. For the purpose of this study, we identify individuals' exposures in early childhood using a 2-km buffer.

The objectives of the present study are to assess patterns of mobility and identify maternal and child characteristics that may predict residential mobility in early childhood, and examine the impact of mobility on early childhood exposure measures for agriculturally applied pesticides and childhood cancers in California.

3.3 Methods

Study Population

We obtained information on all childhood cancer cases diagnosed before 6 years of age born in 1998–2011, from the California Cancer Registry (http://www.ccrcal.org). This study was conducted as part of the Air Pollution and Childhood Cancers (APCC) study, a large case-control investigation of children ages 0 to 5 years in CA, as described previously (Julia E. Heck et al., 2013). In brief, cases were linked to birth certificates using first and last names, date of birth, and social security number when available, using a probabilistic linkage program (LinkPlus, CDC) (89% matching rate). From among all cases (n=7,160), we excluded 682 cases without address at diagnosis listed on cancer reports, mostly diagnosed in 2012 and 2013. For other years, less than 1-2% were missing address at diagnosis. The final case dataset included 6,478 childhood cancer cases. Controls free of cancer by age of 6 were randomly selected from birth certificates and

frequency matched (20:1) by year of birth to all childhood cancer cases. Controls who were likely nonviable births (birth weight <500 g or birth before 20 weeks of gestation) (n=461), with unknown sex (n=2), those with a birth address outside of California (n=494), with missing census tract information (n=319), or who died before age of 6 according to a death certificate (n=1,599) were excluded. When analyzing LexisNexis addresses and related exposure estimates, we excluded all subjects born before 2001 and in 2006 due to an error occurred during the delivery of a dataset containing address information to LexisNexis, leaving for analyses 99,269 controls.

Addresses

Maternal residence at birth of each case and control was collected from birth certificates and each case's residence at diagnosis (latitude and longitude only) was obtained from the California Cancer Registry (CCR). Additional addresses were acquired from LexisNexis, through a combination of sources including Gramm-Leach-Bliley-compliant proprietary data, bankruptcy filings, court filings, incorporation documents, judgments, jury verdicts and settlements, real estate property records, sanctions, Uniform Commercial Code-1 liens, motor vehicle and driver's license records, professional licenses and voter registration, liquor licenses, IRS enrolled agents, and inactive business directory contacts. LexisNexis returned a dataset containing all known addresses and the first seen and last seen dates associated with each address. We geocoded birth certificate addresses and LexisNexis addresses using an automated approach (Goldberg et al., 2008).

Following previously developed methods (Hurley et al., 2017; Wheeler and Wang, 2015), we cleaned and processed all addresses: first, we removed all post office box (P.O. Box) addresses

that are not residential locations, believed to introduce substantial geographically-based exposure misclassification (Hurley et al., 2003). Individuals having a P.O. Box address are likely to have other residential addresses during the same period. Second, we identified and removed duplicate addresses compiled from multiple sources using geographic distance between a set of geocoded addresses. Third, we created a residential history timeline for each individual. We limited the LexisNexis data to the time period from the date of birth to the date of diagnosis for each case and the relevant early life period (<age of 5 years) for each control. We then defined the earliest known date of each address as the "start" date, and the next sequential "start" date as the "end" date. The last address was assigned an artificial "end" date corresponding to date of diagnosis for cases or the end of the fifth year of life for each control.

Geographic Measures

We calculated distance (kilometers) between geocoded birth and diagnosis addresses. Birth and diagnosis residences cannot be directly compared in terms of street number and name because only geocoded address at diagnosis (i.e., latitude and longitude) was available on the report from CCR. Previous geographic studies suggested that generally 70-80% of the addresses during automated geocoding have a positional error of 100 m or less depending on geocoding platforms, although this could be up to a few kilometers in rural areas (Cayo and Talbot, 2003; Faure et al., 2017). To differentiate between potential positional error occurring in geocoding and moving within neighborhoods, we defined any address change of >100m as a move, and considered alternative distance cutoff of 200m in sensitivity analyses.

Among cases who moved between birth and diagnosis of cancer, we examined the distribution of distance between the two residences, categorized into five levels (≤ 500 m, >500m – 2 km, >2

km – 4 km, >4 km – 10 km, >10 km) by child and maternal characteristics. These cutoffs were primarily selected for estimating the level of misclassification in buffer-based exposure assessment, adopted by our group and other studies using similar buffer sizes of 500 m to >8km (Bell et al., 2001a; Gemmill et al., 2013; Gunier et al., 2011; Shaw et al., 2018; Shelton et al., 2014; Wofford et al., 2013) to estimate exposures to agricultural pesticide applied in close proximity to residences, but can also be applied to investigate Euclidean distance-based exposure assessment in future studies. For example, a distance of 2 km between the two addresses both with a 2 km-buffer yielded an intersection about 40% in size of the entire buffer; while the same 2 km-buffers with their centers 4 km apart indicates no overlap at all. We also examined the total number of different addresses and the distance between addresses, as listed on LexisNexis records, for cases and controls separately in their first year of life. Using LexisNexis, we depicted patterns of residential mobility among this study population by calculating the cumulative proportion of mothers who changed residences during the child's early life period, from birth to diagnosis of cancer by age at diagnosis for cases, or within the first six years for controls. Among those who moved, we examined the timing of moves in child's first year of life, for cases diagnosed at or after age of 1 and controls. Those who moved more than once were counted multiple times in calculating the distance moved, and in estimating the timing of moves.

Pesticide Exposures

We calculated measures of agricultural pesticide exposures using a GIS-based Residential Ambient Pesticide Estimation System, as previously described (Rull and Ritz, 2003). In brief, since 1974 agricultural pesticide applications for commercial use are recorded in Pesticide Use Reports (PUR) mandated by the CA Department of Pesticide Regulation (CDPR). Each PUR record includes the name of the pesticide's active ingredient, the poundage applied, the crop

type, and the location and the date of application. The California Department of Water Resources (CDWR) performs countywide, large-scale surveys of land use and crop cover every 7–10 years. Land use maps increase spatial resolution because they provide more detailed land use geography that allows us to refine the location of pesticide applications (Rull and Ritz, 2003). We then combined PUR records, land use maps, and geocoded birth and diagnosis addresses to produce estimates of pesticide exposure in each child's first year of life. Annual exposure estimates (pounds per acre) were calculated by adding the poundage of pesticide applied in a 2-km buffer around each address and weighting the total poundage by the proportion of acreage treated within the buffer.

We selected eight known or probable carcinogens from the top 200 frequently applied pesticides in our study population, while also considering the summary rating provided by the Pesticide Action Network (PAN) pesticide database (http://www.pesticideinfo.org/) that incorporates the most carcinogenic ranking assigned by organizations including International Agency for Research on Cancer (IARC), U.S. Environmental Protection Agency (EPA) and the U.S. National Institutes of Health (NIH). For each of the carcinogens examined in this study, we summed the annual pounds applied per acre to obtain exposure values for each calendar year using the 2km-buffer around each address. In the children's first year of life, we used weighted averages with weights representing the proportions (in days) of the relevant exposure period falling into each calendar year. Three estimates for exposures in the first year of life were calculated accordingly, using 1) address at birth, 2) address at diagnosis, and 3) LexisNexis addresses (in available years). We then dichotomized children's exposures in their first year of life as ever/never exposed to a specific carcinogen.

Statistical Analysis

To examine the associations between maternal and child characteristics and the cases' likelihood of moving between birth and diagnosis, we conducted univariate and multivariate logistic regression analysis and estimated odds ratios (ORs) and 95% confidence intervals (CIs). Based on previous literature (Canfield et al., 2006; Margerison-Zilko et al., 2016; Urayama et al., 2009), we considered factors that potentially influence mobility in pregnancy or early childhood including age at diagnosis (0, 1, ≥2 years), year of birth (1998-2004 vs 2005-2011), maternal age at delivery (≤19, 20-24, 25-29, 30-34, ≥35), maternal race/ethnicity (non-Hispanic White, Hispanic, Black, Asian/Pacific islander, others), maternal birthplace (California, other U.S. states, Mexico, other foreign countries), maternal education (<12 years, 12 years, 13-15 years, ≥16 years), parity (1, 2, ≥3), rural/urban classification of residence at birth (metropolitan vs non-metropolitan), and several socioeconomic variables including payment source for prenatal care as a proxy for family income (private/HMO/ Blue Cross Blue Shield vs MediCal/government/ self-pay) and neighborhood level SES.

For cases and all controls, we examined the agreement between exposures during the first year of life assigned to birth residence and those assigned to LexisNexis addresses. Restricting to cases diagnosed at or after 1 year of age, we assessed the level of agreement between exposures assigned to birth residence and those assigned to diagnosis residence, for movers and non-movers combined, and movers by distance moved (≤ 2km, >2 km – 4 km, >4 km). These included: 1) continuous cumulative exposure estimates (pounds per acer) using Spearman correlation coefficients, since the exposure estimates were not normally distributed and, 2) dichotomous exposure indicators using Cohen's kappa statistics, a robust agreement measure by taking into account the possibility of the agreement occurring by chance.

3.4 Results

Table 3.1 shows the child and maternal characteristics by residential mobility. Of 6,478 childhood cancer cases born in 1998-2011, 3,548 (54.8%) had a residential location at diagnosis at least 100 m away from address at birth. Cases diagnosed at an older age (1 or ≥2) compared to those diagnosed within the first year of life were more likely to move between birth and diagnosis. Mothers of younger age, with lower education, a non-Hispanic ethnic background, those who used public health insurance, or resided in non-metropolitan areas at delivery were more likely to move. Using 200m distance moved as an alternative cutoff, we classified 3,297 (50.1%) cases as movers accordingly; despite that, the predicting factors for residential mobility remained the same.

The information from LexisNexis suggested more than 20% of case and control mothers moved in child's first year of life, with less than 4% moving multiple times (Figure 3.1). Using LexisNexis addresses, we identified similar predictors for residential mobility among cases and controls in their first year of life, and these patterns did not differ from those in comparing cases' residential mobility from birth to diagnosis (Table 3.2). Noticeably, for 42% of case mothers and 45% of control mothers LexisNexis provided only partial residential information at best during the child's first year of life and these children were more likely to be born in earlier years (2001-2005), born to mothers of younger age, with lower education, having a Hispanic background or from Mexico, using public insurance type, or with a lower neighborhood SES.

Based on LexisNexis, we calculated the cumulative proportions of mothers who moved over time for cases (from birth to diagnosis) and controls (< age of 6) (Figure 3.2). About 12% of the case mothers and 23% of the control mothers moved in the child's first year of life. The proportions who moved increased with each year of the child's age and the proportion for control

mothers was slightly higher than that for case mothers at any time point. Within the first year of life, both control and case mothers seemed to move smoothly over time, i.e., no striking peaks appeared (Figure 3.3). Case mothers moved more in the latter half of the first year but this could be due to random variation.

With respect to distance moved, the median was 5.05 km among the cases who moved between birth and diagnosis. Overall, 30.1% of all cases moved less than 2 km, while more than half moved more than 4 km (Table 3.3). Cases with an older age at diagnosis, born to younger or Black mothers, or born in metropolitan areas were more likely to move further. Based on LexisNexis addresses, the median distance moved in child's first year of life was 6.97 km for all cases (diagnosed at or after age of 1), and 9.81 km for all controls, though the longest distance could be over 5,000 km, indicating an address out of the continental U.S. at one point. Under some circumstances, the distance moved was longer than 900 km even for some case mothers, because the case families resided outside of California after birth but came back to California before the cancer diagnosis.

Exposures to specific carcinogens during the first years of life calculated for birth residence were compared with those calculated for diagnosis residence or LexisNexis addresses among cases diagnosed at or after age of 1, and birth residence was compared with LexisNexis addresses among all controls. Overall, the correlations between continuous exposure estimates (pounds per acer) within a 2km buffer of birth vs diagnosis residence were moderate to strong (0.67-0.76), and those between birth residence vs LexisNexis addresses were higher (0.75-0.83) and did not differ by outcome status. When stratified by distance between birth and diagnosis residences, the correlations were very strong (0.87-0.94) for those moved less than 2 km, moderate to strong (0.54~0.81) for those moved between 2 km and 4 km, and relatively weak (0.22-0.43) for those

moved more than 4 km (Table 3.4). The kappa statistics between dichotomous exposures (ever vs. never exposed) were similar, also suggesting overall good agreement and decreasing agreement as the distance moved increased (Table 3.4).

3.5 Discussion

This study aims to examine the extent to which using birth residence vs diagnosis address or reconstructed residential histories to estimate exposures to nearby agricultural pesticides in early childhood might lead to misclassification. We investigated the maternal and child characteristics that may predict early life residential mobility and assessed patterns of mobility among childhood cancer cases and controls in California. We found that case's age at diagnosis, maternal age at birth, maternal education, maternal race/ethnicity, payment type for prenatal care, and/or maternal urban/rural residence at birth were associated with both residential mobility and the distance moved between birth and diagnosis. The overall agreement between the first year of life exposures to agricultural pesticides 2-km surrounding the birth residence and diagnosis address or reconstructed LexisNexis residential history was moderate to strong (correlation/kappa=0.7~0.8), but level of misclassification might depend on the demographic characteristics and distance moved.

Few studies have examined the patterns of residential mobility in early childhood to identify the potential for exposure misclassification (Brokamp et al., 2016; Margerison-Zilko et al., 2016). As with previous studies that focused on residential mobility during pregnancy, higher residential mobility in early childhood was associated with a range of maternal socio-demographic characteristics such as lower maternal age, lower maternal education, and lower individual or neighborhood level SES measures (Bell and Belanger, 2012; Canfield et al., 2006; Margerison-Zilko et al., 2016; Urayama et al., 2009). We found cases born to Hispanic mothers

were less likely to move; however, findings for maternal race/ethnicity vary across studies at different geographic locations, years, and population compositions (Bell and Belanger, 2012). The likelihood of moving between birth and diagnosis of cancer increases with case's age at diagnosis, suggesting that assessed at the birth residence may be less likely to represent the true exposures as children grow up. If demographic factors are potential confounders that affect outcome risks, exposure misclassification will likely be differential. Other factors proposed by previous studies that were linked to mobility during pregnancy but not available in the present study include marital status, smoking and alcohol use (Bell and Belanger, 2012); they may also be associated with residential mobility in early childhood. Using address information obtained from LexisNexis, we found similar predictors for mobility in cases and controls; however, we observed that those with complete address information in the first year of life from LexisNexis were quite different from those with missing or partially missing address information regarding maternal and child characteristics. Earlier validation studies (Hurley et al., 2017; Jacquez et al., 2011; Wheeler and Wang, 2015) suggested a match rate of 70-85% when comparing interview-based residential history (gold standard) with reconstructed LexisNexis history, but subjects were mostly mid-aged or older and their residential mobility might be quite different from women at child-bearing age. For example, findings from the California Teachers Study (CTS) suggested that women under the age of 40 years had a lower match rate (Hurley et al., 2017).

Regarding distances moved from birth to diagnosis, our study reported a median of 5.05 km among all cases, with the smallest median (2.60 km) for cases diagnosed at less than 12 months and largest median for cases diagnosed at age 2+. The median distance moved between LexisNexis addresses in the first year of life was 6.97 km for cases age of 1+ years and 9.81 km for controls. Our findings are consistent with previous studies that focused on residential

mobility during pregnancy (Bell and Belanger, 2012) that reported median distances <10 km. The degree of exposure misclassification is a function of the distance moved in relation to the spatial heterogeneity of the exposure. For given environmental exposures such as pesticides, spatial variation may depend on geographic areas or by the buffer size used. For example, estimated exposures to agricultural pesticides within 500 m of a residence will be more sensitive to the variation of exposures due to mobility compared to those using 2 km or even larger buffer radius. Similarly, other environmental epidemiological studies of child health outcomes that used a smaller buffer radius or a shorter distance (typically within several hundred meters) to exposure sources such as traffic-related air pollution, electronic magnetic fields, or powerlines might be more vulnerable to an inaccurate location.

The use of LexisNexis has a remarkable advantage in identifying the timing of moves, providing important information for future research that assesses time-sensitive exposures or involves outcomes with a susceptible period after a child's birth. In our study mothers of case and control children were more likely to move in child's first year of life, compared to the following years in early childhood. Control mothers seemed to have slightly higher mobility than the case mothers throughout the entire study period, likely because the case families were diagnosed within California and therefore their residences were California-based at least at birth and at diagnosis, while control families could completely move out of California but were still captured in the LexisNexis database with the nationwide search ability. Within the first year of life, case mothers moved more in the latter half of the first year but this could be random variation due to a relatively smaller sample size compared to the controls.

In general, we had good agreement between exposures to agricultural pesticides within a 2-km buffer of birth residence and LexisNexis addresses for cases and controls in their first year of

life. The level of misclassification introduced by residential mobility may be acceptable if our study period of interest is the child's first year of life, since only around 20% of cases (diagnosed at age of 1+) and control mothers changed their residence during that period and it wasn't differential with regard to disease status. For all cases who moved between birth and diagnosis, we have moderate to good agreement between exposures to agricultural pesticides within a 2-km buffer of birth residence and diagnosis residence. For those moved within a short distance (≤ 2km), misclassification is minimal; yet a longer distance (>4km) could be problematic with regards to exposure assessment, in particular when the buffer radius is smaller than the change in location. The misclassification will be differential if the factors associated with residential mobility are also risk factors for the disease.

In assessing patterns of and examining factors that may predict residential mobility in early childhood, our strength is that we identified a large number of childhood cancer cases born and diagnosed in California through California birth certificates and the California cancer registry. Unlike smaller questionnaire-based studies, our results were unlikely to be influenced by selection bias introduced by participation or recall bias; though the analysis based on LexisNexis addresses could be subject to potential selection bias, the conclusions drawn from it were comparable to those derived by examining birth vs diagnosis residence in cases only. To our knowledge, only a couple of studies examined the post-partum residential mobility either in a statewide sample of California women (Margerison-Zilko et al., 2016) or in enrolled childhood leukemia cases of a Northern California Study (Urayama et al., 2009) but both focused on factors associated with residential mobility and changes in neighborhood SES. Our study, on the other hand, for the first time calculated distance moved in early life of cases and examined the potential for exposure misclassification by distance moved. Though pregnancy period is the most

critical period for most environmental exposures, first year of life exposures could also substantially influence young children's health outcomes (Ma et al., 2002b). Therefore, it is crucial to assess exposures not only during pregnancy but also in the early life of children.

This study also has a few limitations. We were unable to obtain a secondary address from a registry for our population-based controls that is comparable to cases' diagnosis residence, limiting our ability to examine the patterns of residential mobility parallel in cases and controls; however, the reconstructed LexisNexis residential histories allowed us to compare moving patterns in cases vs controls. Additionally, only the latitude and longitude of the diagnosis residence on the cancer reports were available, so we cannot directly compare the street number and names of birth and diagnosis residences to ascertain residential mobility. We had to rely on the readily-geocoded diagnosis address which doesn't guarantee a same level of geocoding accuracy as that of birth addresses geocoded using our automated approach. However, the use of 100m as cutoff as well as alternative 200m should take account into the possible positional errors during geocoding. Besides, there might be intended or unintended misreporting in birth residence and diagnosis residence among individuals seeking health care services. Address information from LexisNexis has several intrinsic issues including multiple unique addresses for the same time period, inaccurate or missing first seen and last seen dates associated with certain addresses (Hurley et al., 2017), disagreement between LexisNexis addresses and registry-obtained addresses at the time of self-reporting, inconsistent quality in different sub-groups of general population, and time-varying sources of addresses over years, therefore limiting the power to rely solely on it for large-scale records-based epidemiological studies. Future research attempting to reconstruct residential histories for study subjects using LexisNexis should also be aware of the potential selection bias, introduced by varying availability of public records by sub-groups of

populations. Despite that, LexisNexis' rich data could augment existing address information and assist in reconstructing residential histories. Future approaches with the advancing technology (i.e., better tracking of people's residences) in the big data era may help to obtain a more accurate residential history for populations with or without diseases and evaluate the impact on estimating associations between environmental exposures and childhood cancers. Though such data sources would be ideal for studies in environmental epidemiology, confidentiality is a concern.

In conclusion, residential mobility among childhood cancer cases diagnosed in California and their matched controls was associated with a number of child and maternal factors. Unlike adult cancers or other childhood outcomes such as asthma, which have a range of known demographic risk factors, the etiologies of childhood cancers remain largely unknown and therefore they do not have as many established risk factors, so this may be less of an issue. The overall agreement between exposures to agricultural pesticides in early life of children assessed using a 2-km buffer of residences at birth and alternative addresses was moderate to good. These findings suggest that birth residence should be used with caution when estimating environmental exposures in early childhood, especially after the first year of life. LexisNexis data, or other similar methods for reconstructing residential histories, may be useful for augmenting existing address information and constructing residential histories in estimating environmental exposures for large records-based epidemiological studies. Future research should consider factors that might help correct for the misclassification introduced by residential mobility.

Table 3.1 Cases' characteristics associated with residential mobility from birth to diagnosis, 1998-2011.

	Movers[a]		Non-movers[a]		Crude OR	Adjusted OR[b]
	N= 3,548	%	N= 2,930	%	(95% CI)	(95% CI)
Year of birth						
1998-2004	2,201	62.0	1,676	57.2	1.00	1.00
2005-2011	1,347	38.0	1,254	42.8	0.83 (0.75, 0.92)	0.94 (0.85, 1.05)
Age at diagnosis						
0	550	15.5	929	31.7	1.00	1.00
1	664	18.7	676	23.1	1.65 (1.42, 1.93)	1.69 (1.45, 1.98)
2-5	2,334	65.8	1,325	45.2	3.00 (2.64, 3.41)	3.10 (2.71, 3.54)
Maternal Age						
19 or less	416	11.7	184	6.3	3.28 (2.66, 4.06)	2.54 (1.95, 3.29)
20-24	861	24.3	480	16.4	2.54 (2.16, 2.98)	2.18 (1.80, 2.64)
25-29	959	27.0	713	24.3	1.92 (1.65, 2.24)	1.87 (1.58, 2.20)
30-34	798	22.5	826	28.2	1.36 (1.17, 1.59)	1.38 (1.18, 1.62)
35 and older	514	14.5	727	24.8	1.00	1.00
Maternal Education						
<12 years	1,034	29.1	694	23.7	1.83 (1.59, 2.10)	1.35 (1.10, 1.66)
12 years	1,049	29.6	752	25.7	1.71 (1.49, 1.96)	1.24 (1.04, 1.47)
13-15 years	676	19.1	563	19.2	1.47 (1.27, 1.71)	1.24 (1.05, 1.47)
16+ years	697	19.6	851	29.0	1.00	1.00
Missing	92	2.6	70	2.4	-	-
Maternal Race/Ethnicity						
White, non-Hispanic	1,166	32.9	949	32.4	1.00	1.00
Hispanic, any race	1,795	50.6	1,433	48.9	1.02 (0.91, 1.14)	0.70 (0.60, 0.82)
Black	181	5.1	112	3.8	1.30 (1.01, 1.68)	1.01 (0.77, 1.33)
Asian/PI	289	8.1	324	11.1	0.74 (0.62, 0.89)	0.81 (0.65, 1.02)
Other/Refused	117	3.3	112	3.8	0.84 (0.60, 1.17)	0.78 (0.54, 1.12)
Parity						
1	1,469	41.4	1,049	35.8	1.00	1.00
2	1,045	29.5	945	32.3	0.78 (0.69, 0.88)	0.88 (0.77, 1.00)
3 or more	1,034	29.1	936	31.9	0.78 (0.69, 0.88)	0.92 (0.80, 1.07)
Payment type of prenantal care						
Private/HMO/BCBS	1,740	49.0	1,817	62.0	1.00	1.00
MediCal/Govt/self-pay	1,784	50.3	1,097	37.4	1.67 (1.51, 1.85)	1.54 (1.35, 1.76)
Missing	24	0.7	16	0.5	-	-
Maternal birthplace						
California	1,634	46.1	1,246	42.5	1.00	1.00
Mexico	931	26.2	731	24.9	0.95 (0.84, 1.08)	0.99 (0.84, 1.17)
Other US States	412	11.6	373	12.7	0.84 (0.71, 0.98)	1.02 (0.85, 1.22)

Other foreign countries	567	16.0	577	19.7	0.75 (0.65, 0.86)	0.97 (0.81, 1.17)
Missing	4	0.1	3	0.1	-	-
Urban/rural status at birth						
Metropolitan	3,256	91.8	2,803	95.7	1.00	1.00
Non-metropolitan	292	8.2	127	4.3	1.98 (1.59, 2.46)	1.67 (1.32, 2.11)
Quintiles of neighborhood SES at birth						
1 (Lowest)	929	26.2	715	24.4	1.45 (1.23, 1.71)	0.89 (0.72, 1.09)
2	884	24.9	647	22.1	1.54 (1.30, 1.82)	0.95 (0.78, 1.16)
3	719	20.3	565	19.3	1.45 (1.22, 1.72)	0.97 (0.80, 1.18)
4	590	16.6	519	17.7	1.28 (1.07, 1.53)	1.02 (0.84, 1.24)
5 (Highest)	426	12.0	484	16.5	1.00	1.00

[a] Movers (55%): distance between addresses at birth and diagnosis > 100m; Non-movers (45%): distance ≤ 100m

[b] Adjusted to all variables in the model

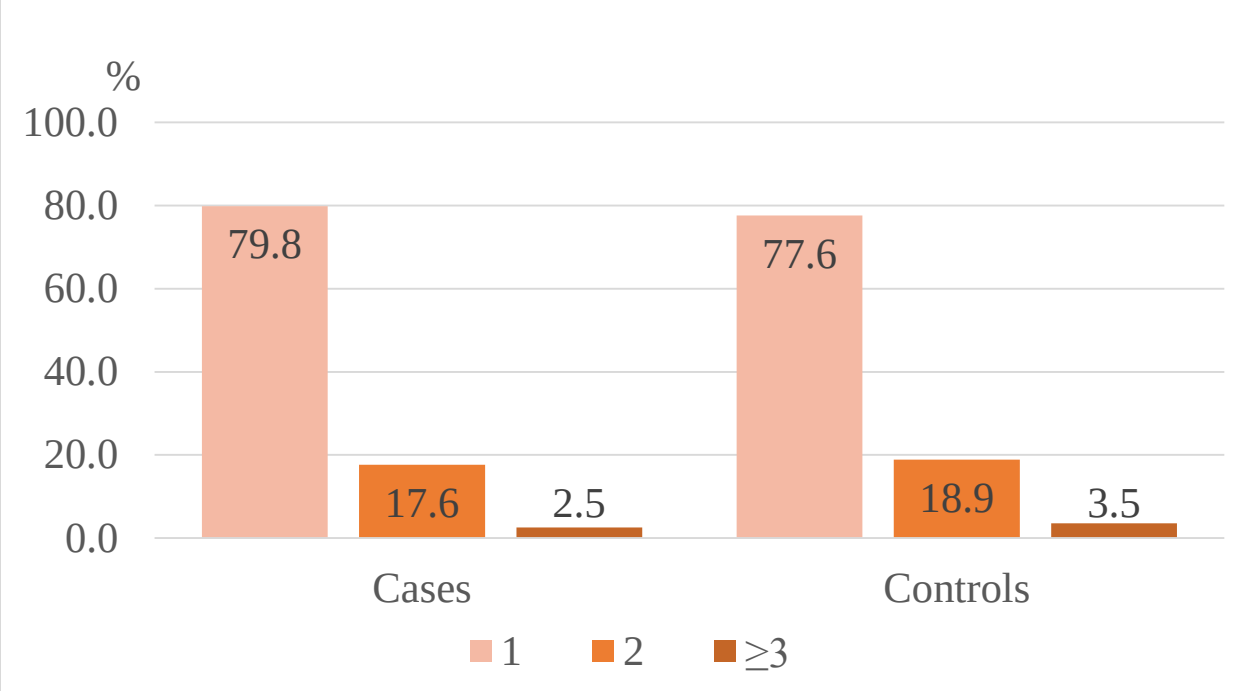


Figure 3.1 Number of addresses for mothers of case (age at diagnosis 1-5) and control children within their first year of life, based on LexisNexis records

Table 3.2 Maternal and child demographics associated with residential mobility in child's first year of life based on LexisNexis, 2001-2011.

	Cases, age at Dx ≥1						**Controls**					
	Movers		Non-movers		Not captured[a]		Movers		Non-movers		Not captured[a]	
	N= 481	%	N= 1,751	%	N= 1,638	%	N= 13,008	%	N= 41,531	%	N= 44,730	%
Year of birth												
2001-2005	195	40.5	981	56.0	1,195	73.0	4,795	36.9	21,840	52.6	31,450	70.3
2006-2011	286	59.5	770	44.0	443	27.0	8,213	63.1	19,691	47.4	13,280	29.7
Age at diagnosis												
1	132	27.4	505	28.8	426	26.0	-	-	-	-	-	-
2-5	349	72.6	1,246	71.2	1,212	74.0	-	-	-	-	-	-
Maternal Age												
19 or less	35	7.3	49	2.8	251	15.3	1,068	8.2	1,273	3.1	6,977	15.6
20-24	151	31.4	313	17.9	341	20.8	3,917	30.1	7,982	19.2	10,448	23.4
25-29	136	28.3	463	26.4	395	24.1	3,807	29.3	11,355	27.3	11,265	25.2
30-34	91	18.9	505	28.8	386	23.6	2,660	20.4	11,878	28.6	9,781	21.9
35 and older	68	14.1	421	24.0	265	16.2	1,556	12.0	9,043	21.8	6,248	14.0
Missing	-	-	-	-	-	-	-	-	-	-	11	0.0
Maternal Education												
<12 years	99	20.6	282	16.1	638	38.9	2,761	21.2	6,738	16.2	18,310	40.9
12 years	163	33.9	447	25.5	453	27.7	4,127	31.7	10,521	25.3	11,153	24.9
13-15 years	130	27.0	417	23.8	215	13.1	3,327	25.6	10,136	24.4	6,616	14.8
16+ years	72	15.0	561	32.0	286	17.5	2,446	18.8	13,138	31.6	7,353	16.4
Missing	17	3.5	44	2.5	46	2.8	347	2.7	998	2.4	1,298	2.9
Maternal Race/Ethnicity												
White, non-Hispanic	150	31.2	651	37.2	405	24.7	3,896	30.0	14,978	36.1	10,019	22.4
Hispanic, any race	228	47.4	735	42.0	989	60.4	5,921	45.5	17,167	41.3	27,542	61.6
Black	30	6.2	80	4.6	69	4.2	1,276	9.8	2,447	5.9	1,810	4.0
Asian/PI	49	10.2	213	12.2	114	7.0	1,318	10.1	5,261	12.7	3,741	8.4

Other/Refused	24	5.0	72	4.1	61	3.7	597	4.6	1,678	4.0	1,618	3.6
Parity												
1	190	39.5	657	37.5	678	41.4	5,207	40.0	14,865	35.8	18,507	41.4
2	144	29.9	568	32.4	447	27.3	4,028	31.0	14,088	33.9	13,224	29.6
3 or more	147	30.6	526	30.0	513	31.3	3,767	29.0	12,552	30.2	12,976	29.0
Missing	-	-	-	-	-	-	6	0.0	26	0.1	23	0.1
Payment type of prenantal care												
Private/HMO/BCBS	238	49.5	1,139	65.0	710	43.3	5,908	45.4	25,957	62.5	16,672	37.3
MediCal/Govt/self-pay	243	50.5	606	34.6	919	56.1	6,991	53.7	15,352	37.0	27,625	61.8
Missing	-	-	6	0.3	9	0.5	109	0.8	222	0.5	433	1.0
Maternal birthplace												
California	269	55.9	927	52.9	582	35.5	7,176	55.2	21,420	51.6	14,002	31.3
Mexico	79	16.4	274	15.6	633	38.6	1,939	14.9	6,357	15.3	18,408	41.2
Other US States	51	10.6	238	13.6	125	7.6	1,754	13.5	5,590	13.5	3,706	8.3
Other foreign countries	82	17.0	312	17.8	295	18.0	2,132	16.4	8,128	19.6	8,552	19.1
Missing	-	-	-	-	3	0.2	7	0.1	36	0.1	62	0.1
Urban/rural status at birth												
Metropolitan	443	92.1	1,654	94.5	1,507	92.0	12,131	93.3	39,100	94.1	41,098	91.9
Non-metropolitan	38	7.9	97	5.5	131	8.0	877	6.7	2,431	5.9	3,632	8.1
Quintiles of neighborhood SES at birth												
1 (Lowest)	114	23.7	387	22.1	473	28.9	3,460	26.6	9,200	22.2	14,054	31.4
2	127	26.4	374	21.4	425	25.9	3,295	25.3	9,123	22.0	11,204	25.0
3	102	21.2	364	20.8	309	18.9	2,694	20.7	8,427	20.3	8,693	19.4
4	86	17.9	327	18.7	267	16.3	2,121	16.3	7,501	18.1	6,167	13.8
5 (Highest)	52	10.8	299	17.1	164	10.0	1438	11.1	7280	17.5	4612	10.3

[a] Not captured: with missing or only partial residential information in the first year of life from LexisNexis

Table 3.3 Distance (kilometers) between birth address and diagnosis address among the cases who moved between birth and diagnosis

	Distance ≤ 500m		500m < Distance ≤ 2km		2km < Distance ≤ 4km		4km < Distance ≤ 10km		Distance > 10km	
	N	%	N	%	N	%	N	%	N	%
All	459	12.9	609	17.2	523	14.7	730	20.6	1,227	34.6
Age at diagnosis										
0	148	26.9	102	18.5	76	13.8	81	14.7	143	26.0
1	98	14.8	122	18.4	103	15.5	126	19.0	215	32.4
2-5	213	9.1	385	16.5	344	14.7	523	22.4	869	37.2
Maternal Age										
19 or less	39	9.4	73	17.5	68	16.3	106	25.5	130	31.3
20-24	73	8.5	161	18.7	137	15.9	188	21.8	302	35.1
25-29	118	12.3	148	15.4	141	14.7	196	20.4	356	37.1
30-34	129	16.2	134	16.8	109	13.7	146	18.3	280	35.1
35 and older	100	19.5	93	18.1	68	13.2	94	18.3	159	30.9
Maternal Race/Ethnicity										
White, non-Hispanic	168	14.4	179	15.4	155	13.3	219	18.8	445	38.2
Hispanic, any race	228	12.7	347	19.3	286	15.9	373	20.8	561	31.3
Black	14	7.7	29	16.0	27	14.9	38	21.0	73	40.3
Asian/PI	36	12.5	34	11.8	38	13.1	70	24.2	111	38.4
Other/Refused	13	11.1	20	17.1	17	14.5	30	25.6	37	31.6
Urban/rural status at birth										
Metropolitan	407	12.5	544	16.7	485	14.9	683	21.0	1137	34.9
Non-metropolitan	52	17.8	65	22.3	38	13.0	47	16.1	90	30.8

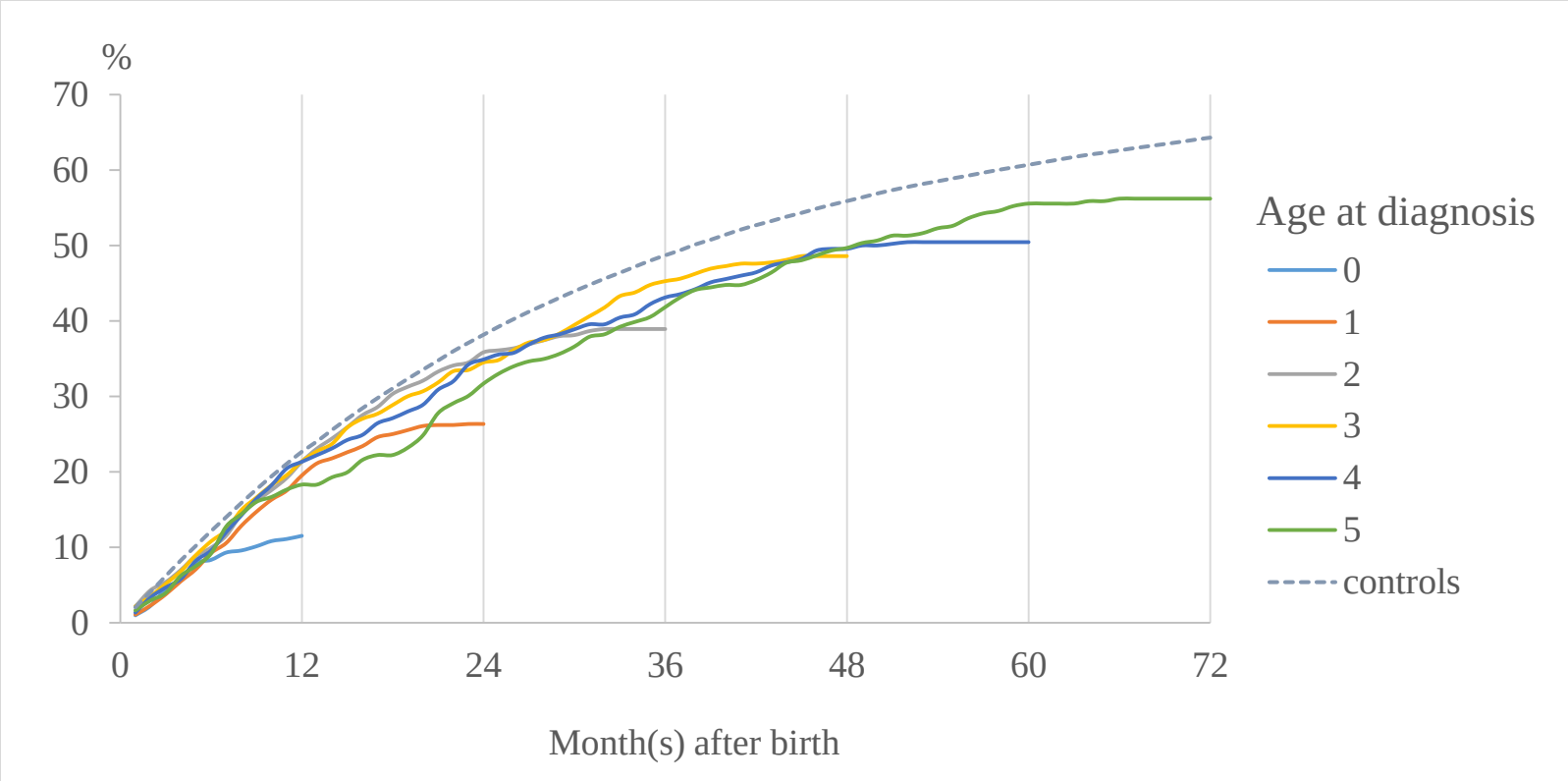


Figure 3.2 Cumulative percentage of children moved over time, for cases through diagnosis (by age at diagnosis) and controls, based on LexisNexis

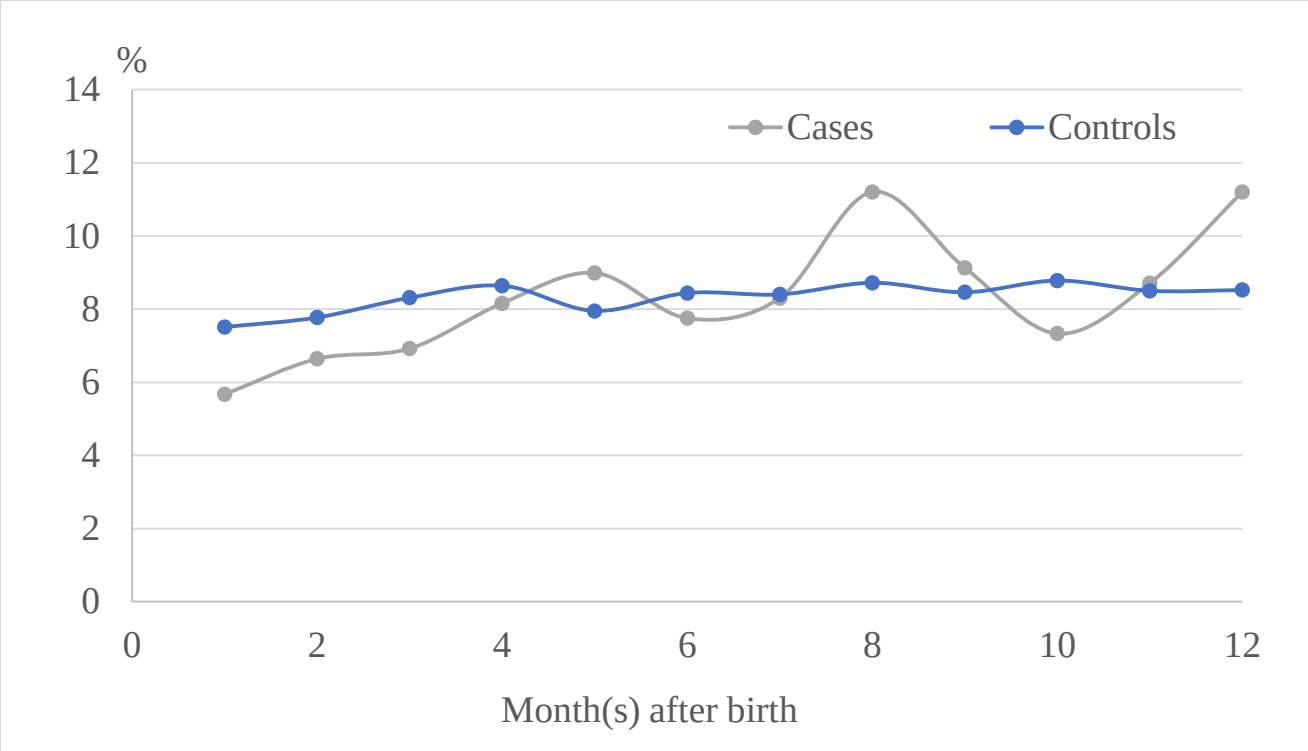


Figure 3.3 Timing of moves among case (age at diagnosis 1-5) and control children who moved in their first year of life, based on LexisNexis

Table 3.4 Agreement between the first year of life exposures assigned to address at birth vs alternative addresses among cases (age at diagnosis 1-5) and controls born in 2001-2011

		Birth vs LexisNexis				Birth vs Diagnosis (cases only)							
		Controls		Cases		Movers and non-movers		Movers					
								100m < Distance ≤ 2km		2km < Distance ≤ 4km		Distance > 4km	
Chemical	Cancer Ratings	r^b	κ^c	r^b	κ^c	r^b	κ^c	r^b	κ^c	r^b	κ^c	r^b	κ^c
Petroleum oil, unclassified	Known	0.78	0.76	0.78	0.77	0.69	0.67	0.91	0.89	0.67	0.62	0.24	0.20
Mineral oil	Known	0.79	0.78	0.80	0.79	0.69	0.68	0.91	0.89	0.67	0.63	0.29	0.27
Diuron	Known	0.79	0.78	0.80	0.80	0.70	0.69	0.93	0.92	0.74	0.72	0.33	0.31
Thiophanate-methyl	Probable	0.77	0.75	0.76	0.75	0.67	0.66	0.88	0.85	0.54	0.51	0.22	0.20
Permethrin	Probable	0.79	0.77	0.78	0.76	0.70	0.68	0.93	0.92	0.63	0.55	0.29	0.25
Oxyfluorfen	Probable	0.83	0.81	0.83	0.81	0.76	0.74	0.94	0.91	0.81	0.77	0.43	0.39
Hexythiazox	Probable	0.77	0.76	0.79	0.78	0.67	0.65	0.87	0.85	0.60	0.56	0.25	0.22
Pyrethrins	Probable	0.77	0.76	0.78	0.77	0.71	0.69	0.92	0.91	0.64	0.61	0.24	0.22

[a] Mover: distance between addresses at birth and diagnosis < 100m; Non-mover: distance ≥ 100m

[b] Spearman correlation coefficients were calculated using continuous exposure estimates (pounds per acre) in child's first year of life

[c] Kappa statistics were calculated using binary exposure indicators for child's first year of life

4. The Impact of Pesticide Exposure Misclassification due to Residential Mobility during Early Childhood in Investigations of Childhood Brain Tumors in California

4.1 Abstract

Background: Studies of environmental exposures and childhood cancers in the US often rely on maternal address at birth obtained from the birth certificate to assess exposure in early childhood, possibly impacting estimates of associations.

Objective: To estimate and compare the effect estimates for pesticide exposure in California during children's early life based on birth residence and/or diagnosis address with those estimated using reconstructed address history based on LexisNexis records, using childhood brain tumors as an example, and to examine whether selection bias may occur when restricting our study population to children with available LexisNexis records.

Methods: For each brain tumor case we randomly selected 19 children from a birth year frequency matched control set to assign the case's date of diagnosis as the reference date. We assigned lifetime exposure to pesticides based on different addresses (birth, diagnosis of cancer, and LexisNexis) for all study participants. Conditional multivariate adjusted logistic regression models were employed to estimate the effects using different address sources. We also compared estimates for the sets of children with and without LexisNexis addresses.

Results: In the subset of children with all three types of addresses, we found no associations between children's lifetime exposures to agricultural pesticides of interest and brain tumors. Among these children, effect estimates based on birth and diagnosis addresses were generally higher than those estimated based on LexisNexis addresses. Interestingly, among the children for

whom LexisNexis addresses were not available, we observed the largest increased risks for brain tumor for several pesticides based on birth and diagnosis addresses alone.

Conclusions: Using a single source of address to assess children's early life environmental exposure to pesticides does not account for residential mobility and cause exposure misclassification. While public record databases can be used to retrieve residential information, as long as these data do not represent the whole population with the same accuracy, researchers should be cautious about the potential for selection bias introduced by the limitations of such data sources as LexisNexis.

4.2 Background

In large-scale records-based epidemiologic studies of environmental exposures in early childhood, relying solely on maternal address at birth (Carozza et al., 2009; Reynolds et al., 2005) and birth or diagnosis address (available for cases only) (García-Pérez et al., 2016, 2015) may be insufficient to produce accurate exposure measures in studies of childhood cancers. Recently large data linkage studies of childhood cancer have been conducted in which exposure measures were derived for residential addresses at birth or diagnosis; and alternative becoming available now is a public records database, LexisNexis, that provides all known addresses for a set of individuals upon request. It might be a useful source of augmenting address histories when estimating environmental exposures for such studies.

Residential mobility in early childhood that is associated with maternal or child demographics may cause exposure misclassification for agricultural pesticides applied in proximity to the residences (chapter 3). For the estimation of pesticide exposures from agricultural application

near homes, we previously showed that the overall agreement between exposures assessed within a 2-km buffer of residences in early life of children based on birth, diagnosis, or LexisNexis addresses was moderate to good, the agreement decreased with in increased distance between the two residences. Degree of misclassification also depends on the length of stay in each residence, as well as the accuracy of birth and diagnosis addresses.

Childhood brain tumors are the second most prevalent (21%) childhood cancer among children (age 0-14) in the United States (Ward et al., 2014). Numerous studies that have examined the potential impact of household use of pesticides in early childhood on brain tumors suggest overall positive associations (Baldwin and Preston-Martin, 2004; Rosso et al., 2008; Vinson et al., 2011; Zahm and Ward, 1998). There are relatively fewer studies of the childhood brain tumor risk from residential proximity to agricultural pesticide applications, but they have suggested mostly null associations with low precision (Carozza et al., 2009; Reynolds et al., 2005, 2002) except one ecologic study (Carozza et al., 2008) showed increased risk. These earlier inconsistent findings might partly be explained by the lack of spatiotemporally accurate exposure assessment, which has been largely improved by GIS-based estimation systems. Here we explore the impact of exposure misclassification due to residential mobility between birth and diagnosis.

The primary objective of the present study was to estimate and compare the effect estimates for agricultural pesticide exposures during children's early life based on birth residence only and birth or diagnosis address (available for cases only) with those based on reconstructed address histories using LexisNexis, as the 'alloyed gold standard'. Earlier validation studies have shown that addresses acquired from LexisNexis are useful for reconstructing residential histories with an overall match rate of ~70-85% with detailed address histories obtained from personal interviews (Hurley et al., 2017; Jacquez et al., 2011; Wheeler and Wang, 2015). However, not all

residents' records can be matched to records in the LexisNexis public records. Thus a secondary objective of our study is to examine whether selection bias is likely to occur when we restrict our study population to individuals with available LexisNexis addresses only.

4.3 Methods

Study Population

The Air Pollution and Childhood Cancers (APCC) study population and the three sources of addresses (birth, diagnosis, and LexisNexis) have previously been described in section 3.3. Cases with missing diagnosis address (<4%) were excluded. In brief, for each individual requested, LexisNexis provided all known addresses and the first and last dates associated with them. Following previously developed methods (Hurley et al., 2017; Wheeler and Wang, 2015), we removed all P.O. Box addresses, identified and removed duplicate addresses compiled from multiple sources, and created a residential history timeline from birth to diagnosis for each case and to the reference date for each control. We define the time from birth to diagnosis (or reference date for controls) as the children's lifetime, and consider those whose California LexisNexis addresses covered more than 80% of their lifetime as having LexisNexis addresses available, and the rest as unavailable. A 80% cut-off was chosen to account for the uncertainties and random errors of first and last dates reported for addresses in LexisNexis.

Cases diagnosed with brain tumors were defined as International Classification of Childhood Cancer, Third edition (ICCC-3; (Steliarova-Foucher et al., 2005)) code 031-036. Included in the primary analysis were cases of childhood brain tumors diagnosed ≤ 5 years of age and controls born in 2001-2008 (except 2007) with California addresses available from birth certificates, at cancer diagnosis, and from LexisNexis records. Our cases were limited to children age 5 and

younger who may inherently be more susceptible to prenatal and early life exposures (Carozza et al., 2008) than children or adolescents diagnosed with cancer at an older age. Because our pesticide estimates were only available through December, 2012, children born 2009 onward only have pesticide exposure estimates from their birth until a maximum of 4 years of age. Among children born in 2001-2008, 397 (63%) of 634 cases of brain tumors and 6,614 (53%) of 12,502 controls had at least one California address available on LexisNexis records which covered more than 80% of their lifetime. In the secondary analysis, we compared the former subset with the rest of the cases (n=237) and controls (n=5,888) with only birth and diagnosis addresses but without available LexisNexis records.

Selection of Chemicals

We reviewed previous published articles which examined associations between specific chemical agents and childhood brain tumors, and selected those carcinogens that have been reported to be positively associated with these outcomes of interest. Following two previously California based studies (Reynolds et al., 2005, 2002) that examined the associations between childhood cancers and residential pesticide exposure, we selected the following potentially high-risk pesticides: propargite, methyl bromide, metam-sodium, trifluralin, simazine, dicofol, and chlorothalonil. These agents also have wide usage in California, high genotoxicity, carcinogenic potency based on U.S. Environmental Protection Agency (EPA), field volatilization flux, and persistence (Gunier et al., 2001) (Table 4.1).

Pesticide Exposure Assessment

Pesticide estimation was described in detail in in section 3.3. For each of the pesticides examined in this study, we summed the annual pounds applied per acre to obtain exposure values for each

calendar year using the 2km buffer surrounding each address. These annual exposure estimates were then summed across the multi-year range for cases and controls. From the date of birth to the date of diagnosis for cases and reference date for matched controls, we used weighted averages with weights representing the proportions (in days for each year) of the relevant exposure period falling into each calendar year. Three estimates were calculated accordingly, using 1) birth address for both cases and controls, 2) diagnosis address for cases and birth residence for controls (hereinafter referred to as 'diagnosis address'), and 3) LexisNexis addresses for both cases and controls address throughout the entire period. After obtaining the pesticide exposure estimates using annual PUR records, we further categorized children's exposure status into lifetime "ever exposed" versus "never exposed".

Statistical Analysis

We conducted univariate and multivariate conditional logistic regression analyses adjusting for year of birth and estimated odds ratios (ORs) and 95% confidence intervals (CIs). Based on the literature (Johnson et al., 2014) as well as our own explorations of associations in our data (Julia E Heck et al., 2013; von Ehrenstein et al., 2016), we considered the following potential confounders in the adjusted models: maternal and paternal age at birth (≤19, 20-24, 25-29, 30-34, ≥35), maternal race/ethnicity (non-Hispanic White, Hispanic, Black, Asian/Pacific islander, others), maternal education (<12 years, 12 years, 13-15 years, ≥16 years), child's sex, parity (1, 2, ≥3), payment source for prenatal care as a proxy for family income (private/HMO/ Blue Cross Blue Shield vs MediCal/government/self-pay), maternal place of birth (California, other U.S. states, Mexico, other foreign countries), and rural/urban status of residence at birth according to the Rural-Urban Commuting Area (RUCA) Codes (United States Department of Agriculture, 2005), for which we dichotomized 1-3 as urban and 4-10 as rural, in addition to the matching

factor year of birth, and left out the covariates that introduced < 10% change in estimate. Final models were adjusted for year of birth (categorical), child's sex, maternal age, maternal race/ethnicity, and maternal education.

4.4 Results

Table 4.2 shows the child and maternal characteristics by availability of maternal LexisNexis records in their early life from birth through diagnosis for cases and reference for controls. The availability of LexisNexis addresses showed a clear temporal trend, with substantially less missing records in more recent years, indicating an improvement in data collection over time. Cases diagnosed at an older age (1 or ≥2) compared with those diagnosed within their first year of life were more likely to have LexisNexis addresses available through their lifetime; similar pattern was observed for controls when age was calculated based on the reference date. Among both cases and controls, mothers of older age, with higher education, a non-Hispanic background, a higher parity, those who used private insurance, born in California, or resided in metropolitan areas or neighborhoods with higher SES at delivery were more likely to have available LexisNexis records (Table 4.2).

In adjusted models, there were modestly elevated ORs for childhood brain tumors associated with several pesticides including methyl bromide, simazine and propagate when assigning exposures to birth address for both cases and controls, and chlorothalonil, trifluralin, simazine, and propargite propagate when assigning exposures to birth address for controls and to diagnosis address for cases (Table 4.3). However, when assigning exposures according to LexisNexis addresses for both, most associations were attenuated and the point estimates were close to the null (Figure 4.1).

Restricting to children for whom only birth and diagnosis addresses but no LexisNexis data were available, we observed null associations for childhood brain tumors and all select pesticides using birth addresses but positive associations for trifluralin, metam-sodium, and propargite using diagnosis for cases and birth address for controls (Table 4.4, Figure 4.2). Adjusted ORs were generally attenuated when additionally adjusting for child's sex, maternal age, maternal education, and maternal race/ethnicity, except for propargite which had a slightly higher adjusted than crude OR. Among all five types of estimates, LexisNexis-based exposures tend to produce the most conservative (attenuated) effect estimates for most pesticides (Figure 4.3). Comparing the subpopulation with available LexisNexis addresses with those without available LexisNexis addresses, ORs based on birth or diagnosis address were generally higher in those who did not have LexisNexis information available.

4.5 Discussion

This study aimed to assess the extent to which using a single source of address from birth certificates or cancer diagnosis records, or a reconstructed address history using public records, to estimate children's early life exposures to agricultural pesticides might impact effect estimates for childhood brain tumors. We relied upon an innovative method to reconstruct residential histories as a "alloyed gold standard" accounting for mobility in children's early life using a public database (i.e., LexisNexis), and compared the effect estimates based on exposures assigned to birth and diagnosis addresses with those based on LexisNexis addresses. In a subset of the children for whom all three types of addresses were all available for analysis, we found generally higher point estimates using diagnosis address compared to those estimated using LexisNexis addresses. However, among children for whom we did not have LexisNexis

addresses available, we observed the strongest effect estimates based on birth and diagnosis address compared to those with LexisNexis data as a source.

The reason for the largely null associations estimated using LexisNexis addresses is that pesticide exposure prevalence increased for both cases and controls compared with the prevalence based on birth and diagnosis addresses (shown in Tables 4.3 and 4.4). This possibly due to the change in addresses in the early life of children such that more than one address applies and this seems to increase the chance of being exposed at the residential locations. There are several possible scenarios that may lead to such a result.

Early life exposures (between birth and diagnosis) that have been estimated based on birth addresses may represent prenatal exposure levels prior to birth but not early life exposures if the child moved after birth. While it has yet to be determined what the critical windows are for the development of childhood brain tumors, a study of childhood leukemia tried to distinguish between pre-pregnancy, pregnancy and postnatal (to 3 years after birth) exposures as critical windows for pesticide exposure, and exposure during pregnancy seemed to have a higher impact than other periods (Ma et al., 2002a), although the findings do not necessarily transfer to brain tumors. However, in this study, we primarily focused on early childhood exposures as the susceptible window and did not address prenatal exposures that future research needs to examine.

Diagnosis address of cases possibly represents exposures closer to cancer diagnosis, indicating a different time window. The 'two-hit' hypothesis (Knudson, 2001) could possibly explain the elevated ORs when exposures were assigned according to diagnosis address: if a second hit is required for cancer initiation, exposures during that period may also have substantial impact on

the development of cancer. It is not known whether the 'two-hit' hypothesis is relevant for brain tumors, however.

Another explanation could be the inaccuracy in reporting of birth and diagnosis address. Although a literature search did not yield validation studies for birth and diagnosis addresses on birth certificates and in Cancer Registry records, it is feasible that families sometimes deliberately misreport their home address at birth due to concerns about legal status or inability to pay for hospital services (Pamela Kempert, personal communication). Addresses may also be subject to misclassification due to data entry errors. Yet, LexisNexis addresses may also have errors, because there are many cases with multiple addresses for the same time period, inaccurate or missing 'first seen' and 'last seen' dates associated with each address, and inadequate reporting in earlier years. If LexisNexis-based exposures estimates accounting for residential mobility of children's families are considered to represent exposure levels more accurately and thus would provide effect estimates that are closer to the true associations, then using a single address (birth or diagnosis address) for each child may underestimate cases and controls' exposures differentially, for example, if case families tend to move more or closer to the fields more than control families. Of course, besides all other possible explanations, there might be random error in effect estimates because of small numbers of exposed cases in our analysis.

Comparing to the subset of children for whom all three addresses were available, the subset with missing LexisNexis information generally showed elevated ORs based on either birth address or diagnosis address. A few scenarios may explain this difference. According to Table 4.1, the former subset with LexisNexis data represents mothers of older maternal age, higher maternal education and SES, and more Whites, compared to the latter subset. Thus, a likely explanation is that those without LexisNexis records represent a group of individuals with higher pesticide

exposure levels in general, insofar they are lower income, lower education, and more Hispanic. Exposure difference exists indeed when we compare exposure prevalence of cases and controls in these two subsets confirming the higher exposure prevalence amongst the subset without LexisNexis. Another possible scenario involves unmeasured variables that may have confounded the associations. In our multivariate adjusted models, we have included most established confounders and confirmed that the other potential confounders such as parity, payment for prenatal care, and neighborhood SES did not change our model results substantially. Thus, uncontrolled confounding would be unlikely in this situation. However, since this subset without LexisNexis addresses has very similar demographic characteristics (e.g., maternal age, education, and SES) as those with higher residential mobility shown in earlier studies (Margerison-Zilko et al., 2016; Urayama et al., 2009) as well as our own findings, it is also possible that those children who moved into or within rural areas might have greater risks of early life exposures to other rural exposures including other pesticides or to livestock and zoonosis (Efird et al., 2003; Gold et al., 1979) that maybe relevant for childhood brain tumors. As previously mentioned, if diagnosis address reflects true exposures prior to cancer diagnosis, and given that in the group without LexisNexis address exposures prevalence was particularly high in the cases this would explain elevated ORs. However, since controls' addresses at the reference date are unknown in the current study, we cannot assume that their exposure levels remain the same throughout their early life.

To our knowledge, this is the first population-based record-linkage study to examine the impact of residential mobility in early childhood on the associations between agricultural pesticides and childhood brain tumors using a public records database for addresses. We quantitatively assessed the magnitude of potential bias introduced by exposure misclassification using a real datasets,

while the only previous study that examined the degree of bias resulting from misclassification due to residential mobility in pregnancy used simulated data (Pennington et al., 2016). Another contribution of this study is that we examined potential bias introduced by restricting to children with available LexisNexis addresses and provided some cautions to conducting environmental epidemiological studies that rely on LexisNexis records only. Nevertheless, the coverage of LexisNexis records has been improving substantially over the years as shown in Table 4.1, providing future large record-linkage studies with a possibly valuable source of residential addresses besides the ones routinely collected on birth certifies and cases diagnosis records.

This study has a few limitations. A major issue with our current data is that we were not able to obtain a full residential history as a "gold standard" for everyone in this study, limiting our ability to examine the full scope of the impact of residential mobility on effect estimates for the entire study population. Although LexisNexis records have a promising potential for the future research because they became more complete over time, current studies trying to track down child-bearing age women may still face some challenges. On top of that, reconstructed residential histories from LexisNexis records are by no means the "gold standard". They have several intrinsic limitations including providing multiple addresses for the same time period, inaccurate or missing 'first seen' and 'last seen' dates associated with certain addresses (Hurley et al., 2017), and time-varying sources of addresses over years, therefore limiting its usefulness for large-scale record-based epidemiological studies. In addition to concerns regarding the quality of reconstructed residential histories from LexisNexis records, our approach assumes that infants or young children spent most of their time at home during the day when pesticides are sprayed on nearby fields, while they could be in the day care centers or kindergartens. Although

childcare centers are usually near homes, this could still introduce exposure misclassification when a smaller buffer such as 500m or 1km is used.

Using a single source of address to assess children's early life exposure to pesticides does not account for their residential mobility and may lead to exposure misclassification that may even be differential as well as non-differential. Databases with public records could be used to augment routinely collected residential information from birth certificates and cancer registries but researchers should be cautious about the potential selection bias introduced by the availability and accuracy of such data sources.

Table 4.1 Select high-risk chemicals for childhood cancers.

ChemCode	Chemical Name	Use type	Cancer Rating	IARC Carcinogens	US EPA Carcinogens	CA Prop 65
677	Chlorothalonil	Fungicide	Known, P65 only	2B, Possible	B2, Probable	Yes
597	Trifluralin	Herbicide	Possible	3, Unclassifiable	C, Possible	Not Listed
385	Methyl bromide	Fumigant, Insecticide, Herbicide, Nematicide	Unclassifiable	3, Unclassifiable	Not Likely	Not Listed
531	Simazine	Herbicide	Possible	3, Unclassifiable	C, Possible	Not Listed
346	Dicofol	Insecticide	Possible	3, Unclassifiable	C, Possible	Not Listed
616	Metam-sodium	Fumigant, Herbicide, Fungicide, Microbiocide, Algaecide	Known, P65 only	Not Listed	B2, Probable	Yes
445	Propargite	Insecticide	Known, P65 only	Not Listed	B2, Probable	Yes

Table 4.2 Child and maternal demographics associated with availability of LexisNexis in child's early life (from birth to diagnosis), 2001-2008.

	Brain tumor cases				Controls			
	LexisNexis Records Available[a]		LexisNexis Records Unavailable[a]		LexisNexis Records Available[a]		LexisNexis Records Unavailable[a]	
	N=397	%	N=237	%	N=6,614	%	N=5,888	%
Year of birth								
2001	42	44.7	52	55.3	735	41.2	1,051	58.8
2002	39	47.6	43	52.4	718	46.1	840	53.9
2003	67	61.5	42	38.5	975	47.1	1,096	52.9
2004	66	68.8	30	31.3	1,025	55.6	818	44.4
2005	68	70.8	28	29.2	1,091	58.6	771	41.4
2006	71	71.0	29	29.0	1,191	60.9	766	39.1
2008	44	77.2	13	22.8	879	61.7	546	38.3
Age at diagnosis or ref age								
0	63	54.8	52	45.2	1,044	47.4	1,160	52.6
1	77	64.7	42	35.3	1,272	55.8	1,008	44.2
2-5	257	64.3	143	35.8	4,298	53.6	3,720	46.4
Maternal Age								
19 or less	17	37.8	28	62.2	400	34.4	763	65.6
20-24	81	61.8	50	38.2	1,458	50.9	1,404	49.1
25-29	93	59.2	64	40.8	1,805	54.4	1,510	45.6
30-34	115	68.0	54	32.0	1,701	56.0	1,339	44.0
35 and older	91	68.9	41	31.1	1,249	58.9	871	41.1
Missing	-	-	-	-	1	50.0	1	50.0
Maternal Education								
<12 years	74	47.1	83	52.9	1,343	37.4	2,249	62.6
12 years	96	66.2	49	33.8	1,849	56.3	1,434	43.7
13-15 years	93	69.4	41	30.6	1,486	61.5	930	38.5
16+ years	123	66.5	62	33.5	1,791	61.7	1,114	38.3

Missing	11	84.6	2	15.4	145	47.4	161	52.6
Maternal Race/Ethnicity								
White, non-Hispanic	155	64.6	85	35.4	2,186	59.5	1,488	40.5
Hispanic, any race	154	55.2	125	44.8	2,939	46.4	3,393	53.6
Black	30	81.1	7	18.9	446	64.6	244	35.4
Asian/PI	42	72.4	16	27.6	827	60.8	533	39.2
Other/Refused	16	80.0	4	20.0	216	48.4	230	51.6
Parity								
1	160	59.3	110	40.7	2,457	50.5	2,405	49.5
2	119	63.0	70	37.0	2,226	55.1	1,812	44.9
3 or more	118	67.4	57	32.6	1,926	53.6	1,666	46.4
Missing	-	-	-	-	5	50.0	5	50.0
Payment type of prenantal care								
Private/HMO/BCBS	261	69.2	116	30.8	3,855	62.1	2,349	37.9
MediCal/Govt/self-pay	131	52.8	117	47.2	2,708	43.7	3,487	56.3
Missing	5	55.6	4	44.4	51	49.5	52	50.5
Maternal birthplace								
California	215	70.5	90	29.5	3,455	66.0	1,781	34.0
Mexico	58	41.1	83	58.9	1,122	32.9	2,291	67.1
Other US States	55	67.9	26	32.1	742	52.4	675	47.6
Other foreign countries	69	64.5	38	35.5	1,289	53.2	1,133	46.8
Missing	-	-	-	-	6	42.9	8	57.1
Urban/rural status at birth								
Metropolitan	374	63.4	216	36.6	6,230	53.6	5,400	46.4
Non-metropolitan	23	52.3	21	47.7	384	44.0	488	56.0
Quintiles of neighborhood SES at birth								
1 (Lowest)	81	59.1	56	40.9	1,626	47.8	1,774	52.2
2	91	61.9	56	38.1	1,501	51.2	1,428	48.8
3	83	63.8	47	36.2	1,340	53.3	1,175	46.7
4	67	59.8	45	40.2	1,109	56.7	846	43.3
5 (Highest)	75	69.4	33	30.6	1038	61.0	665	39.0

Table 4.3 Odds ratios (95% confidence intervals) for early life exposures to pesticides and brain tumors, among those with at least 80% of maternal LexisNexis residential history in lifetime (from birth to diagnosis or reference)

				Lifetime exposure					
Pesticide	Brain tumors (n=397)	Controls (n=6,614)	aOR[1]	Brain tumors (n=397)	Controls (n=6,614)	aOR[1]	Brain tumors (n=397)	Controls (n=6,614)	aOR[1]
	Birth Addresses			Dx Address (for cases) and Birth Address (for controls)			LexisNexis Addresses		
Chlorothalonil	104 (26.2%)	1702 (25.7%)	1.03 (0.81, 1.31)	112 (28.2%)	1702 (25.7%)	1.15 (0.91, 1.46)	116 (29.2%)	1981 (30.0%)	0.97 (0.77, 1.23)
Trifluralin	67 (16.9%)	1088 (16.4%)	1.06 (0.80, 1.40)	69 (17.4%)	1088 (16.4%)	1.10 (0.83, 1.46)	76 (19.1%)	1282 (19.4%)	1.05 (0.81, 1.38)
Methyl bromide	54 (13.6%)	851 (12.9%)	1.13 (0.83, 1.54)	50 (12.6%)	851 (12.9%)	1.02 (0.75, 1.41)	61 (15.4%)	1007 (15.2%)	1.07 (0.80, 1.43)
Simazine	64 (16.1%)	935 (14.1%)	1.21 (0.91, 1.62)	65 (16.4%)	935 (14.1%)	1.24 (0.93, 1.65)	63 (15.9%)	1118 (16.9%)	0.96 (0.72, 1.27)
Dicofol	28 (7.1%)	527 (8.0%)	0.84 (0.55, 1.28)	31 (7.8%)	527 (8.0%)	0.98 (0.66, 1.46)	33 (8.3%)	598 (9.0%)	0.92 (0.63, 1.35)
Metam-sodium	30 (7.6%)	521 (7.9%)	1.05 (0.71, 1.55)	29 (7.3%)	521 (7.9%)	0.96 (0.64, 1.45)	32 (8.1%)	601 (9.1%)	0.88 (0.60, 1.30)
Propargite	39 (9.8%)	557 (8.4%)	1.28 (0.90, 1.83)	34 (8.6%)	557 (8.4%)	1.10 (0.75, 1.59)	38 (9.6%)	663 (10.0%)	1.03 (0.72, 1.47)

OR[1]: adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity

Table 4.4 Odds ratios (95% confidence intervals) for early life exposures to pesticides and brain tumors, among those with more than 20% missing in lifetime maternal LexisNexis residential history (from birth to diagnosis or reference)

	Lifetime exposure							
Pesticide	CNS tumors (n=237)	Controls (n=5,888)	cOR[1]	aOR[2]	CNS tumors (n=237)	Controls (n=5,888)	cOR[1]	aOR[2]
	Birth Addresses				Dx Address (for cases) and Birth Address (for controls)			
Chlorothalonil	67 (28.3%)	1519 (25.8%)	1.13 (0.84, 1.53)	1.11 (0.81, 1.51)	68 (28.7%)	1519 (25.8%)	1.14 (0.85, 1.54)	1.12 (0.82, 1.52)
Trifluralin	43 (18.1%)	998 (16.9%)	1.05 (0.74, 1.48)	1.02 (0.71, 1.47)	57 (24.1%)	998 (16.9%)	1.50 (1.09, 2.06)	1.49 (1.07, 2.07)
Methyl bromide	45 (19.0%)	851 (14.5%)	1.32 (0.93, 1.87)	1.27 (0.88, 1.81)	43 (18.1%)	851 (14.5%)	1.24 (0.87, 1.77)	1.19 (0.83, 1.71)
Simazine	42 (17.7%)	851 (14.5%)	1.27 (0.89, 1.81)	1.22 (0.85, 1.75)	46 (19.4%)	851 (14.5%)	1.41 (1.00, 1.99)	1.37 (0.96, 1.95)
Dicofol	23 (9.7%)	538 (9.1%)	1.08 (0.68, 1.71)	1.06 (0.66, 1.70)	25 (10.5%)	538 (9.1%)	1.19 (0.76, 1.85)	1.16 (0.74, 1.84)
Metam-sodium	30 (12.7%)	537 (9.1%)	1.45 (0.96, 2.20)	1.42 (0.92, 2.20)	32 (13.5%)	537 (9.1%)	1.57 (1.04, 2.36)	1.55 (1.02, 2.38)
Propargite	29 (12.2%)	553 (9.4%)	1.32 (0.87, 1.99)	1.33 (0.87, 2.03)	34 (14.3%)	553 (9.4%)	1.59 (1.07, 2.34)	1.62 (1.08, 2.42)

OR[1]: adjusted for year of birth

OR[2]: adjusted for year of birth, sex, maternal age, maternal education, maternal race/ethnicity

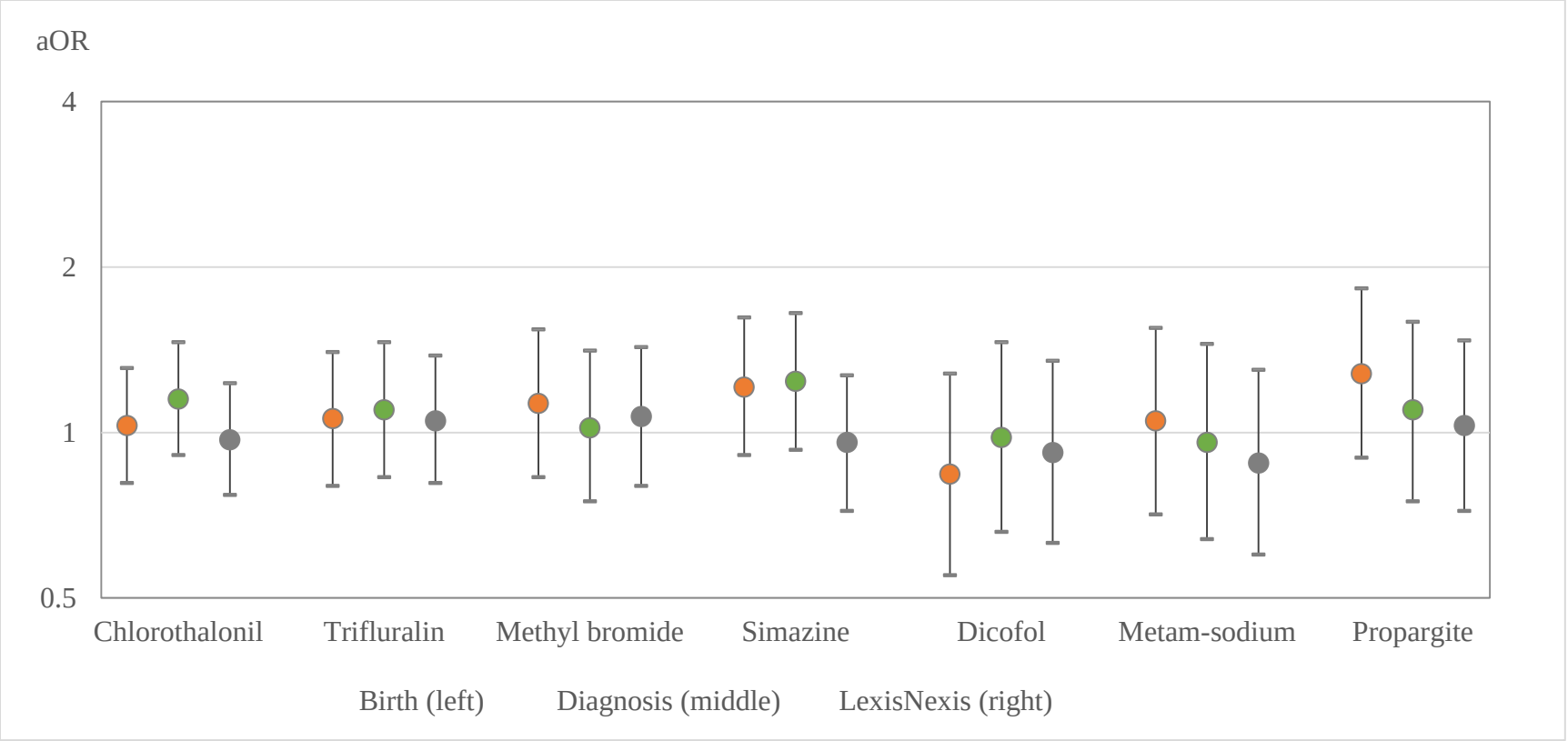


Figure 4.1 Adjusted ORs for lifetime pesticide exposures and brain tumors, among children with available LexisNexis addresses

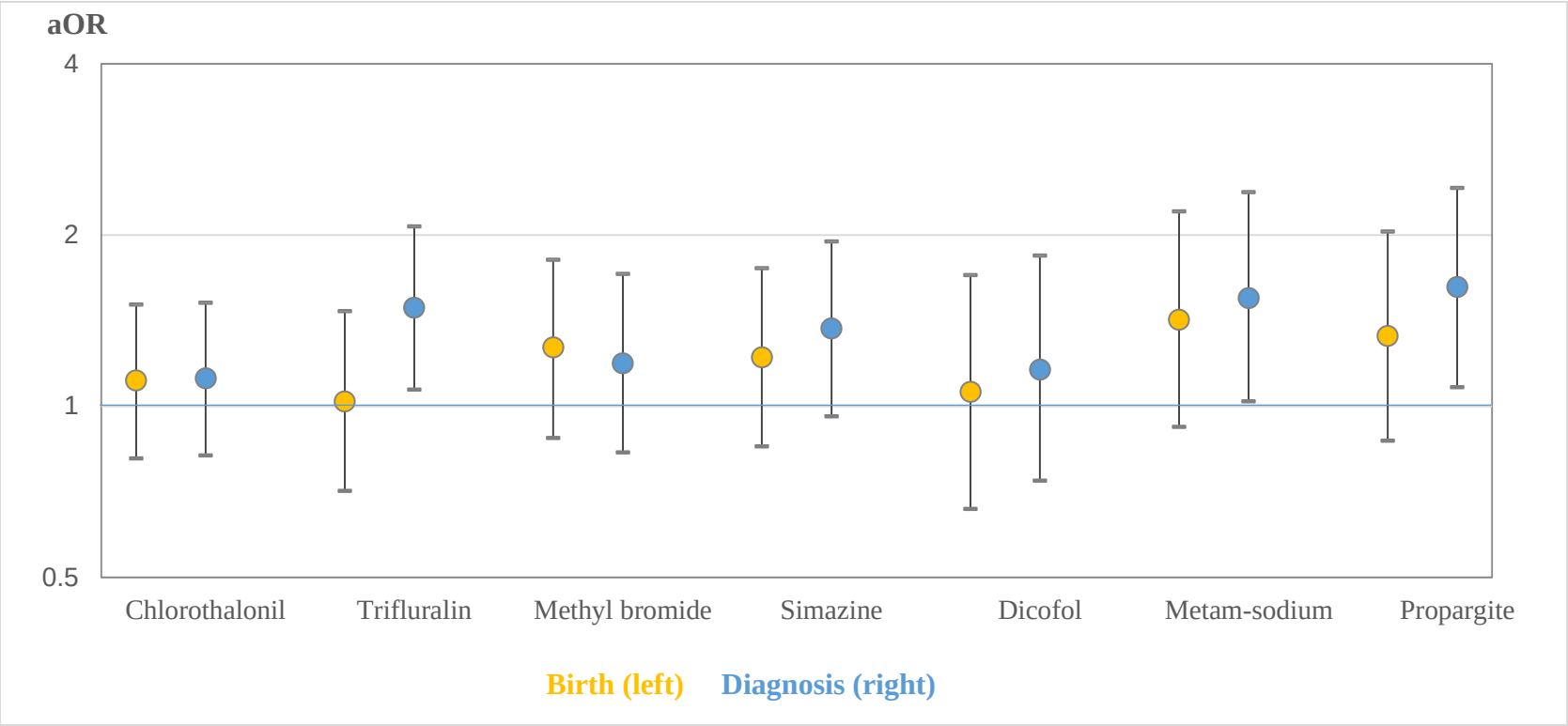


Figure 4.2 Adjusted ORs for lifetime pesticide exposures and brain tumors, among children with only birth and diagnosis addresses available

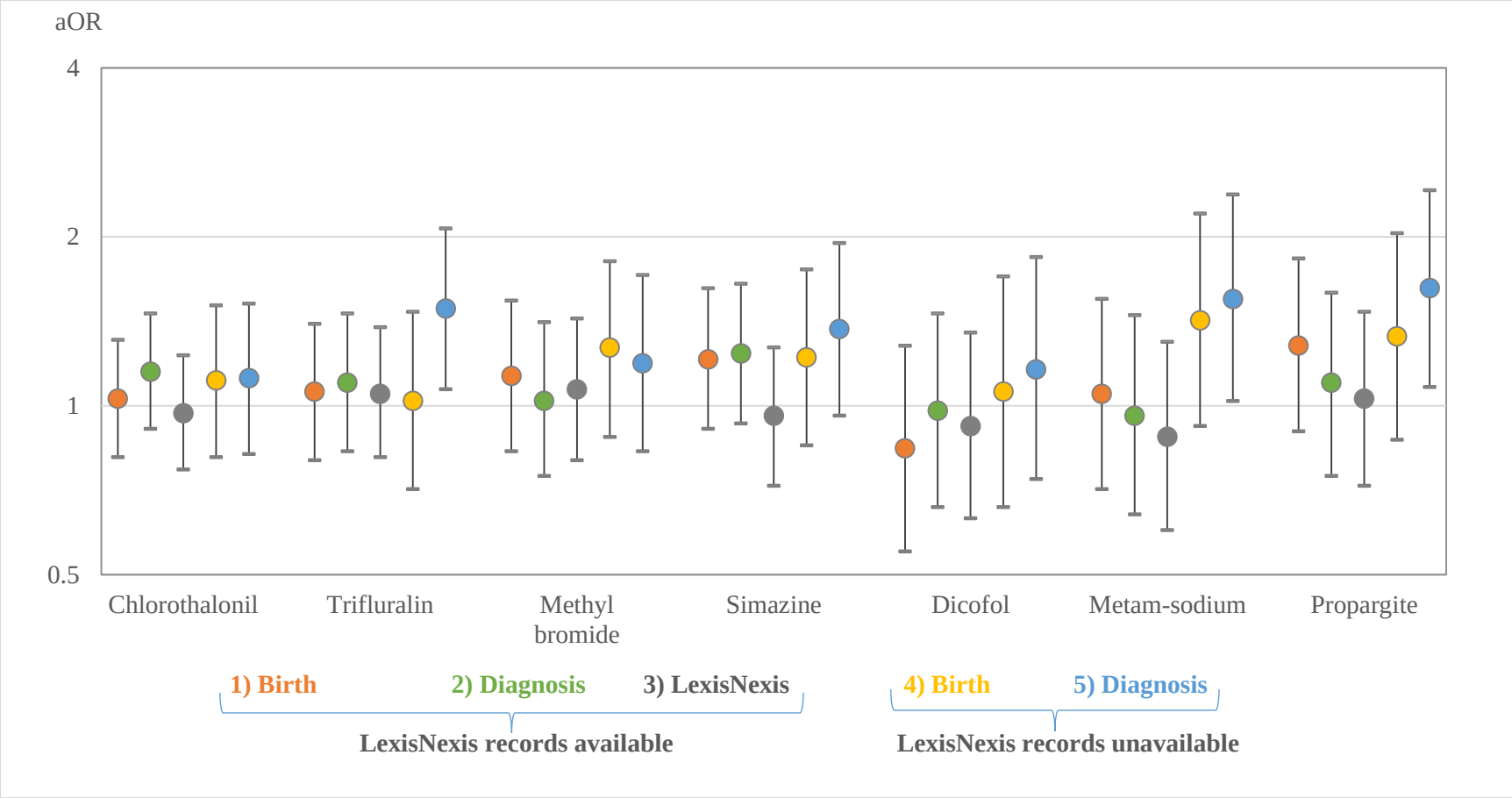


Figure 4.3 Adjusted ORs for lifetime pesticide exposures and brain tumors, all methods combined

5. Conclusion and Public Health Implications

This dissertation first examined prenatal exposures to pesticides known or suspected to be reproductive toxicants in relation to adverse birth outcomes among women living near agricultural fields in California, and found that first and second trimester exposures to most selected pesticides were associated with preterm delivery but the evidence for term low birthweight was limited. Our findings corroborate previous evidence suggesting early or mid-pregnancy is the critical period of fetal development and underscore the importance of protecting pregnant women from exposures to pesticides.

Synthetic pesticides have been a double-edged sword in the past century. While they control the harm caused by pests and improve productivity of agricultural crops, many compounds are only tested for its environmental safety in the laboratory or in field trials, but their impact on human health is unknown. Earlier pesticides have been constantly linked to chronic adverse effects in later research and eventually phased out or replaced with less toxic and more selective agrochemicals. Because of the trade-off between the health and environmental effects and the need to produce food (Milner and Boyd, 2017), it is a long-term process for national and international agencies to collect evidence for the harmful effect of pesticides and requires a comprehensive search for literature to conduct scientific review to ban toxic pesticides. Our study makes a significant contribution by providing knowledge of susceptibility of fetal growth to maternal pesticide exposure, for the references of public awareness, future research, and health policy making.

In the latter part of this dissertation, we then assessed patterns of residential mobility and examined the impact of mobility on the first year of life exposure measures for agricultural pesticides. We also estimated and compared the effect estimates for pesticide exposure during

children's early life based on birth residence and/or diagnosis address with those estimated using reconstructed residential history based on a public records database LexisNexis, using childhood brain tumors as an example. We highlight the importance of accounting for residential mobility in estimating environmental exposures during children's early life and provide new information on the application of LexisNexis records in augmenting existing address information and estimating environmental exposures for large record-linkage epidemiological studies of childhood health outcomes. However, researchers should be aware of the potential selection bias introduced by the availability and accuracy of such data sources, because individuals with lower socioeconomic status or underrepresented are likely those with sub-optimal living environment and having higher risk of being exposed to agricultural pesticides and therefore subject to chronic adverse outcomes more than other groups.

Recent literature has been increasingly focused on the health effects of pesticide exposure including pregnancy outcomes, neurodevelopment, and cancer in lower SES population, or among Latino migrant farmworkers and their offspring throughout the US (Di Renzo et al., 2015; Eskenazi et al., 2007) and suggests that they may also be more vulnerable to pesticide exposure because of poor housing condition and insufficient protection from occupational hazards (Arcury et al., 2014a, 2014b). Furthermore, our findings suggest that some population subgroups living in agricultural regions, whether or not they are actively farming, may represent potential high-risk populations. Future studies should pay more attention to these vulnerable population groups, develop better strategies to obtain accurate residential information or synthesize data from different sources to provide more accurate exposure and effect measures for agricultural pesticides.

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