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Los Angeles

Prenatal Exposure to Pesticides and Air Pollution in California: Childhood Cancer Risk and
Neonatal Metabolic Signatures

A dissertation submitted in partial satisfaction
of the requirements for the degree Doctor of Philosophy
in Epidemiology

by

Darcy Van Deventer

2026

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ABSTRACT OF THE DISSERTATION

Prenatal Exposure to Pesticides and Air Pollution in California: Childhood Cancer Risk and Neonatal Metabolic Signatures

by

Darcy Van Deventer

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2026

Professor Julia E. Heck, Co-Chair

Professor Beate R. Ritz, Co-Chair

Childhood cancer is the leading disease-related cause of death among children in the United States, yet the etiology of most childhood cancers remains poorly understood. Because many childhood cancers originate during fetal development, prenatal environmental exposures may play an important role in disease initiation. traffic-related air pollution and childhood cancer risk and explores biological pathways linking prenatal pesticide exposure to retinoblastoma using neonatal dried blood spot metabolomics.

The first study evaluated prenatal residential exposure to agricultural pesticides and neuroblastoma risk in a population-based case-control study of California children born 1998-2016 (199 cases, 202,796 controls). Prenatal pesticide exposure was estimated using California's Pesticide Use Reporting system linked with GIS-based land-use models. Hierarchical logistic

regression identified elevated risks associated with prenatal exposure to flonicamid (adjusted odds ratio [aOR]: 1.33; 95% confidence interval [CI]: 1.02-1.73), with positive associations also observed for benomyl (aOR: 1.53; 95% CI: 0.98-2.38), cypermethrin (aOR: 1.24; 95% CI: 0.96-1.60), and permethrin (aOR: 1.20; 95% CI: 0.96-1.50).

The second study examined prenatal exposure to criteria air pollutants and traffic-related air toxics in relation to childhood cancer using a population-based case-control study of California children born 1998-2016 residing in Los Angeles County (2,940 cases, 63,516 controls). Prenatal exposure to PM_{2.5}, NO₂, O₃, benzene, 1,3-butadiene, chromium, lead, and nickel was estimated using machine learning-enhanced land-use regression models. Prenatal PM_{2.5} exposure was associated with rhabdomyosarcoma (OR: 1.59; 95% CI: 1.05-2.40), 1,3-butadiene with soft tissue sarcoma (OR: 1.71; 95% CI: 1.12-2.61), benzene with ependymoma (OR: 3.35; 95% CI: 1.18-9.53), chromium with non-Hodgkin lymphoma (OR: 1.27; 95% CI: 1.05-1.54), and lead with both non-Hodgkin lymphoma (OR: 1.36; 95% CI: 1.10-1.68) and Wilms' tumor (OR: 1.30; 95% CI: 1.03-1.64). Air toxic mixture analyses additionally identified associations with all childhood cancers combined, ependymoma, and soft tissue sarcoma.

The third study integrated GIS-based pesticide exposure assessment with high-resolution metabolomics of archived neonatal dried blood spots to investigate metabolic pathways associated with prenatal pesticide exposure in retinoblastoma, using a population-based case-control study of California children born 1998-2011 (226 retinoblastoma cases, 366 controls). Prenatal exposure to two or more retinoblastoma-associated pesticides increased the odds of retinoblastoma overall (aOR: 1.59; 95% CI: 1.11-2.26), with a stronger association observed for bilateral disease (aOR: 2.07; 95% CI: 1.27-3.36). Metabolome-wide association studies revealed that pesticide-associated metabolic responses differed between retinoblastoma cases and

controls, with weak correlations between case- and control-specific effect estimates (C18: $r = 0.09$; HILIC: $r = 0.20$) and broader pathway enrichment among cases, including inflammatory lipid metabolism, central energy metabolism, amino acid metabolism, and oxidative stress-related pathways.

Together, these studies provide evidence that prenatal exposure to certain agricultural pesticides and traffic-related air pollution is associated with increased risk of several childhood cancers and suggest that perturbations in inflammatory and central energy metabolism pathways are associated with prenatal pesticide exposure among children who develop retinoblastoma. These findings extend the evidence on environmental risk factors for childhood cancer and identify hypothesis-generating biological pathways to guide future mechanistic and etiologic research.

The dissertation of Darcy Van Deventer is approved.

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ABBREVIATIONS AND ACRONYMS

AI	Artificial Intelligence
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
aOR	Adjusted Odds Ratio
AOD	Aerosol Optical Depth
C18	C18 Reversed-Phase Liquid Chromatography
CARB	California Air Resources Board
CCR	California Cancer Registry
CDWR	California Department of Water Resources
CI	Confidence Interval
CNS	Central Nervous System
CTI	California Toxics Inventory
DBS	Dried Blood Spots
EPA	Environmental Protection Agency
ESI	Electrospray Ionization
FDR	False Discovery Rate
GABA	Gamma-Aminobutyric Acid
GCT	Germ Cell Tumor
GIS	Geographic Information System
GRAPES	GIS-Based Residential Ambient Pesticide Estimation System
GSEA	Gene Set Enrichment Analysis
HILIC	Hydrophilic Interaction Liquid Chromatography
HLM	Hierarchical Logistic Model
HMDB	Human Metabolome Database
HRM	High-Resolution Metabolomics
HRMS	High-Resolution Mass Spectrometry
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
IQR	Interquartile Range
KEGG	Kyoto Encyclopedia of Genes and Genomes
LC	Liquid Chromatography
LC-HRMS	Liquid Chromatography-High-Resolution Mass Spectrometry
LUR	Land-Use Regression
m/z	Mass-To-Charge Ratio
MWAS	Metabolome-Wide Association Study
NHL	Non-Hodgkin Lymphoma
NIST	National Institute of Standards and Technology

NO ₂	Nitrogen Dioxide
O ₃	Ozone
OR	Odds Ratio
ORA	Over-Representation Analysis
PAN	Pesticide Action Network
PCNB	Pentachloronitrobenzene
PLSS	Public Land Survey System
PM	Particulate Matter
PM _{2.5}	Fine Particulate Matter (Aerodynamic Diameter $\leq 2.5 \mu\text{m}$)
PUR	Pesticide Use Reporting
SAS	Statistical Analysis System
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic Status
SI	Simulation Interval
SMPDB	Small Molecule Pathway Database
TCA	Tricarboxylic Acid
WHO	World Health Organization

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Van Deventer D, Park SL, Cheng I, et al. Exposure to industrial air toxics and risk of breast cancer in California: The Multiethnic Cohort Study. *J Occup Environ Med*. Published online March 3, 2026. doi:10.1097/JOM.0000000000003687

Van Deventer D, Ritz B, Cockburn M, Heck JE. Prenatal pesticide exposure and neuroblastoma: A statewide case–control study in California. *Environmental Research*. Published online October 5, 2025. doi:10.1016/j.envres.2025.123027

Van Deventer D, Contreras ZA, Li S, et al. Childhood cancer risk in Hispanic enclaves in California. *Journal of Immigrant and Minority Health*. 2025;27(3):472–479.

Van Deventer D, Sidell M, Lee C, Young DR, Hedderson MM, Cohen DA, Liu EF, Barton LJ, Inzhakova G, Han BH. Heterogeneity in body mass index percentile and weight status among Asian American youths. *AJPM Focus*. 2025;4(5):100381. doi:10.1016/j.focus.2025.100381

Chen Y, Van Deventer D, Nianogo R, et al. Maternal exposure to heavy metals from industrial sources during pregnancy and childhood cancer risk in California. *Journal of Occupational and Environmental Medicine*. 2024;66(9):714–721. doi:10.1097/JOM.0000000000003160

Chen Y, Van Deventer D, Nianogo R, et al. Maternal residential exposure to solvents from industrial sources during pregnancy and childhood cancer risk in California. *International Journal of Hygiene and Environmental Health*. 2024;259:114388. doi:10.1016/j.ijheh.2024.114388

Van Deventer D, Marecaux J, Doubleday A, Errett N, Isaksen TMB. Wildfire smoke risk communication efficacy: A content analysis of Washington State's 2018 statewide smoke event public health messaging. *Journal of Public Health Management and Practice*. 2021;27(6):607–614.
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Chapter 1 Background and introduction

1.1 Childhood cancer

Cancer is the second leading cause of death among children aged 1-14 years, with an estimated 9,680 diagnosed cases and 1,090 deaths in 2026. The most common childhood cancer is leukemia, followed by central nervous system (CNS) tumors and lymphoma.¹

Childhood cancer is a diverse group of diseases that differ from adult cancers in their histology, biology, and risk factors.²⁻⁴ While inherited cancer predisposition syndromes and germline mutations account for a subset of childhood cancers, they are estimated to explain only 8-10% of cases, leaving substantial room for environmental and developmental contributors.⁵⁻⁷

Research on environmental risk factors for childhood cancer remains limited. Ionizing radiation is the only well-established environmental risk factor,⁸ while previous studies have suggested associations between childhood cancer and ambient air pollution, agricultural pesticides, residential proximity to industrial sources, and parental occupational chemical exposures.⁹

However, findings have been inconsistent, and many studies have relied on retrospective parental interviews or proxy measures such as occupational titles or residential proximity to pollution sources rather than quantitative estimates of specific environmental exposures. Improved exposure assessment methods are needed to better characterize the role of prenatal environmental exposures in childhood cancer etiology.

1.1.1 Neuroblastoma

Neuroblastoma is a malignant embryonal tumor arising from neural crest cells and accounts for approximately 15% of pediatric cancer-related deaths in the United States.¹⁰⁻¹³ It is the most common malignant tumor diagnosed during infancy and typically develops in the adrenal glands,

although it can arise anywhere along the sympathetic nervous system.^{11,13} Neuroblastoma primarily affects young children, with approximately 90% of cases diagnosed before the age of 5 and a median age at diagnosis of 18 months, and it is more common in boys than girls.¹⁴⁻¹⁶ Genetic predisposition is estimated to account for only a small proportion of neuroblastoma cases, and the causes of most tumors remain unknown.¹⁷

The etiology of neuroblastoma remains poorly understood. Previous studies have identified associations with low birth weight, congenital anomalies, maternal substance use during pregnancy, and paternal occupational exposures, although these factors explain only a small proportion of cases.¹⁸⁻²¹

1.1.2 Retinoblastoma

Retinoblastoma, a tumor of the retina, is the most common extracranial solid tumor in children and accounts for approximately 3% of childhood cancers, with 200-300 cases diagnosed annually in the United States.²²⁻²⁵ It is typically diagnosed before five years of age and develops following biallelic inactivation of the *RBI* tumor suppressor gene within a developing retinal cell through a proposed “two-hit” mechanism.^{24,25} This two-hit hypothesis and early age of diagnosis support the idea that perinatal exposures may contribute to *RBI* mutations and subsequent tumor development.²⁶

Previous epidemiologic studies have identified increased retinoblastoma risk in relation to older parental age, maternal smoking, prenatal and early life exposure to air toxics, and parental residential pesticide exposure.²⁷⁻³²

1.2 Traffic-related air pollution

Traffic-related air pollution is a major source of ambient air pollution in urban areas and consists of a complex mixture of exhaust and non-exhaust emissions, including criteria air pollutants

(PM_{2.5}, NO₂, and O₃) and hazardous air toxics such as benzene, 1,3-butadiene, chromium, lead, and nickel. Several of these pollutants have been classified as Group 1 carcinogens by the International Agency for Research on Cancer.³³⁻³⁷ Experimental studies suggest these pollutants may contribute to carcinogenesis through oxidative stress, inflammation, and DNA damage.³⁸⁻⁴⁰

Given that many childhood cancers are believed to originate during fetal development, prenatal exposure to traffic-related air pollution has been investigated as a potential risk factor.⁴¹⁻⁴³

Previous epidemiologic studies have reported mixed findings, with positive associations observed for several childhood cancer subtypes, including leukemia, central nervous system tumors, retinoblastoma, and germ cell tumors, while others have reported largely null results.^{9,44-49} Differences in exposure assessment methods, exposure windows, and study populations likely contribute to the heterogeneity of previous findings.

Many previous studies have relied on roadway proximity, traffic density, or other proxy exposure measures rather than quantitative estimates of individual pollutants. Recent advances in land-use regression modeling provide improved spatial resolution and enable estimation of pollutant-specific exposures during pregnancy, facilitating investigation of both individual pollutants and pollutant mixtures in relation to childhood cancer risk.

1.3 Agricultural pesticides

Pesticides are widely used throughout California, with approximately 176 million pounds of active ingredients applied across 96 million acres in 2023.⁵⁰ The United States Environmental Protection Agency (EPA) has classified more than 200 pesticides as possible or probable human carcinogens.⁵¹ Experimental and epidemiologic studies suggest that pesticides may contribute to carcinogenesis through several biological mechanisms, including oxidative stress, DNA damage, endocrine disruption, and immune dysregulation.⁵²⁻⁵⁶

Many pesticides can cross the placenta and have been detected in cord blood, suggesting that prenatal exposure may directly affect the developing fetus.^{57,58} Previous studies have reported associations between prenatal pesticide exposure and several childhood cancers, including leukemia, central nervous system tumors, neuroblastoma, and retinoblastoma.^{28,59-62} However, many studies have relied on parental occupation, self-reported pesticide use, or residential proximity to agricultural land as proxy measures of exposure, limiting the ability to identify individual pesticides that may contribute to disease risk.

California's mandatory Pesticide Use Reporting (PUR) system provides a unique opportunity to overcome these limitations by combining detailed records of agricultural pesticide applications with GIS-based land-use models to estimate ambient residential exposure to individual pesticides during pregnancy.^{63,64}

1.3.1 Neuroblastoma

Previous studies of prenatal pesticide exposure and neuroblastoma have primarily evaluated parental occupational exposure and reported mixed findings.⁶⁵⁻⁶⁸ Two recent meta-analyses concluded that parental occupational pesticide exposure was associated with increased neuroblastoma risk, although substantial heterogeneity across studies was noted.⁶⁹⁻⁷³

Studies of residential pesticide exposure have been comparatively limited and have produced inconsistent findings.⁷⁴⁻⁷⁶ Prior to our study, no studies had evaluated ambient residential exposure to specific agricultural pesticides in relation to neuroblastoma risk.

1.3.2 Retinoblastoma

Previous studies have also suggested that prenatal pesticide exposure may increase retinoblastoma risk, although findings have been inconsistent. Occupational studies have generally reported null associations but were limited by small numbers of exposed cases and

reliance on job titles or retrospective interviews to assess exposure,^{68,77-80} while one study reported an increased risk of bilateral retinoblastoma associated with paternal pesticide exposure.⁸¹ Studies evaluating residential proximity to agricultural land have similarly produced inconsistent findings.^{75,76}

A previous study by our research group was the first to evaluate ambient residential exposure to individual agricultural pesticides using California's Pesticide Use Reporting system linked with GIS-based land-use models and identified positive associations with several pesticides.²⁸

Although these epidemiologic findings suggest that prenatal agricultural pesticide exposure may contribute to retinoblastoma risk, the biological pathways underlying these associations remain poorly understood.

1.4 High-resolution metabolomics

High-resolution metabolomics (HRM) enables the untargeted characterization of thousands of endogenous and exogenous small molecules in biological samples and has become an important tool for investigating biological responses to environmental exposures.⁸² Applied through metabolome-wide association studies (MWAS), HRM can identify metabolic features and biological pathways associated with environmental exposures and disease, providing insight into potential mechanisms that may not be captured through traditional epidemiologic approaches.

Neonatal dried blood spots (DBS), collected routinely through newborn screening programs shortly after birth, provide a unique opportunity to investigate metabolic alterations present at birth before disease diagnosis. Previous studies have demonstrated that archived DBS remain suitable for HRM analyses after long-term storage and have been successfully used to identify metabolic signatures associated with prenatal environmental exposures and childhood diseases.⁸³

Previous metabolomic studies of pesticide exposure have consistently implicated disruptions in lipid metabolism, energy metabolism, and oxidative stress pathways,^{52-54 55,56} while metabolomic studies of retinoblastoma have identified alterations in lipid metabolism, central energy metabolism, and related pathways in both tumor tissue and neonatal dried blood spots.^{84 85,86} However, no previous study had used metabolomics to investigate the biological pathways linking prenatal exposure to specific agricultural pesticides with retinoblastoma risk.

By characterizing metabolic responses to prenatal environmental exposures before disease diagnosis, HRM provides an opportunity to bridge epidemiologic associations with potential biological mechanisms and generate hypotheses regarding childhood cancer etiology.

1.5 Objectives

This dissertation investigated prenatal agricultural pesticide and traffic-related air pollution exposures in relation to childhood cancer risk and explored biological mechanisms linking prenatal pesticide exposure with retinoblastoma using high-resolution metabolomics.

We first evaluated prenatal residential exposure to agricultural pesticides and neuroblastoma risk using California's Pesticide Use Reporting system linked with GIS-based land-use models to estimate ambient exposure to individual agricultural pesticides during pregnancy. By estimating exposure to specific pesticides rather than broad pesticide categories or proxy measures, this study sought to identify individual pesticides associated with neuroblastoma risk.

We next examined prenatal exposure to traffic-related air pollution and childhood cancer risk using machine learning-enhanced land-use regression models to estimate residential exposure to criteria air pollutants and traffic-related air toxics during pregnancy. In addition to evaluating individual pollutants, we investigated pollutant mixtures to better characterize the combined effects of traffic-related air pollution on childhood cancer risk.

Lastly, to better understand the biological pathways through which prenatal pesticide exposure may influence retinoblastoma development, we integrated GIS-based pesticide exposure assessment with high-resolution metabolomics of archived neonatal dried blood spots. We first identified a group of retinoblastoma-associated pesticides and then performed an untargeted metabolome-wide association study (MWAS) and pathway enrichment analyses to characterize metabolic perturbations associated with prenatal pesticide exposure and determine whether these associations differed between retinoblastoma cases and controls.

Chapter 2 Prenatal pesticide exposure and neuroblastoma – A statewide case-control study in California

2.1 Abstract

Background: Previous studies investigating neuroblastoma risk and parental pesticide exposure have had mixed findings, with some evidence linking maternal occupational or residential exposure to increased risk. However, most assessed pesticides broadly rather than evaluating specific compounds. To our knowledge, no studies have examined ambient residential exposure to individual pesticides and neuroblastoma risk.

Objective: To evaluate associations between childhood neuroblastoma and prenatal exposure to specific pesticides through residential proximity to agricultural applications.

Methods: We identified neuroblastoma cases from the California Cancer Registry and cancer-free controls from birth certificates. Analyses were restricted to children born 1998-2016 whose mothers lived within 4,000 meters of an agricultural pesticide application during pregnancy (199 cases, 202,796 controls). Probable and possible carcinogens were selected based on U.S. EPA classifications and pesticide use was collected from the California Pesticide Use Reporting system linked to land-use surveys. Exposures were assessed using a 4,000m buffer around geocoded residential addresses at birth. We used a distance decay model and considered pregnancies exposed when the poundage per acre applied exceeded the pesticide-specific median. We analyzed 68 pesticides with at least 5 exposed cases using unconditional logistic regression and hierarchical models co-adjusted for all pesticides.

Results: In hierarchical models, we observed elevated risks of neuroblastoma with prenatal exposure to flonicamid (aOR: 1.33; 95% CI: 1.02-1.73), benomyl (aOR: 1.53; 95% CI: 0.98-

2.38), cypermethrin (aOR: 1.24; 95% CI: 0.96-1.60), and permethrin (aOR: 1.20; 95% CI: 0.96-1.50).

Conclusion: Our findings suggest that ambient exposure to certain pesticides during pregnancy may increase the risk of neuroblastoma.

2.2 Introduction

Neuroblastoma, which accounts for 15% of pediatric cancer-related deaths in the United States, is the most prevalent malignant tumor in children under 1 year of age and is increasing in incidence.¹⁰⁻¹² Originating from neural crest cells, this tumor most frequently manifests in the adrenal glands (48% of cases) but can arise anywhere along the sympathetic nervous system.^{11,13} Genetic predisposition is estimated to account for 5% of neuroblastoma cases but other causative factors are unknown. Previous studies have identified possible associations between neuroblastoma and low birthweight, congenital anomalies, substance use during pregnancy, and paternal exposure to hydrocarbons, wood dusts and solders.¹⁷

Pesticides are widely used in California, with 191 million pounds of active ingredients applied across 95 million acres in 2021.⁸⁷ The United States Environmental Protection Agency (EPA) has classified over 200 pesticides as possible or probable carcinogens, and previous studies have found associations between prenatal pesticide exposure and increased risks of childhood leukemia and central nervous system tumors.^{28,59-62} Since pesticides have been found in cord blood and neuroblastoma is initiated during embryonic development, it is plausible that maternal exposure to pesticides during pregnancy may increase neuroblastoma risk in offspring.^{57,58}

Some previous studies have reported associations between parental occupational pesticide exposure and increased risk of neuroblastoma in offspring,^{65,66,68,88} while others have found no clear associations.^{67,68,71-73} However, several of these studies are limited by small sample sizes leading to imprecise estimates that make it difficult to draw definitive conclusions. Two meta-analyses found associations between prenatal parental occupational pesticide exposure and increased neuroblastoma risk in offspring^{69,70} and additionally one of these studies found a slightly positive association between residential proximity to agricultural sites and

neuroblastoma risk.⁷⁰ However, most of these studies relied on retrospective parental interview or proxy measurements for exposure such as job title and industry. There are very few studies investigating the effects of residential pesticide exposure on neuroblastoma. However, one case-control study which used parental interviews and asked about to retrospectively recall pesticide use in the home and garden found an increased risk of neuroblastoma when both parents reported ever using pesticides at home.⁸⁹ Two other case-control studies indicated that any maternal⁹⁰ or parental⁹¹ exposure to pesticides, whether through occupational activities or home use, was associated with an elevated risk of neuroblastoma. Two previous case-control studies have investigated associations between neuroblastoma and residential proximity to agriculture with one suggesting positive associations between neuroblastoma and residential proximity to vines and viticulture density,⁷⁶ while the other reported a null association with residential proximity to any crop fields.⁷⁵ To our knowledge, none of the existing literature has investigated the effects of ambient residential exposure to specific pesticides applied in agriculture.

We applied an advanced GIS model that combines California's mandatory Pesticide Use Reports with land use-data to estimate exposures to individual pesticides at the residence reported on birth certificates.^{28,59,62,63} Thus, we relied on individual-level pesticide exposure measures to determine whether prenatal exposure to pesticides classified as known or probable carcinogens by the EPA increases the risk of neuroblastoma in California.

2.3 Methods

Study Population

Neuroblastoma cases [International Classification of Childhood Cancer, Third Edition (ICCC) code 041] were identified through the California Cancer Registry (CCR) for incident diagnoses between 1988 and 2018. Since 1988, California law has mandated reporting of all cancer

diagnoses to the CCR, and the registry is routinely validated by the California Department of Public Health to ensure compliance with data standards established by the National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.⁹² Cases were linked to birth certificates using name, date of birth, and, when available, social security number using a probabilistic linkage program;⁹³ 89% of cases were successfully matched, while the remaining 11% were likely born outside of California.

Due to the unavailability of complete residential addresses in the electronic birth certificate dataset prior to 1998, the present analysis was limited to births from 1998-2016. For the parent cohort, controls were randomly selected from California birth records and frequency matched 20:1 to all childhood cancer cases by birth year. For this analysis, we retained neuroblastoma cases and the full set of controls. Non-agricultural commercial pesticide applications, such as home fumigation or treatments in parks and roadways, can be extensive in urban areas but are reported only at the county level in California. To reduce exposure misclassification resulting from these pesticide recording approaches in urban and rural environments, we limited the study's sample to mothers residing within 4,000 meters of a location where at least one pesticide (including carcinogenic and non-carcinogenic agents) was agriculturally applied on any date within their pregnancy period, assuming they lived at the address listed on the birth record. This restriction is also expected to create a more homogeneous rural study sample concerning other unmeasured social and environmental factors that might confound these associations otherwise.

We excluded children with missing or nonviable birthweight (<500 g; n=153), nonviable gestational age (<20 weeks; n=196), missing sex (n=3), missing exposure data (n=1,556), or missing covariate information (n=39). After applying all exclusions, the final analytic sample included 199 neuroblastoma cases and 202,796 controls.

Pesticide Exposures

Since 1990, the California Department of Pesticide Regulation has mandated documentation of all agricultural pesticide applications through Pesticide Use Reports (PUR). These reports provide detailed information including the amount of each pesticide applied, the date and location of application, and the type of crop treated. Our study's GIS-based Residential Ambient Pesticide Estimation System (GRAPES) maps this PUR data onto the PLSS grid, utilizing land-use information from the California Department of Water Resources (CDWR) to more accurately pinpoint pesticide applications.⁶³ The CDWR has made digitized land-use maps available since 1986, allowing for consistent pesticide exposure assessment across the full study period.⁸⁷

We preselected 213 pesticides classified as possibly or probably carcinogenic by the Environmental Protection Agency.⁵¹ Of these, 192 were listed in the PUR data during the study period, and risk estimates are generated for 68 pesticides with at least five exposed neuroblastoma cases. This threshold was applied to avoid unstable estimates and wide confidence intervals arising from sparse data.

Using the maternal residential address listed on the birth certificate, exposure was assessed for any time during pregnancy within a 4,000-meter buffer surrounding the home. This buffer distance is supported by validation studies demonstrating strong correlations between pesticide applications reported in the PUR and measured air concentrations up to 8,000 meters from application sites.⁹⁴⁻⁹⁶ The timing of pregnancy was estimated using the date of the last menstrual period and date of birth to determine whether each mother was likely exposed to a specific pesticide during gestation. To account for both proximity to pesticide application and the intensity of use, we applied a uniform distance decay model. This approach is supported for some of the agents investigated by both experimental research demonstrating an exponential-like

decay in pesticide exposure with distance,⁹⁷ and our group's previous findings showing that associations with childhood cancers were attenuated when using a larger buffer.⁵⁹ For each pesticide, mothers were assigned an exposure score of 0 if there was no reported pesticide use within 4,000 meters of the residence. Those with exposure levels at or below the median within 4,000 meters were assigned a score of 1. Mothers with exposure levels above the median between 2,000 and 4,000 meters were assigned a score of 2. Those with exposure above the median within 2,000 meters of the residence were assigned a score of 3. Median pesticide exposure levels (in pounds) among controls are provided in Supplemental Table 2-1.

Statistical Analysis

Following the analytical approach suggested by Momoli et al, we used unconditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each selected individual pesticide, as well as pesticide class, and neuroblastoma.⁹⁸ All models were adjusted for the matching variable, birth year, as well as maternal age, area-level socioeconomic status (SES), and maternal ethnicity (Hispanic vs. non-Hispanic), based on previous literature.^{16,99,100} Area-level SES was assessed using an index developed by Yost et al., which combines seven census-level indicators—educational attainment, median household income, the percentage of individuals living at or below 200% of the federal poverty line, the proportion of blue-collar workers, the percentage of unemployed individuals over age 16, and median rent and home values—into a composite variable categorized into five levels.¹⁰¹

We also conducted a series of sensitivity analyses. To account for individual-level SES, we additionally adjusted for maternal education. However, because this variable was missing for a subset of participants and had a minimal impact on effect estimates, it was not included in the

final models (see Supplemental Table 2-2). Similarly, we considered maternal smoking. Because smoking information was only recorded on birth certificates beginning in 2007, we imputed this variable for earlier births using a predictive model.¹⁰² However, as including maternal smoking had a minimal effect on estimates and the variable was imputed for a large portion of the population, it was excluded from the final models (see Supplemental Table 2-3). To account for potential changes in pesticide use patterns over time, we also stratified analyses by two birth year periods (see Supplemental Table 2-4). We first estimated associations using single-pesticide models, which evaluated each pesticide individually without adjusting for co-exposures to other pesticides. These models were run using both a continuous distance decay exposure variable—which represents increasing exposure as a combination of pounds applied and distance from applications—and a categorical variable comparing the highest exposure level (above the median within a 2,000-meter buffer) to no exposure.

To co-adjust for the other pesticides and control for multiple comparisons, we employed a semi-Bayesian hierarchical logistic regression model, incorporating a second-stage variance of 0.5. This variance represents a 16-fold uncertainty around the prior effect estimates. The hierarchical model assumes that effect estimates for each pesticide follow separate normal distributions grouped by chemical class, with each class having its own mean effect. This modeling framework allows the individual pesticide estimates to be "shrunk" toward their class-specific group mean, generating posterior estimates that account for both within-class similarity and between-pesticide variability.^{103,104}

Pesticides were grouped into classes defined by the Pesticide Action Network (PAN) database: 2,6-dinitroaniline, aldehyde, alkyl phthalate, amide, anilide, azole, benzimidazole, benzimidazole precursor, chloroacetanilide, dicarboximide, diphenyl ether, dithiocarbonate, halogenated

organic, inorganic zinc, keto-enol, n-methyl carbamate, organophosphorus, oxazole, pyrazole, pyrethroid, pyrimidine, strobil, substituted benzene, tetrazine, thiophthalimide, triazine, triazolopyrimidine, or urea.¹⁰⁵ Class-level analyses included all carcinogenic pesticides within each class, even when the number of neuroblastoma-exposed cases for some individual pesticides was fewer than five, and thus not evaluated in single-pesticide models (see Supplemental Table 2-5).

All statistical analyses were conducted using R Studio version 4.4.1 and SAS version 9.4.

2.4 Results

Demographic characteristics of neuroblastoma cases and controls are presented in Table 2-1. Compared to control mothers, mothers of cases were slightly older, less likely to be Hispanic, more likely to reside in higher SES neighborhoods, and had, on average, more years of education.

Supplemental Figure 2-1 displays correlations between all pesticides with at least five exposed cases within the 4,000-meter buffer. Among all pesticides analyzed, propyzamide showed the highest correlation with other compounds, including chlorthal dimethyl and dicloran.

Associations between neuroblastoma and pesticide classes are shown in Table 2-2. We did not observe associations between neuroblastoma and a specific pesticide class.

Table 2-3 presents odds ratios and 95% confidence intervals for both single-pesticide logistic regression models and hierarchical logistic regression models adjusted for other pesticides using a pesticide class effect. In the single-pesticide models, we observed elevated risks of neuroblastoma with prenatal exposure to carbaryl (aOR: 1.19; 95% CI: 1.00-1.42), and flonicamid (aOR: 1.19; 95% CI: 1.00-1.43). Additionally, we observed elevated point estimates

with prenatal exposure to cypermethrin (aOR: 1.17; 95% CI: 0.99-1.39), dimethoate (aOR: 1.12; 95% CI: 0.96-1.32), malathion (aOR: 1.124; 95% CI: 0.99-1.32), metolachlor (aOR: 1.26; 95% CI: 0.98-1.62), permethrin (aOR: 1.12; 95% CI: 0.96-1.30), and prodiamine (aOR: 1.17; 95% CI: 0.96-1.44). In the hierarchical models, a positive association with flonicamid (aOR: 1.33; 95% CI: 1.02-1.73) persisted and a negative association with iprodione (aOR: 0.78; 95% CI: 0.61-0.98) emerged. We also observed elevated point estimates for exposure to benomyl (aOR: 1.53; 95% CI: 0.98-2.38), cypermethrin (aOR: 1.24; 95% CI: 0.96-1.60), and permethrin (aOR: 1.20; 95% CI: 0.96-1.50), but the confidence intervals crossed the null.

Table 2-4 shows results from categorical models comparing the highest exposure level (above the median within a 2,000-meter buffer) to no exposure. These results mirrored the continuous score models, with increased neuroblastoma risk observed for flonicamid (aOR: 2.41; 95% CI: 1.21-4.83) and decreased risk for iprodione (aOR: 0.51; 95% CI: 0.27-0.98).

Supplemental Table 2-2 shows the results of a sensitivity analysis adjusting for maternal education. Associations remained consistent in both direction and magnitude. Notably, the associations with flonicamid and iprodione remained robust, and elevated estimates for permethrin, and cypermethrin persisted with confidence intervals overlapping the main analysis.

Sensitivity analyses adjusting for maternal smoking (Supplemental Table 2-3) yielded results consistent with the main analysis, with only minor differences and complete overlap of confidence intervals.

The results of the analyses stratified by birth year period are shown in Supplemental Table 2-4. All pesticides displayed in the table (those with ≥ 5 exposed cases in both time periods) had overlapping confidence intervals for single-pesticide and hierarchical models.

2.5 Discussion

In this rural population-based case-control study, we found evidence that prenatal ambient exposure to certain pesticides may increase the risk of neuroblastoma. These findings are particularly relevant in California, which is a leading agricultural state and applies a considerable amount and variety of pesticides each year.^{87,106} Many of these applications occur near homes, schools, and other populated areas, raising concerns about non-occupational exposure pathways such as via pesticide drift and volatilization.¹⁰⁷⁻¹⁰⁹ Among the pesticides evaluated, flonicamid was most consistently associated with elevated neuroblastoma risk, supported by both single-pesticide and hierarchical models. In hierarchical models, we also observed elevated point estimates for benomyl, permethrin, and cypermethrin, and an inverse association for iprodione. These findings add to a small but growing body of literature examining the potential link between pesticide exposure and neuroblastoma. Most previous studies have focused on parental occupational exposures, relying on proxy measures such as job title, industry classification, or retrospective parental interviews to estimate exposure. While several of these studies have reported elevated risks associated with maternal⁶⁶ or paternal⁷¹ employment in agriculture or landscaping, findings have been inconsistent, and exposure misclassification remains a concern due to the reliance on indirect or self-reported data.⁷⁴

Most prior studies relied on parental recall with the possibility for recall bias or on proxy measures of pesticide use, and only two have evaluated ambient residential exposure to agricultural pesticides, yielding mixed results.^{75,76} Neither of these studies accounted for the type, timing, or amount of pesticide applications, limiting their ability to detect associations with specific pesticides. By leveraging California's comprehensive Pesticide Use Reporting system and a validated GIS-based exposure model, our study provides exposure estimates for more

specific agents not available in prior research and contributes novel evidence for associations between prenatal exposure to specific pesticides and neuroblastoma risk.

Flonicamid, a systemic insecticide, was most consistently associated with increased neuroblastoma risk in our study across different models. In the categorical exposure model, the elevated risk was primarily driven by the highest exposure level, suggesting that closer proximity to application sites may be associated with a stronger effect. Flonicamid is a chordotonal organ nicotinamide inhibitor and functions by disrupting the activity of chordotonal stretch receptor organs—structures critical for sensory processes including hearing, balance, and proprioception—ultimately interfering with feeding behavior in insects.¹¹⁰ Based on increases in lung tumors in mice, the EPA classified the agent as having suggestive evidence of carcinogenicity, but not sufficient evidence to assess human carcinogenic potential. In developmental toxicity studies, adverse effects in offspring were observed only at maternally toxic doses, leading the EPA to conclude that flonicamid does not raise developmental toxicity concerns.¹¹¹ To our knowledge, no previous epidemiologic studies have examined flonicamid in relation to human cancer risk.

Benomyl, a broad-spectrum benzimidazole fungicide, was positively associated with neuroblastoma in our study. Although benomyl is no longer registered for use in the United States, it was widely applied until 2001. Benomyl inhibits fungal growth by disrupting tubulin polymerization, interfering with mitotic spindle formation. In mammals, it induces neurotoxicity by inhibiting aldehyde dehydrogenase, causing accumulation of 3,4-dihydroxyphenylacetaldehyde, a metabolite toxic to dopaminergic neurons. Additionally, benomyl has been shown to induce oxidative stress, similar to mechanisms observed with other neurotoxic pesticides such as cypermethrin.¹¹² The EPA classified benomyl, along with its

primary metabolite carbendazim, as a possible human carcinogen (Group C) based on increased liver tumors in mice.¹¹³ Developmental and reproductive toxicity associated with gestational benomyl exposure have also been reported. In rodent models, maternal exposure was found to lead to testicular toxicity and infertility in male offspring, as well as fetal abnormalities including brain and ocular malformations, reduced birthweight, and disrupted neural development.¹¹³⁻¹¹⁶ To our knowledge, no previous studies have investigated associations between benomyl and cancer in humans.

Cypermethrin and permethrin, both synthetic pyrethroid insecticides, showed suggestive positive associations with neuroblastoma in our study. They are classified as sodium channel modulators and their mechanism of action involves disrupting the sodium channels in the nerve axons of insects, leading to neurotoxicity and paralysis.^{110,117} The EPA has classified cypermethrin as a possible human carcinogen (Group C) based on an increase in benign lung tumors in female mice.¹¹⁸ Permethrin was classified as a probable human carcinogen (Group B2) by the EPA based on reproducible lung and liver tumor in mice and rat studies.¹¹⁹ Both cypermethrin and permethrin were recommended to the International Agency for Research on Cancer (IARC) for review in their Monographs program.¹²⁰ Prenatal exposure to permethrin in rodents has been associated with neurodevelopmental effects, including altered neurotransmitter levels and cognitive impairment.¹²¹ Elevated risks of childhood leukemia and astrocytoma have been observed in relation to pyrethroid exposure, including urinary metabolites of cypermethrin and permethrin, though some estimates were imprecise.^{59,62,122}

In single-pesticide models, carbaryl was positively associated with neuroblastoma, while malathion, and metolachlor showed elevated point estimates with confidence intervals crossing the null; these associations were attenuated in hierarchical models accounting for co-exposures.

Carbaryl, an N-methyl carbamate insecticide and likely human carcinogen per the EPA, inhibits acetylcholinesterase and has been linked to fetal skeletal abnormalities and reduced birthweight.¹²³ Malathion, a Group 2A carcinogen per IARC, has been associated with non-Hodgkin lymphoma, prostate cancer, and reduced cognitive development;^{124,125} our prior study also linked it to increased childhood ALL risk in single-pesticide models.⁵⁹ Metolachlor, classified by the EPA as a possible human carcinogen (Group C), has been linked to liver tumors in rodents and liver and lung cancers in the Agricultural Health Study.¹²⁶⁻¹²⁹ Both carbaryl and malathion have also been recommend for evaluation by IARC's Monograph program.¹²⁰ The attenuation of associations in hierarchical models suggests that single-pesticide associations may partly reflect co-exposures.

In contrast, iprodione was consistently associated with a reduced risk of neuroblastoma in our study. This negative association may be due to chance, given the relatively low number of cases in this study. Alternatively, this inverse association may reflect live birth bias, which arises when prenatal exposures that increase the risk of fetal loss selectively remove the most susceptible fetuses from the population under study, potentially underestimating or reversing the true effect among live births.¹³⁰ Animal studies of iprodione have identified reproductive and developmental toxicity, including decreased pup viability and reductions in the average number of offspring.¹³¹

While we did not observe significant associations at the pesticide class level, the associations with specific compounds highlight the potential limitations of grouping pesticides by class alone. Pesticides within the same chemical class may differ substantially in their toxicity profiles, use patterns, or environmental persistence. Our findings highlight the importance of evaluating

individual pesticides rather than relying on aggregated class-level data or treating pesticides as a uniform exposure group.

A major strength of this study is the use of a validated GIS-based pesticide exposure model that links California's PUR data with land-use maps to estimate prenatal residential exposure to specific pesticide compounds. This approach offers spatially refined exposure estimates and avoids recall bias inherent in studies relying on parental self-report or occupational classification.⁶⁴ Additionally, this study employed both single-pesticide logistic regression models and a semi-Bayesian hierarchical modeling approach to account for potential co-exposures. While hierarchical models improve precision and address multiple comparisons, they rely on the assumption that pesticides within the same class have similar effects on neuroblastoma risk, which may not be true.

There are several additional limitations. First, pesticide exposure was assigned based on maternal residential address listed on the birth certificate. While this method captures key exposure windows during pregnancy, it assumes that the residential address was the same throughout the pregnancy.¹³² Second, we were unable to account for pesticide exposure through parental occupation, diet, or residential use, which may result in underestimation of total pesticide exposure. Similarly, we were unable to adjust for maternal alcohol consumption; however, alcohol use is not an established risk factor for neuroblastoma, and meta-analyses have reported inconsistent findings.^{133,134} Finally, while individuals are likely exposed to multiple pesticides simultaneously, we were not able to evaluate the effects of exposure to pesticide mixtures. Despite these limitations, our study provides novel insights into the relationship between prenatal exposure to specific pesticide compounds and neuroblastoma risk, and underscores the importance of high-resolution, pesticide-specific exposure modeling.

In conclusion, our results suggest that prenatal exposure to specific pesticides—including flonicamid, benomyl, permethrin, and cypermethrin—may be associated with increased risk of neuroblastoma. To our knowledge, this is the first study to estimate effects for specific pesticides in relation to neuroblastoma. These findings underscore the importance of evaluating individual pesticide exposures in childhood cancer studies and support the need for policy interventions to reduce pesticide exposure in individuals residing near agricultural sites.

2.6 Tables and figures

Table 2-1. Demographic characteristics of analytical population (N = 202,995)

Characteristics	Neuroblastoma Cases (N=199)	Controls (N=202,796)	Overall (N=202,995)
Child's sex (n, %)			
Female	99 (49.7)	99,531 (49.1)	99,630 (49.1)
Male	100 (50.3)	103,265 (50.9)	103,365 (50.9)
Maternal age (mean, SD)	29.15 (6.16)	27.97 (6.30)	27.97 (6.30)
Maternal race/ethnicity (n, %)			
Hispanic	74 (37.2)	105,474 (52.0)	105,474 (52.0)
Other	49 (24.6)	39,373 (19.4)	39,422 (19.4)
White non-Hispanic	76 (38.2)	57,949 (28.6)	58,025 (28.6)
Neighborhood socioeconomic status¹⁰¹			
Quintile 1 (low)	44 (22.1)	57,131 (28.2)	57,175 (28.2)
Quintile 2	46 (23.1)	47,858 (23.6)	47,904 (23.6)
Quintile 3	36 (18.1)	38,486 (19.0)	38,522 (19.0)
Quintile 4	40 (20.1)	32,353 (16.0)	32,393 (16.0)
Quintile 5 (high)	33 (16.6)	26,968 (13.3)	27,001 (13.3)
Maternal educational attainment			
8 or less years	12 (6.0)	20,735 (10.2)	20,747 (10.2)
9-11 years	26 (13.1)	34,904 (17.2)	34,930 (17.2)
12 years	50 (25.1)	54,784 (27.0)	54,834 (27.0)
13-15 years	38 (19.1)	42,865 (21.1)	43,903 (21.1)
16 or more years	67 (33.7)	46,568 (23.0)	46,635 (23.0)
Missing	6 (3.0)	2,940 (1.4)	2,946 (1.5)

Table 2-2. Associations between neuroblastoma and exposure to agricultural pesticide applications within 4000m of the residential address, using a distance decay model, by pesticide class (N = 202,995)

Pesticide Class	Exposed Cases N = 199	Exposed Controls N = 202,796	aOR ^a (95% CI)	aOR ^b (95% CI)
2,6-Dinitroaniline	120 (60.3)	121,151 (59.7)	1.01 (0.76, 1.34)	1.05 (0.79, 1.40)
Aldehyde	57 (28.6)	62,956 (31.0)	1.13 (0.83, 1.54)	1.13 (0.83, 1.54)
Alkyl phthalate	20 (10.1)	21,038 (10.4)	0.95 (0.60, 1.50)	1.05 (0.66, 1.68)
Amide	17 (8.5)	18,801 (9.3)	0.79 (0.60, 1.04)	0.82 (0.62, 1.08)
Anilide	87 (43.7)	42,256 (20.8)	1.05 (0.78, 1.40)	1.06 (0.79, 1.43)
Azole	119 (59.8)	102,293 (50.4)	1.17 (0.88, 1.56)	1.19 (0.89, 1.59)
Benzimidazole	13 (6.5)	31,201 (15.4)	1.85 (1.02, 3.35)	1.42 (0.75, 2.68)
Benzimidazole precursor	89 (44.7)	92,445 (45.6)	1.05 (0.79, 1.39)	1.11 (0.84, 1.48)
Chloroacetanilide	35 (17.6)	32,220 (15.9)	1.00 (0.70, 1.45)	1.02 (0.71, 1.48)
Chlorophenoxy acid	5 (2.5)	2,802 (1.4)	0.86 (0.35, 2.10)	0.89 (0.36, 2.16)
Dicarboximide	71 (35.7)	99,283 (49.0)	0.79 (0.59, 1.05)	0.79 (0.59, 1.06)
Diphenyl ether	78 (39.2)	84,850 (41.8)	0.90 (0.68, 1.19)	0.92 (0.69, 1.23)
Dithiocarbamate	81 (40.7)	97,530 (48.1)	0.91 (0.69, 1.21)	0.95 (0.71, 1.27)
Ester	5 (2.5)	2,802 (1.4)	0.86 (0.35, 2.10)	0.89 (0.36, 2.16)
Halogenate organic	34 (17.1)	29,632 (14.6)	0.90 (0.62, 1.30)	0.97 (0.67, 1.41)
Keto-enol	17 (8.5)	6,495 (3.2)	1.05 (0.64, 1.74)	1.11 (0.67, 1.85)
N-methyl carbamate	58 (29.1)	63,389 (31.3)	1.16 (0.85, 1.57)	1.15 (0.84, 1.57)
Organochlorine	13 (6.5)	35,246 (17.4)	1.20 (0.67, 2.16)	1.10 (0.60, 2.02)
Organophosphorus	124 (62.3)	156,146 (77.0)	0.78 (0.59, 1.05)	0.86 (0.64, 1.16)
Other carbamate	8 (4.0)	17,030 (8.4)	1.17 (0.57, 2.41)	1.27 (0.61, 2.65)
Oxazole	41 (20.6)	32,610 (16.1)	0.91 (0.65, 1.29)	0.91 (0.64, 1.28)
Pyrazole	27 (13.6)	13,194 (6.5)	0.79 (0.52, 1.20)	0.81 (0.53, 1.24)
Pyrazolylphenyl	25 (12.6)	8,657 (4.3)	0.95 (0.62, 1.46)	0.92 (0.59, 1.42)
Pyrethroid	108 (54.3)	118,553 (58.5)	0.78 (0.59, 1.03)	0.84 (0.64, 1.12)
Pyridazinone	11 (5.5)	20,485 (10.1)	0.89 (0.48, 1.64)	0.93 (0.50, 1.74)
Pyrimidine	26 (13.1)	13,867 (6.8)	0.85 (0.56, 1.28)	0.91 (0.60, 1.39)
Salt	5 (2.5)	2,802 (1.4)	0.86 (0.35, 2.10)	0.89 (0.36, 2.16)
Strobin	21 (10.6)	14,505 (7.2)	0.87 (0.55, 1.36)	0.91 (0.58, 1.45)
Substituted benzene	96 (48.2)	103,831 (51.2)	0.95 (0.72, 1.25)	0.94 (0.71, 1.25)
Sulfonylurea	18 (9.0)	6,028 (3.0)	1.06 (0.65, 1.74)	0.99 (0.60, 1.63)
Tetrazine	11 (5.5)	11,927 (5.9)	0.88 (0.48, 1.62)	0.93 (0.50, 1.72)
Thiophthalimide	40 (20.1)	59,160 (29.2)	0.93 (0.66, 1.32)	0.98 (0.69, 1.40)
Triazine	30 (15.1)	33,879 (16.7)	0.81 (0.55, 1.19)	0.91 (0.61, 1.34)
Triazolopyrimidine	17 (8.5)	3,910 (1.9)	1.31 (0.79, 2.17)	1.22 (0.73, 2.04)
Unclassified	105 (52.8)	118,009 (58.2)	0.84 (0.64, 1.11)	0.91 (0.68, 1.20)

Urea	42 (21.1)	56,135 (27.7)	0.76 (0.54, 1.07)	0.80 (0.56, 1.13)
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^a Adjusted for matching variable, birth year.

^b Adjusted for birth year, SES-index variable, maternal age, and mother's race/ethnicity.

Table 2-3. Associations between neuroblastoma and exposure to agricultural pesticide applications within 4000m of the residential address, using a distance decay model (N = 202,995)

Pesticide Class	Pesticide	Exposed Cases N = 199	Exposed Controls N = 202,796	Single-pesticide model ^a	HLM OR (95% CI) ^b
2,6-Dinitroaniline	Oryzalin	74 (37.2)	76,962 (38.0)	1.04 (0.90, 1.20)	1.06 (0.86, 1.31)
2,6-Dinitroaniline	Pendimethalin	74 (37.2)	63,560 (31.4)	1.03 (0.89, 1.19)	0.95 (0.76, 1.20)
2,6-Dinitroaniline	Prodiamine	27 (13.6)	26,581 (13.1)	1.17 (0.96, 1.44)	1.11 (0.85, 1.46)
2,6-Dinitroaniline	Trifluralin	49 (24.6)	57,006 (28.1)	1.09 (0.92, 1.28)	1.07 (0.85, 1.33)
Aldehyde	Metaldehyde	57 (28.6)	62,949 (31.0)	1.25 (0.99, 1.57)	1.17 (0.93, 1.48)
Alkyl phthalate	Chlorthal dimethyl	20 (10.1)	21,030 (10.4)	1.07 (0.85, 1.35)	1.09 (0.77, 1.54)
Amide	Cyflufenamid	11 (5.5)	2,561 (1.3)	0.95 (0.68, 1.31)	0.95 (0.64, 1.42)
Amide	Propyzamide (Pronamide)	9 (4.5)	16,856 (8.3)	0.84 (0.59, 1.21)	0.73 (0.44, 1.19)
Anilide	Boscalid	85 (42.7)	40,029 (19.7)	0.98 (0.84, 1.15)	1.01 (0.76, 1.34)
Anilide	Propanil	6 (3.0)	3,657 (1.8)	1.28 (0.88, 1.85)	1.32 (0.78, 2.24)
Azole	Difenoconazole	36 (18.1)	7,718 (3.8)	1.09 (0.91, 1.32)	1.13 (0.86, 1.49)
Azole	Fenbuconazole	13 (6.5)	7,183 (3.5)	1.17 (0.88, 1.55)	1.23 (0.86, 1.77)
Azole	Propiconazole	81 (40.7)	68,698 (33.9)	1.06 (0.92, 1.23)	1.03 (0.82, 1.29)
Azole	Tebuconazole	42 (21.1)	29,347 (14.5)	0.97 (0.80, 1.17)	0.90 (0.67, 1.20)
Azole	Terrazole	7 (3.5)	5,193 (2.6)	0.90 (0.62, 1.30)	0.88 (0.59, 1.33)
Azole	Triadimefon	25 (12.6)	39,583 (19.5)	0.97 (0.78, 1.22)	0.88 (0.66, 1.19)
Azole	Uniconazole-P	17 (8.5)	13,733 (6.8)	1.05 (0.79, 1.40)	0.92 (0.62, 1.38)
Benzimidazole	Benomyl	10 (5.0)	29,452 (14.5)	1.43 (0.95, 2.15)	1.53 (0.98, 2.38)
Benzimidazole precursor	Thiophanate methyl	89 (44.7)	92,432 (45.6)	1.08 (0.94, 1.25)	1.12 (0.91, 1.37)
Chloroacetanilide	Alachlor	8 (4.0)	6,984 (3.4)	1.30 (0.93, 1.83)	1.29 (0.85, 1.95)
Chloroacetanilide	Metolachlor	17 (8.5)	10,213 (5.0)	1.26 (0.98, 1.62)	1.16 (0.85, 1.58)
Chloroacetanilide	S-Metolachlor	28 (14.1)	19,910 (9.8)	1.06 (0.87, 1.30)	0.97 (0.73, 1.28)
Dicarboximide	Iprodione	71 (35.7)	97,805 (48.2)	0.91 (0.78, 1.06)	0.78 (0.61, 0.98)
Dicarboximide	Vinclozolin	5 (2.5)	17,250 (8.5)	1.12 (0.68, 1.85)	1.12 (0.64, 1.95)
Diphenyl ether	Oxyfluorfen	78 (39.2)	84,830 (41.8)	1.03 (0.89, 1.18)	0.95 (0.73, 1.25)
Dithiocarbamate	Mancozeb	67 (33.7)	76,607 (37.8)	1.06 (0.91, 1.22)	1.06 (0.87, 1.31)
Dithiocarbamate	Maneb	9 (4.5)	29,660 (14.6)	0.85 (0.58, 1.24)	0.73 (0.46, 1.15)
Dithiocarbamate	Meta sodium	19 (9.5)	25,482 (12.6)	1.10 (0.94, 1.29)	1.25 (0.93, 1.68)

Dithiocarbamate	Ziram	21 (10.6)	20,595 (10.2)	0.99 (0.77, 1.28)	0.99 (0.69, 1.42)
Halogenated organic	1,3-Dichloropropene	34 (17.1)	29,630 (14.6)	1.03 (0.86, 1.24)	1.08 (0.83, 1.41)
Keto-enol	Spirodiclofen	17 (8.5)	6,495 (3.2)	1.03 (0.79, 1.34)	1.00 (0.72, 1.39)
N-Methyl carbamate	Carbaryl	57 (28.6)	62,204 (30.7)	1.19 (1.00, 1.42)	1.16 (0.94, 1.42)
Organochlorine	Dicofol	11 (5.5)	33,387 (16.5)	1.10 (0.79, 1.53)	1.03 (0.71, 1.47)
Organophosphorus	Acephate	90 (45.2)	110,239 (54.4)	0.98 (0.85, 1.13)	0.91 (0.74, 1.12)
Organophosphorus	Dimethoate	47 (23.6)	59,728 (29.5)	1.12 (0.96, 1.32)	1.04 (0.82, 1.32)
Organophosphorus	Malathion	85 (42.7)	105,243 (51.9)	1.14 (0.99, 1.32)	1.10 (0.91, 1.32)
Organophosphorus	Methidathion	5 (2.5)	12,139 (6.0)	1.17 (0.75, 1.81)	1.33 (0.81, 2.16)
Organophosphorus	Phosmet	17 (8.5)	27,020 (13.3)	1.09 (0.84, 1.43)	1.01 (0.71, 1.44)
Other carbamate	Fenoxycarb	8 (4.0)	17,027 (8.4)	1.30 (0.93, 1.80)	1.32 (0.85, 2.06)
Oxazole	Isoxaben	41 (20.6)	32,610 (16.1)	1.04 (0.88, 1.23)	1.04 (0.83, 1.31)
Pyrazole	Chlorfenapyr	12 (6.0)	9,728 (4.8)	0.91 (0.68, 1.21)	0.88 (0.62, 1.26)
Pyrazole	Penthiopyrad	19 (9.5)	3,544 (1.7)	0.94 (0.71, 1.24)	0.89 (0.62, 1.28)
Pyrazolylphenyl	Pyraflufen-ethyl	25 (12.6)	8,656 (4.3)	0.99 (0.80, 1.22)	0.89 (0.65, 1.22)
Pyrethroid	Bifenthrin	89 (44.7)	89,715 (44.2)	1.02 (0.89, 1.18)	0.90 (0.74, 1.11)
Pyrethroid	Cypermethrin	41 (20.6)	22,632 (11.2)	1.17 (0.99, 1.39)	1.24 (0.96, 1.60)
Pyrethroid	Permethrin	73 (36.7)	79,395 (39.2)	1.12 (0.96, 1.30)	1.20 (0.96, 1.50)
Pyridazinone	Norflurazon	11 (5.5)	20,485 (10.1)	1.02 (0.73, 1.42)	0.92 (0.61, 1.38)
Pyrimidine	Pyrimethanil	26 (13.1)	13,865 (6.8)	0.98 (0.79, 1.22)	0.94 (0.68, 1.29)
Strobin	Kresoxim-methyl	21 (10.6)	14,505 (7.2)	0.95 (0.75, 1.20)	0.89 (0.64, 1.23)
Substituted benzene	Chlorothalonil	95 (47.7)	99,576 (49.1)	1.01 (0.88, 1.17)	0.84 (0.68, 1.05)
Substituted benzene	Dicloran	14 (7.0)	18,680 (9.2)	1.13 (0.88, 1.44)	1.15 (0.79, 1.69)
Substituted benzene	PCNB (Pentachloronitrobenzene)	13 (6.5)	21,058 (10.4)	1.18 (0.87, 1.59)	1.08 (0.73, 1.60)
Sulfonylurea	Tribenuron methyl	15 (7.5)	3,882 (1.9)	0.94 (0.70, 1.25)	0.85 (0.60, 1.19)
Tetrazine	Clofentezine	11 (5.5)	11,925 (5.9)	1.01 (0.74, 1.39)	1.03 (0.70, 1.51)
Thiophthalimide	Captan	40 (20.1)	59,141 (29.2)	1.00 (0.83, 1.20)	0.83 (0.63, 1.11)
Triazine	Pymetrozine	29 (14.6)	31,883 (15.7)	1.00 (0.82, 1.22)	0.94 (0.70, 1.26)
Triazolopyrimidine	Penoxsulam	17 (8.5)	3,910 (1.9)	1.21 (0.95, 1.53)	1.24 (0.89, 1.73)
Unclassified	Buprofezin	26 (13.1)	15,180 (7.5)	0.98 (0.80, 1.21)	1.06 (0.80, 1.41)
Unclassified	Flonicamid	29 (14.6)	10,013 (4.9)	1.19 (1.00, 1.43)	1.33 (1.02, 1.73)
Unclassified	Hexythiazox	55 (27.6)	53,221 (26.2)	1.00 (0.86, 1.16)	0.95 (0.76, 1.18)
Unclassified	Hydramethylnon	12 (6.0)	16,968 (8.4)	0.99 (0.72, 1.35)	0.79 (0.52, 1.21)
Unclassified	Metrafenone	9 (4.5)	2,088 (1.0)	1.00 (0.72, 1.39)	1.04 (0.67, 1.62)
Unclassified	Oxadiazon	18 (9.0)	32,556 (16.1)	0.91 (0.69, 1.19)	0.85 (0.61, 1.18)

Unclassified	Oxythioquinox	5 (2.5)	11,804 (5.8)	1.43 (0.86, 2.39)	1.32 (0.78, 2.24)
Unclassified	Piperonyl butoxide	25 (12.6)	35,205 (17.4)	0.98 (0.79, 1.21)	0.88 (0.65, 1.19)
Unclassified	Propargite	19 (9.5)	27,964 (13.8)	1.07 (0.84, 1.36)	1.00 (0.72, 1.39)
Urea	Diuron	33 (16.6)	48,002 (23.7)	1.00 (0.83, 1.20)	0.90 (0.70, 1.16)
Urea	Linuron	10 (5.0)	15,667 (7.7)	0.89 (0.67, 1.19)	0.71 (0.47, 1.07)

^a Adjusted for birth year, SES-index variable, maternal age, and mother's race/ethnicity.

^b Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, and other pesticides, using a pesticide class effect in the hierarchical model.

Table 2-4. Associations between neuroblastoma and exposure to agricultural pesticide applications above the median (lbs) within 2000m of the residential address (N = 202,995)

Pesticide Class	Name	Exposed Cases N = 199	Exposed Controls N = 202,796	Single-pesticide model ^a	HLM OR (95% CI) ^b
2,6-Dinitroaniline	Prodiamine	6 (3.0)	2,585 (1.3)	1.30 (0.57, 2.97)	1.27 (0.57, 2.81)
2,6-Dinitroaniline	Trifluralin	17 (8.5)	4,549 (2.2)	1.34 (0.79, 2.28)	1.09 (0.58, 2.04)
2,6-Dinitroaniline	Oryzalin	21 (10.6)	1,272 (0.6)	1.01 (0.61, 1.66)	0.99 (0.54, 1.82)
2,6-Dinitroaniline	Pendimethalin	31 (15.6)	7,146 (3.5)	1.10 (0.70, 1.72)	0.92 (0.49, 1.70)
Aldehyde	Metalddehyde	14 (7.0)	1,902 (0.9)	1.15 (0.65, 2.03)	1.27 (0.66, 2.42)
Alkyl Phthalate	Chlorthal dimethyl	5 (2.5)	2,286 (1.1)	0.97 (0.39, 2.40)	0.96 (0.39, 2.34)
Anilide	Boscalid	20 (10.1)	3,082 (1.5)	0.93 (0.55, 1.59)	1.04 (0.49, 2.17)
Azole	Tebuconazole	7 (3.5)	756 (0.4)	0.68 (0.31, 1.49)	0.70 (0.31, 1.56)
Azole	Difenoconazole	13 (6.5)	1,970 (1.0)	1.39 (0.76, 2.55)	1.55 (0.75, 3.20)
Azole	Propiconazole	24 (12.1)	590 (0.3)	1.06 (0.65, 1.71)	1.14 (0.60, 2.17)
Benzimidazole precursor	Thiophanate methyl	22 (11.1)	6,043 (3.0)	1.04 (0.63, 1.70)	1.12 (0.62, 2.01)
Chloroacetanilide	S-Metolachlor	8 (4.0)	5,137 (2.5)	1.17 (0.57, 2.43)	0.90 (0.41, 1.99)
Dicarboximide	Iprodione	19 (9.5)	1,003 (0.5)	0.68 (0.41, 1.15)	0.51 (0.27, 0.98)
Diphenyl ether	Oxyfluorfen	37 (18.6)	2,358 (1.2)	1.09 (0.72, 1.67)	0.94 (0.48, 1.86)
Dithiocarbamate	Metam sodium	7 (3.5)	8,929 (4.4)	2.23 (1.02, 4.84)	1.47 (0.66, 3.28)
Dithiocarbamate	Mancozeb	23 (11.6)	1,927 (1.0)	1.07 (0.66, 1.73)	1.10 (0.61, 1.98)
Halogenated organic	1,3-Dichloropropene	12 (6.0)	35,084 (17.3)	1.13 (0.61, 2.09)	1.27 (0.62, 2.61)
N-Methyl carbamate	Carbaryl	9 (4.5)	13,383 (6.6)	1.25 (0.62, 2.53)	1.07 (0.54, 2.12)
Organophosphorus	Acephate	18 (9.0)	16,231 (8.0)	0.79 (0.46, 1.34)	0.61 (0.33, 1.12)
Organophosphorus	Dimethoate	19 (9.5)	31,273 (15.4)	1.52 (0.91, 2.53)	1.13 (0.60, 2.12)
Organophosphorus	Malathion	32 (16.1)	7,297 (3.6)	1.49 (0.95, 2.32)	1.30 (0.78, 2.16)
Oxazole	Isoxaben	13 (6.5)	6,986 (3.4)	1.18 (0.65, 2.12)	1.62 (0.85, 3.10)
Pyrazolylphenyl	Pyraflufen-ethyl	9 (4.5)	16,450 (8.1)	0.99 (0.49, 2.01)	0.85 (0.38, 1.88)
Pyrethroid	Cypermethrin	17 (8.5)	17,541 (8.7)	1.63 (0.95, 2.80)	1.67 (0.84, 3.33)
Pyrethroid	Permethrin	22 (11.1)	36,286 (17.9)	1.36 (0.83, 2.24)	1.35 (0.72, 2.52)
Pyrethroid	Bifenthrin	31 (15.6)	3,714 (1.8)	0.91 (0.58, 1.45)	0.76 (0.43, 1.36)
Pyrimidine	Pyrimethanil	7 (3.5)	32,706 (16.1)	0.93 (0.43, 2.01)	1.00 (0.45, 2.27)
Substituted Benzene	Dicloran	7 (3.5)	6,112 (3.0)	1.71 (0.79, 3.71)	1.44 (0.59, 3.55)
Substituted Benzene	Chlorothalonil	26 (13.1)	17,904 (8.8)	0.94 (0.58, 1.52)	0.78 (0.42, 1.44)

Thiophthalimide	Captan	8 (4.0)	19,898 (9.8)	0.77 (0.37, 1.60)	0.58 (0.25, 1.34)
Triazine	Pymetrozine	8 (4.0)	1,048 (0.5)	0.92 (0.45, 1.91)	0.94 (0.42, 2.13)
Triazolopyrimidine	Penoxsulam	7 (3.5)	24,448 (12.1)	1.94 (0.88, 4.28)	1.85 (0.81, 4.24)
Unclassified	Piperonyl Butoxide	5 (2.5)	5,612 (2.8)	0.74 (0.30, 1.81)	0.81 (0.34, 1.92)
Unclassified	Propargite	5 (2.5)	9,013 (4.4)	1.05 (0.42, 2.62)	0.73 (0.31, 1.72)
Unclassified	Buprofezin	6 (3.0)	8,621 (4.3)	0.69 (0.30, 1.60)	0.87 (0.39, 1.93)
Unclassified	Flonicamid	17 (8.5)	3,071 (1.5)	1.95 (1.14, 3.34)	2.41 (1.21, 4.83)
Unclassified	Hexythiazox	23 (11.6)	4,249 (2.1)	1.09 (0.68, 1.76)	1.18 (0.64, 2.18)
Urea	Diuron	12 (6.0)	17,657 (8.7)	1.03 (0.56, 1.90)	0.79 (0.41, 1.56)

^a Adjusted for birth year, SES-index variable, maternal age, and mother's race/ethnicity.

^b Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, and other pesticides, using a pesticide class effect in the hierarchical model.

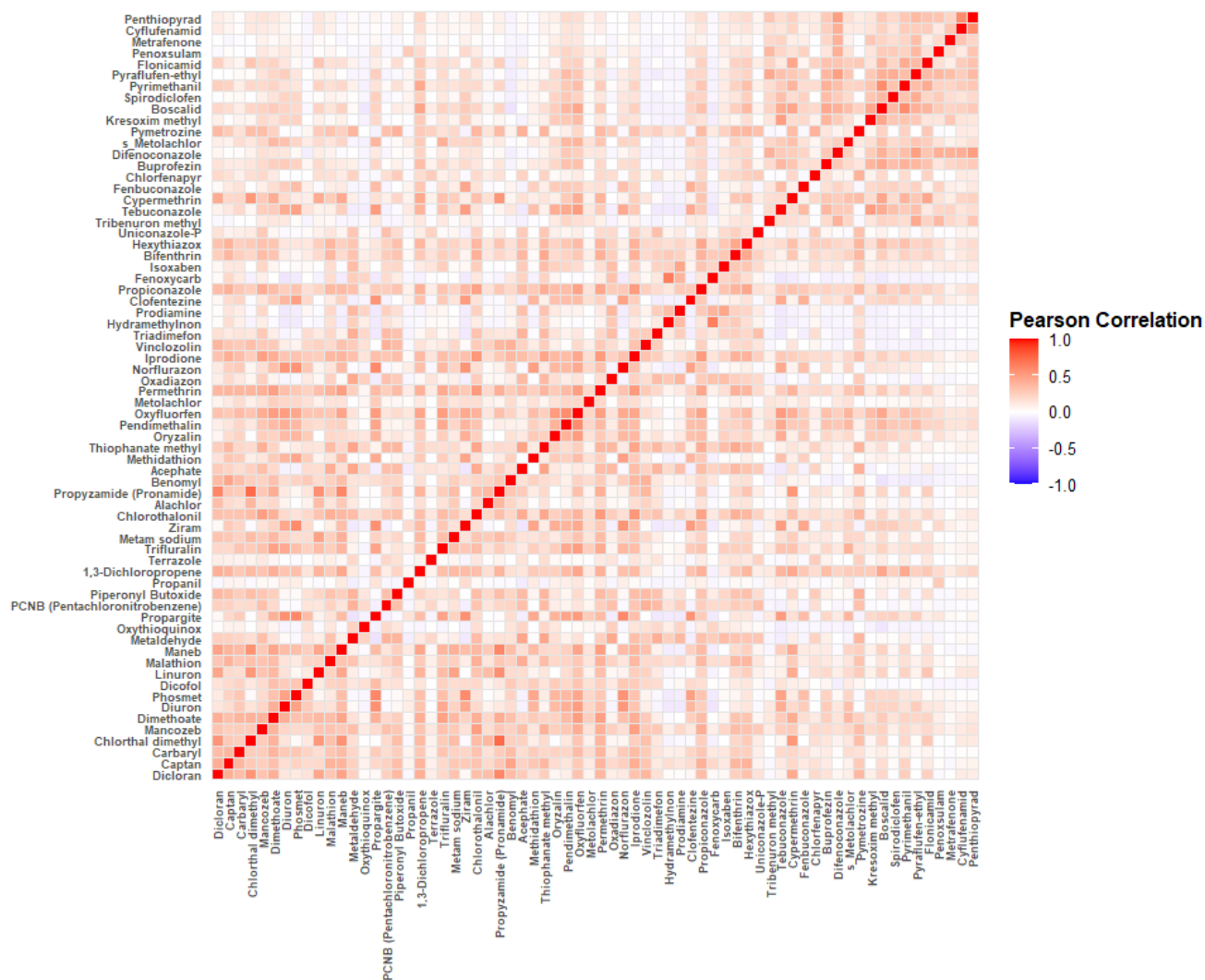


Figure 2-1. Correlations of pesticides (pounds per acre) in 4000m buffer

2.7 Supplemental materials

Supplemental Table 2-1. Median pounds exposed during pregnancy, among controls (lbs)

Pesticide	2000m Buffer	4000m Buffer
1,3-Dichloropropene	950.519	2404.696
Acephate	0.849	1.940
Alachlor	6.613	16.393
Benomyl	1.494	3.736
Bifenthrin	0.110	0.243
Boscalid	3.033	6.552
Buprofezin	1.890	4.725
Captan	12.743	28.678
Carbaryl	1.796	3.663
Chlorfenapyr	0.031	0.077
Chlorothalonil	2.114	4.320
Chlorthal dimethyl	18.103	53.094
Clofentezine	1.388	3.826
Cyflufenamid	0.300	0.828
Cypermethrin	0.591	1.987
Dicloran	13.818	37.948
Dicofol	0.853	1.468
Difenoconazole	1.033	3.067
Dimethoate	3.637	7.894
Diuron	8.352	22.086
Fenbuconazole	0.958	1.958
Fenoxycarb	0.017	0.041
Flonicamid	0.614	1.769
Hexythiazox	0.191	0.317
Hydramethylnon	0.014	0.029
Iprodione	1.341	2.739
Isoxaben	0.308	0.639
Kresoxim-methyl	0.817	1.826
Linuron	4.207	14.333
Malathion	1.863	3.105
Mancozeb	2.178	4.576
Maneb	27.944	66.324
Metaldehyde	0.702	1.696
Metam sodium	649.191	1253.367
Methidathion	15.641	34.725
Metolachlor	7.070	15.261
Metrafenone	2.770	7.438
Norflurazon	7.923	19.656
Oryzalin	1.889	3.750
Oxadiazon	0.425	0.920
Oxyfluorfen	2.421	6.227
Oxythioquinox	0.184	0.363
PCNB (Pentachloronitrobenzene)	0.938	1.437
Pendimethalin	3.296	6.667
Penoxsulam	0.193	0.427
Penthiopyrad	3.743	11.564
Permethrin	0.930	1.606
Phosmet	18.439	40.572
Piperonyl butoxide	0.281	0.573
Prodamine	0.749	1.461
Pronamide	10.350	31.125

Propanil	199.150	459.426
Propargite	34.925	104.373
Propiconazole	0.228	0.406
Pymetrozine	0.157	0.359
Pyraflufen-ethyl	0.030	0.080
Pyrimethanil	4.076	12.282
S-Metolachlor	8.184	18.201
Spirodiclofen	2.843	7.911
Tebuconazole	1.486	3.826
Terrazole	0.025	0.069
Thiophanate methyl	0.703	1.736
Triadimefon	0.060	0.125
Tribenuron methyl	0.230	0.590
Trifluralin	3.000	5.440
Uniconazole-P	0.001	0.001
Vinclozolin	1.163	1.469
Ziram	72.973	159.803

Supplemental Table 2-2. Associations between neuroblastoma and exposure to agricultural pesticide applications within 4000m of the residential address, additionally adjusted for maternal education (N = 202,049)

Pesticide Class	Name	Exposed Cases N = 193	Exposed Controls N = 199,856	Single-pesticide model ^a	HLM OR (95% CI) ^b
2,6-Dinitroaniline	Oryzalin	57	65064	1.06 (0.92, 1.23)	1.08 (0.88, 1.33)
2,6-Dinitroaniline	Pendimethalin	60	54842	1.05 (0.91, 1.22)	0.97 (0.77, 1.22)
2,6-Dinitroaniline	Prodiamine	18	22483	1.13 (0.92, 1.39)	1.05 (0.79, 1.40)
2,6-Dinitroaniline	Trifluralin	43	49688	1.11 (0.94, 1.30)	1.07 (0.86, 1.34)
Aldehyde	Metaldehyde	44	52695	1.08 (0.92, 1.27)	1.15 (0.91, 1.46)
Alkyl Phthalate	Chlorthal dimethyl	20	19330	1.08 (0.85, 1.35)	1.10 (0.78, 1.55)
Amide	Cyflufenamid	10	2265	0.96 (0.69, 1.33)	0.95 (0.64, 1.40)
Amide	Pronamide	9	15932	1.09 (0.86, 1.38)	0.72 (0.44, 1.18)
Anilide	Boscalid	64	33517	1.00 (0.85, 1.18)	1.02 (0.77, 1.35)
Azole	Difenoconazole	30	6874	1.11 (0.92, 1.34)	1.11 (0.84, 1.47)
Azole	Fenbuconazole	13	6893	1.19 (0.90, 1.58)	1.21 (0.84, 1.74)
Azole	Propiconazole	64	60180	0.84 (0.58, 1.21)	1.07 (0.85, 1.35)
Azole	Tebuconazole	34	26776	0.99 (0.82, 1.20)	0.90 (0.67, 1.20)
Azole	Terrazole	6	4474	0.91 (0.63, 1.32)	0.89 (0.59, 1.35)
Azole	Triadimefon	19	32868	0.98 (0.78, 1.23)	0.90 (0.67, 1.21)
Azole	Uniconazole-P	13	11983	1.04 (0.78, 1.39)	0.89 (0.60, 1.34)
Benzimidazole	Benomyl	10	27177	1.43 (0.95, 2.15)	1.53 (0.98, 2.39)
Benzimidazole precursor	Thiophanate methyl	65	75781	1.07 (0.93, 1.24)	1.12 (0.91, 1.37)
Chloroacetanilide	Alachlor	6	6213	1.31 (0.93, 1.85)	1.29 (0.85, 1.95)
Chloroacetanilide	Metolachlor	16	9431	1.29 (1.00, 1.65)	1.17 (0.86, 1.59)
Chloroacetanilide	S-Metolachlor	26	18263	1.09 (0.89, 1.33)	0.96 (0.73, 1.28)
Dicarboximide	Iprodione	59	82556	0.92 (0.79, 1.07)	0.77 (0.61, 0.98)
Diphenyl ether	Oxyfluorfen	63	74144	1.04 (0.91, 1.20)	0.95 (0.72, 1.24)
Dithiocarbamate	Mancozeb	59	65431	1.06 (0.91, 1.23)	1.05 (0.85, 1.29)
Dithiocarbamate	Maneb	9	28174	0.85 (0.58, 1.24)	0.72 (0.45, 1.14)
Dithiocarbamate	Metam sodium	17	23559	1.26 (1.00, 1.58)	1.25 (0.93, 1.67)
Dithiocarbamate	Ziram	20	19302	1.02 (0.79, 1.31)	0.98 (0.69, 1.41)
Halogenated organic	1,3-Dichloropropene	32	27995	1.04 (0.87, 1.25)	1.07 (0.82, 1.41)
Keto-enol	Spirodiclofen	15	6043	1.05 (0.81, 1.37)	1.01 (0.73, 1.40)
N-Methyl carbamate	Carbaryl	49	53513	1.20 (1.01, 1.43)	1.16 (0.95, 1.43)
Organochlorine	Dicofol	8	29322	1.07 (0.77, 1.51)	0.99 (0.68, 1.43)
Organophosphorus	Acephate	62	85739	0.96 (0.83, 1.12)	0.89 (0.72, 1.10)
Organophosphorus	Dimethoate	41	53628	1.14 (0.97, 1.33)	1.05 (0.83, 1.33)
Organophosphorus	Malathion	68	87424	1.13 (0.97, 1.31)	1.07 (0.89, 1.30)

Organophosphorus	Phosmet	15	24984	1.11 (0.85, 1.45)	1.01 (0.71, 1.44)
Other carbamate	Fenoxycarb	5	15176	1.22 (0.86, 1.72)	1.29 (0.82, 2.05)
Oxazole	Isoxaben	32	27414	1.05 (0.89, 1.25)	1.06 (0.84, 1.34)
Pyrazole	Chlorfenapyr	11	8469	0.92 (0.69, 1.22)	0.89 (0.62, 1.28)
Pyrazole	Penthiopyrad	18	3266	0.96 (0.73, 1.26)	0.89 (0.62, 1.28)
Pyrazolylphenyl	Pyraflufen-ethyl	22	8137	1.01 (0.82, 1.25)	0.89 (0.65, 1.22)
Pyrethroid	Bifenthrin	74	75122	1.03 (0.89, 1.18)	0.91 (0.74, 1.12)
Pyrethroid	Cypermethrin	39	21100	1.19 (1.01, 1.41)	1.25 (0.97, 1.62)
Pyrethroid	Permethrin	62	69603	1.12 (0.96, 1.30)	1.19 (0.95, 1.49)
Pyridazinone	Norflurazon	10	19765	1.01 (0.72, 1.42)	0.92 (0.61, 1.38)
Pyrimidine	Pyrimethanil	21	12796	0.99 (0.80, 1.23)	0.94 (0.69, 1.30)
Strobin	Kresoxim-methyl	17	13116	0.97 (0.77, 1.22)	0.88 (0.63, 1.23)
Substituted benzene	Chlorothalonil	72	82679	1.02 (0.88, 1.18)	0.83 (0.67, 1.04)
Substituted benzene	Dicloran	12	17736	1.13 (0.88, 1.44)	1.16 (0.79, 1.69)
Substituted benzene	PCNB (Pentachloronitrobenzene)	11	19034	1.17 (0.86, 1.58)	1.09 (0.73, 1.62)
Sulfonylurea	Tribenuron methyl	14	3488	0.96 (0.72, 1.28)	0.84 (0.60, 1.19)
Tetrazine	Clofentezine	11	11524	1.04 (0.75, 1.42)	1.02 (0.70, 1.50)
Thiophthalimide	Captan	34	52876	0.99 (0.82, 1.20)	0.83 (0.62, 1.10)
Triazine	Pymetrozine	26	28266	1.01 (0.82, 1.23)	0.96 (0.71, 1.29)
Triazolopyrimidine	Penoxsulam	16	3547	1.24 (0.98, 1.57)	1.24 (0.89, 1.73)
Unclassified	Buprofezin	23	13848	0.98 (0.80, 1.21)	1.04 (0.78, 1.38)
Unclassified	Flonicamid	26	9110	1.21 (1.01, 1.44)	1.33 (1.02, 1.74)
Unclassified	Hexythiazox	46	46971	1.01 (0.87, 1.18)	0.96 (0.77, 1.20)
Unclassified	Hydramethylnon	8	15055	0.91 (0.65, 1.28)	0.74 (0.47, 1.17)
Unclassified	Metrafenone	6	1836	1.02 (0.74, 1.42)	1.05 (0.67, 1.63)
Unclassified	Oxadiazon	16	28166	0.91 (0.69, 1.19)	0.86 (0.62, 1.20)
Unclassified	Piperonyl butoxide	23	30442	0.98 (0.79, 1.21)	0.88 (0.65, 1.20)
Unclassified	Propargite	19	26668	1.08 (0.93, 1.25)	0.99 (0.71, 1.38)
Urea	Diuron	26	43037	1.01 (0.84, 1.21)	0.90 (0.70, 1.16)
Urea	Linuron	9	14397	0.89 (0.67, 1.20)	0.71 (0.47, 1.07)

^a Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, and maternal education.

^b Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, maternal education, and other pesticides, using a pesticide class effect in the hierarchical model.

Supplemental Table 2-3. Associations between neuroblastoma and exposure to agricultural pesticide applications within 4000m of the residential address, additionally adjusted for maternal smoking (N = 202,995)

Pesticide Class	Name	Exposed Cases N =	Exposed Controls N =	Single-pesticide model ^a	HLM OR (95% CI) ^b
		199	202,796		
2,6-Dinitroaniline	Oryzalin	74	76962	1.04 (0.90, 1.20)	1.06 (0.86, 1.31)
2,6-Dinitroaniline	Pendimethalin	74	63560	1.03 (0.89, 1.19)	0.95 (0.76, 1.20)
2,6-Dinitroaniline	Prodiamine	27	26581	1.17 (0.96, 1.44)	1.11 (0.85, 1.46)
2,6-Dinitroaniline	Trifluralin	49	57006	1.09 (0.93, 1.28)	1.07 (0.85, 1.33)
Aldehyde	Metaldehyde	57	62949	1.10 (0.94, 1.29)	1.17 (0.93, 1.48)
Alkyl phthalate	Chlorthal_dimethyl	20	21030	1.07 (0.85, 1.35)	1.09 (0.77, 1.53)
Amide	Cyflufenamid	11	2561	0.95 (0.68, 1.31)	0.95 (0.64, 1.41)
Amide	Propyzamide (Pronamide)	9	16856	0.84 (0.59, 1.21)	0.73 (0.44, 1.19)
Anilide	Boscalid	85	40029	0.98 (0.84, 1.15)	1.01 (0.76, 1.34)
Anilide	Propanil	6	3657	1.28 (0.88, 1.85)	1.22 (0.80, 1.87)
Azole	Difenoconazole	36	7718	1.09 (0.91, 1.32)	1.13 (0.86, 1.49)
Azole	Fenbuconazole	13	7183	1.17 (0.88, 1.55)	1.23 (0.85, 1.76)
Azole	Propiconazole	81	68698	1.06 (0.92, 1.23)	1.03 (0.82, 1.30)
Azole	Tebuconazole	42	29347	0.97 (0.80, 1.17)	0.90 (0.67, 1.20)
Azole	Terrazole	7	5193	0.90 (0.62, 1.30)	0.88 (0.59, 1.33)
Azole	Triadimefon	25	39583	0.97 (0.78, 1.22)	0.88 (0.66, 1.19)
Azole	Uniconazole-P	17	13733	1.05 (0.79, 1.40)	0.92 (0.62, 1.37)
Benzimidazole	Benomyl	10	29452	1.43 (0.95, 2.15)	1.53 (0.98, 2.38)
Benzimidazole precursor	Thiophanate methyl	89	92432	1.08 (0.94, 1.25)	1.12 (0.91, 1.37)
Chloroacetanilide	Alachlor	8	6984	1.31 (0.93, 1.84)	1.29 (0.85, 1.95)
Chloroacetanilide	Metolachlor	17	10213	1.26 (0.98, 1.62)	1.16 (0.85, 1.58)
Chloroacetanilide	S-Metolachlor	28	19910	1.06 (0.87, 1.30)	0.96 (0.73, 1.28)
Dicarboximide	Iprodione	71	97805	0.91 (0.78, 1.06)	0.78 (0.61, 0.98)
Dicarboximide	Vinclozolin	5	17250	1.12 (0.68, 1.85)	1.12 (0.64, 1.95)
Diphenyl ether	Oxyfluorfen	78	84830	1.02 (0.89, 1.18)	0.95 (0.73, 1.24)
Dithiocarbamate	Mancozeb	67	76607	1.06 (0.91, 1.22)	1.06 (0.87, 1.30)
Dithiocarbamate	Maneb	9	29660	0.85 (0.58, 1.24)	0.73 (0.46, 1.16)
Dithiocarbamate	Metam sodium	19	25482	1.25 (0.99, 1.57)	1.25 (0.93, 1.67)
Dithiocarbamate	Ziram	21	20595	0.99 (0.77, 1.28)	0.99 (0.69, 1.42)
Halogenated organic	1,3-Dichloropropene	34	29630	1.03 (0.86, 1.24)	1.08 (0.83, 1.41)
Keto-enol	Spirodiclofen	17	6495	1.03 (0.79, 1.34)	1.00 (0.72, 1.39)
N-Methyl carbamate	Carbaryl	57	62204	1.19 (1.00, 1.42)	1.16 (0.94, 1.42)
Organochlorine	Dicofol	11	33387	1.10 (0.79, 1.53)	1.03 (0.71, 1.47)

Organophosphorus	Acephate	90	110239	0.98 (0.85, 1.14)	0.91 (0.74, 1.12)
Organophosphorus	Dimethoate	47	59728	1.12 (0.96, 1.32)	1.04 (0.83, 1.32)
Organophosphorus	Malathion	85	105243	1.14 (0.99, 1.32)	1.10 (0.91, 1.32)
Organophosphorus	Methidathion	5	12139	1.17 (0.75, 1.81)	1.33 (0.81, 2.17)
Organophosphorus	Phosmet	17	27020	1.09 (0.84, 1.43)	1.01 (0.71, 1.44)
Other carbamate	Fenoxycarb	8	17027	1.29 (0.93, 1.80)	1.32 (0.85, 2.05)
Oxazole	Isoxaben	41	32610	1.04 (0.88, 1.23)	1.04 (0.83, 1.31)
Pyrazole	Chlorfenapyr	12	9728	0.91 (0.69, 1.21)	0.88 (0.62, 1.26)
Pyrazole	Penthiopyrad	19	3544	0.94 (0.71, 1.24)	0.89 (0.62, 1.27)
Pyrazolylphenyl	Pyraflufen-ethyl	25	8656	0.99 (0.80, 1.22)	0.89 (0.65, 1.22)
Pyrethroid	Bifenthrin	89	89715	1.03 (0.89, 1.18)	0.90 (0.74, 1.11)
Pyrethroid	Cypermethrin	41	22632	1.17 (0.99, 1.39)	1.24 (0.96, 1.60)
Pyrethroid	Permethrin	73	79395	1.12 (0.96, 1.30)	1.20 (0.96, 1.50)
Pyridazinone	Norflurazon	11	20485	1.02 (0.73, 1.42)	0.92 (0.61, 1.38)
Pyrimidine	Pyrimethanil	26	13865	0.98 (0.79, 1.22)	0.94 (0.68, 1.29)
Strobin	Kresoxim-methyl	21	14505	0.95 (0.75, 1.20)	0.88 (0.64, 1.23)
Substituted benzene	Chlorothalonil	95	99576	1.02 (0.88, 1.17)	0.85 (0.68, 1.05)
Substituted benzene	Dicloran	14	18680	1.13 (0.88, 1.44)	1.16 (0.79, 1.69)
Substituted Benzene	PCNB (Pentachloronitrobenzene)	13	21058	1.18 (0.87, 1.59)	1.08 (0.73, 1.60)
Sulfonylurea	Tribenuron methyl	15	3882	0.94 (0.70, 1.25)	0.85 (0.60, 1.19)
Tetrazine	Clofentezine	11	11925	1.01 (0.74, 1.39)	1.03 (0.70, 1.50)
Thiophthalimide	Captan	40	59141	1.00 (0.83, 1.20)	0.83 (0.62, 1.10)
Triazine	Pymetrozine	29	31883	1.00 (0.82, 1.22)	0.94 (0.70, 1.26)
Triazolopyrimidine	Penoxsulam	17	3910	1.21 (0.95, 1.53)	1.24 (0.89, 1.73)
Unclassified	Buprofezin	26	15180	0.98 (0.80, 1.21)	1.06 (0.80, 1.41)
Unclassified	Flonicamid	29	10013	1.19 (1.00, 1.43)	1.33 (1.02, 1.73)
Unclassified	Hexythiazox	55	53221	1.00 (0.86, 1.16)	0.95 (0.76, 1.18)
Unclassified	Hydramethylnon	12	16968	0.99 (0.72, 1.35)	0.80 (0.52, 1.21)
Unclassified	Metrafenone	9	2088	1.00 (0.72, 1.39)	1.04 (0.67, 1.62)
Unclassified	Oxadiazon	18	32556	0.91 (0.69, 1.19)	0.85 (0.61, 1.18)
Unclassified	Oxythioquinox	5	11804	1.43 (0.85, 2.39)	1.32 (0.78, 2.24)
Unclassified	Piperonyl Butoxide	25	35205	0.98 (0.79, 1.21)	0.88 (0.65, 1.19)
Unclassified	Propargite	19	27964	1.07 (0.84, 1.36)	1.00 (0.72, 1.39)
Urea	Diuron	33	48002	1.00 (0.83, 1.20)	0.90 (0.70, 1.16)
Urea	Linuron	10	15667	0.89 (0.67, 1.19)	0.71 (0.47, 1.07)

*For those missing maternal smoking data (n=150,372) this variable was imputed using a predictive model⁴²

^a Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, and maternal education.

^b Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, maternal education, and other pesticides, using a pesticide class effect in the hierarchical model.

Supplemental Table 2-4. Associations between neuroblastoma and exposure to agricultural pesticide applications within 4000m of the residential address (N = 202,995) birth year stratified

Pesticide Class	Name	1998-2007	2008-2016	1998-2007 Single- pesticide model ^a	1998-2007 HLM OR (95% CI) ^b	2008-2016 Single- pesticide model ^a	2008-2016 HLM OR (95% CI) ^b
		Exposed cases (N=36)	Exposed cases (N=163)				
2,6-Dinitroaniline	Trifluralin	7	42	1.00 (0.67, 1.50)	0.87 (0.52, 1.47)	1.11 (0.93, 1.33)	1.03 (0.81, 1.30)
2,6-Dinitroaniline	Oryzalin	8	66	0.84 (0.57, 1.25)	0.75 (0.44, 1.27)	1.08 (0.92, 1.26)	1.07 (0.86, 1.33)
2,6-Dinitroaniline	Pendimethalin	9	65	1.15 (0.76, 1.75)	1.34 (0.81, 2.19)	1.01 (0.87, 1.18)	0.95 (0.74, 1.22)
Aldehyde	Metaldehyde	8	49	0.98 (0.65, 1.46)	0.90 (0.54, 1.53)	1.12 (0.95, 1.33)	1.20 (0.93, 1.53)
Anilide	Boscalid	7	78	1.23 (0.74, 2.06)	1.38 (0.74, 2.59)	0.96 (0.81, 1.14)	0.98 (0.72, 1.32)
Azole	Propiconazole	11	70	1.10 (0.76, 1.60)	1.14 (0.68, 1.90)	1.06 (0.91, 1.24)	1.07 (0.83, 1.37)
Azole	Triadimefon	8	17	0.98 (0.63, 1.53)	0.82 (0.47, 1.44)	0.97 (0.74, 1.26)	0.88 (0.63, 1.24)
Benzimidazole precursor	Thiophanate methyl	12	77	1.01 (0.70, 1.47)	0.72 (0.42, 1.25)	1.09 (0.94, 1.27)	1.17 (0.94, 1.45)
Dicarboximide	Iprodione	16	55	1.10 (0.77, 1.57)	0.85 (0.52, 1.40)	0.87 (0.74, 1.03)	0.71 (0.55, 0.92)
Diphenyl ether	Oxyfluorfen	11	67	0.86 (0.60, 1.24)	0.80 (0.46, 1.39)	1.06 (0.91, 1.23)	0.92 (0.68, 1.24)
Dithiocarbamate	Metam sodium	10	9	1.69 (1.17, 2.45)	1.64 (1.04, 2.60)	1.07 (0.78, 1.46)	0.99 (0.69, 1.43)
Dithiocarbamate	Ziram	5	16	0.93 (0.50, 1.76)	1.02 (0.46, 2.25)	1.01 (0.77, 1.33)	1.00 (0.69, 1.46)
Dithiocarbamate	Mancozeb	10	57	0.99 (0.67, 1.47)	0.89 (0.55, 1.46)	1.07 (0.91, 1.25)	1.14 (0.91, 1.42)
N-Methyl carbamate	Carbaryl	13	44	1.21 (0.84, 1.75)	1.12 (0.73, 1.72)	1.19 (0.97, 1.45)	1.14 (0.91, 1.42)
Organochlorine	Dicofol	5	6	0.83 (0.50, 1.39)	0.80 (0.46, 1.39)	1.44 (0.96, 2.15)	1.33 (0.88, 2.01)
Organophosphorus	Acephate	16	74	0.97 (0.68, 1.39)	0.73 (0.44, 1.21)	0.98 (0.84, 1.15)	0.91 (0.73, 1.14)
Organophosphorus	Dimethoate	11	36	1.17 (0.80, 1.71)	1.13 (0.70, 1.83)	1.11 (0.93, 1.32)	1.00 (0.77, 1.30)
Organophosphorus	Malathion	17	68	1.27 (0.89, 1.82)	1.17 (0.76, 1.81)	1.12 (0.96, 1.31)	1.03 (0.84, 1.26)
Pyrethroid	Permethrin	13	60	1.33 (0.92, 1.92)	1.31 (0.80, 2.14)	1.08 (0.92, 1.28)	1.10 (0.86, 1.40)
Pyrethroid	Bifenthrin	12	77	1.11 (0.76, 1.60)	0.82 (0.52, 1.29)	1.01 (0.87, 1.18)	0.93 (0.74, 1.16)
Substituted Benzene	PCNB (Pentachloronitrobenzene)	6	7	1.36 (0.87, 2.13)	1.03 (0.57, 1.85)	1.06 (0.70, 1.60)	0.83 (0.49, 1.41)
Substituted benzene	Chlorothalonil	16	79	1.18 (0.82, 1.69)	1.03 (0.62, 1.70)	0.99 (0.84, 1.15)	0.82 (0.64, 1.04)
Thiophthalimide	Captan	15	25	1.24 (0.87, 1.76)	1.10 (0.67, 1.80)	0.93 (0.73, 1.17)	0.80 (0.57, 1.10)
Unclassified	Oxadiazon	6	12	1.13 (0.71, 1.80)	1.05 (0.58, 1.87)	0.82 (0.58, 1.16)	0.72 (0.48, 1.08)
Unclassified	Hexythiazox	5	50	0.92 (0.57, 1.49)	0.66 (0.38, 1.17)	1.01 (0.86, 1.18)	0.99 (0.78, 1.26)
Urea	Diuron	5	28	0.88 (0.57, 1.35)	0.80 (0.47, 1.39)	1.03 (0.84, 1.26)	0.84 (0.64, 1.09)

^a Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, and maternal education.

^b Adjusted for birth year, SES-index variable, maternal age, mother's race/ethnicity, maternal education, and other pesticides, using a pesticide class effect in the hierarchical model.

Supplemental Table 2-5. Carcinogenic pesticides included in each pesticide class for class-level analyses (N = 202,995)

		Total Exposed Cases N = 199	Total Exposed Controls N = 202,796
Pesticide Class	Pesticides Included in Class Analysis		
2,6-Dinitroaniline	Trifluralin, Oryzalin, Pendimethalin, Prodiamine	120	121,151
Aldehyde	Metolachlor	57	62,956
Alkyl phthalate	Dimethyl tetrachloroterephthalate	20	21,038
Amide	Propyzamide (Pronamide), Cyflufenamid	17	18,801
Anilide	Propanil, Boscalid	87	42,256
Azole	Triadimefon, Propiconazole, Uniconazole-P, Tebuconazole, Fenbuconazole, Difenconazole, Terrazole	119	102,293
Benzimidazole	Benomyl	13	31,201
Benzimidazole precursor	Thiophanate methyl	89	92,445
Chloroacetanilide	Alachlor, Metolachlor, S-metolachlor	35	32,220
Chlorophenoxy acid	Mecoprop-P	5	2,802
Dicarboximide	Iprodione, Vinclozolin	71	99,283
Diphenyl ether	Oxyfluorfen	78	84,850
Dithiocarbamate	Ziram, Maneb, Mancozeb, Metam sodium	81	97,530
Ester	Mecoprop-P	5	2,802
Halogenate organic	1,3-Dichloropropene	34	29,632
Keto-enol	Spirodiclofen	17	6,495
N-methyl carbamate	Carbaryl	58	63,389
Organochlorine	Dicofol	13	35,246
Organophosphorus	Dimethoate, Phosmet, Malathion, Acephate, Methidathion	124	156,146
Other carbamate	Fenoxycarb	8	17,030
Oxazole	Isoxaben	41	32,610
Pyrazole	Penthiopyrad, Chlorfenapyr	27	13,194
Pyrazolylphenyl	Pyraflufen-ethyl	25	8,657
Pyrethroid	Bifenthrin, Cypermethrin, Permethrin	108	118,553
Pyridazinone	Norflurazon	11	20,485
Pyrimidine	Pyrimethanil	26	13,867
Salt	Mecoprop-P	5	2,802
Strobin	Kresoxim-methyl	21	14,505
Substituted benzene	Dicloran, PCNB (Pentachloronitrobenzene), Chlorothalonil	96	103,831
Sulfonylurea	Tribenuron methyl	18	6,028
Tetrazine	Clofentazine	11	11,927

Thiophthalimide	Captan	40	59,160
Triazine	Pymetrozine	30	33,879
Triazolopyrimidine	Penoxsulam	17	3,910
Unclassified	Daminozide, Oxythioquinox, Propargite, Piperonyl butoxide, Oxadiazon, Hydramethylnon, Hexythiazox, Buprofezin, Flonicamid, Metrafenone	105	118,009
Urea	Diuron, Linuron	42	56,135

Chapter 3 Prenatal exposure to criteria air pollutants and traffic-related air toxics and risk of childhood cancer in Los Angeles, CA

3.1 Abstract

Background: The etiology of many childhood cancers remains unclear, though prenatal environmental exposures may contribute. We investigated associations between prenatal exposure to criteria pollutants and traffic-related air toxics and the risk of specific childhood cancers in Los Angeles, California.

Methods: We conducted a population-based case-control study linking California birth records (1998-2016) with the California Cancer Registry (2,940 cases; 63,516 controls). Prenatal residential exposures to PM_{2.5}, NO₂, O₃, and five traffic-related air toxics (1,3-butadiene, benzene, chromium, lead, nickel) were estimated using machine learning-enhanced land-use regression models. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated per interquartile range increase using unconditional logistic regression. Additional analyses examined trimester-specific and first-year exposures, effect modification by race/ethnicity, and pollutant mixtures via quantile g-computation.

Results: Prenatal PM_{2.5} exposure was associated with increased risk of rhabdomyosarcoma (OR: 1.59; 95% CI: 1.05, 2.40). 1,3-butadiene was associated with soft tissue sarcoma (OR: 1.71; 95% CI: 1.12, 2.61), while benzene was associated with ependymoma (OR: 3.35; 95% CI: 1.18, 9.53). Chromium (OR: 1.27; 95% CI: 1.05, 1.54) and lead (OR: 1.36; 95% CI: 1.10, 1.68) were associated with non-Hodgkin lymphoma, and lead with Wilms' tumor (OR: 1.30; 95% CI: 1.03, 1.64). Air toxic mixtures were associated with ependymoma (OR: 2.17; 95% CI: 1.23, 3.82) and soft tissue sarcoma (OR: 1.41; 95% CI: 1.02, 1.96). Increased risks for all cancers combined were also observed across several exposures (ORs ranging from 1.09 to 1.15).

Conclusions: Prenatal exposure to air toxic mixtures and specific traffic-related air pollutants, including PM_{2.5}, 1,3-butadiene, benzene, lead and chromium, was associated with increased risk of several childhood cancers.

3.2 Introduction

Childhood cancer, though rare, is the second leading cause of death among children aged 1-14 years and the fourth among adolescents aged 15-19 years. In the United States in 2025, an estimated 9,550 children and 5,140 adolescents will be diagnosed with cancer, resulting in approximately 1,050 and 600 deaths, respectively.¹³⁵ Research on environmental risk factors for childhood cancer remains limited; however, ionizing radiation is associated with increased risk,⁸ and emerging evidence suggests pesticides, parental occupational exposures, and air pollution may be associated with certain childhood cancers.⁹

Motor vehicle emissions are a dominant source of ambient air pollution in metropolitan regions such as Los Angeles, California, contributing substantially to exposures to both criteria air pollutants and hazardous air toxics. These emissions include a complex mixture of combustion and non-combustion particles and gases, such as fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), ozone (O₃), and air toxics compounds including benzene, 1,3-butadiene, chromium, lead, and nickel. Outdoor air pollution, particulate matter, diesel exhaust, benzene, 1,3-butadiene, and nickel have all been classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC).³³⁻³⁷ Further, non-combustion sources such as brake and tire wear are increasingly recognized as important contributors to traffic-related air pollution. These processes generate particulate matter enriched with metals, including chromium, lead, and nickel, through mechanical abrasion of brake components and tire materials.¹³⁶⁻¹³⁸ As tailpipe emissions decline with advances in vehicle technology and electrification, brake and tire wear account for an increasing share of traffic-related particulate matter.^{137,138}

Given that the pathogenesis of some childhood cancers is believed to originate in utero, and that the fetus is particularly vulnerable to environmental toxicants, prenatal exposure to air pollution

may represent a critical etiologic window.⁴¹⁻⁴³ Studies of prenatal and early-life exposure to ambient and traffic-related air pollution have reported mixed findings, potentially due to variation in exposure assessment methods and windows, with many relying on proxy measures, such as residential proximity to roadways or petrol stations, that may introduce exposure misclassification. Despite these limitations, some studies suggest associations with leukemias and CNS tumors,^{9,49} including elevated risks with traffic-related pollution specifically,¹³⁹⁻¹⁴² while others report null results.^{140,141,143-147} No prior studies have evaluated brake and tire wear emissions in relation to childhood cancer risk.

Studies using modeled or monitored concentrations of criteria air pollutants and traffic-related air toxics have similarly yielded mixed findings. Early-life exposure to PM_{2.5}, or NO₂ has been associated with childhood leukemia, CNS tumors, and retinoblastoma in some studies,^{47,148,149} while others reported largely null results for leukemia.^{144,145} Prenatal exposure to criteria pollutants has been associated with increased risks of astrocytoma, ALL, retinoblastoma, and germ cell tumors (GCT),^{44,45,47}. Prenatal exposure to traffic-related air toxics has yielded mixed results across cancer types, with positive associations reported between 1,3-butadiene and benzene and ALL,⁴⁶ benzene and AML and medulloblastoma,¹⁵⁰ lead and astrocytoma,¹⁵¹ and several air toxics (1,3-butadiene, benzene, chromium) and GCT, while others have reported null associations.^{48,152}

Though prior studies have yielded inconsistent findings, evidence suggests that prenatal and early-life exposure to certain criteria pollutants and traffic-related air toxics may increase the risk of childhood cancers. In this study, we applied land-use regression models incorporating satellite, meteorologic, and land-use data to estimate prenatal exposures to both criteria air pollutants and traffic-related air toxics at geocoded birth addresses. Using statewide birth records

linked to the California Cancer Registry (CCR) from 1998 to 2016, we evaluated associations between prenatal exposure to PM_{2.5}, NO₂, O₃, and several traffic and brake and tire wear-related air toxics (1,3-butadiene, benzene, chromium, lead, nickel) and the risk of childhood cancers in Los Angeles, California.

3.3 Methods

Study population

Childhood and adolescent cancer cases were identified from the California Cancer Registry (CCR), a statewide, population-based cancer surveillance system with mandatory reporting of all cancer diagnoses since 1988.⁹² Eligible cases included children born in California between 1998 and 2016 who were diagnosed with a malignant neoplasm between the ages of 0 and 19 years from 1998 through 2018. Cancer diagnoses were classified using the International Classification of Childhood Cancer (ICCC) extended classification recode.¹⁵³ The CCR registry is routinely validated by the California Department of Public Health to ensure compliance with data standards established by the National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.⁹² Cases were linked to birth certificates using name, date of birth, and, when available, social security number using a probabilistic linkage program;¹⁵⁴ 89% of cases were successfully matched, while the remaining 11% were likely born outside of California.⁹³

Due to the unavailability of complete residential addresses in the electronic birth certificate dataset prior to 1998, the present analysis was limited to births from 1998-2016. For the parent study, controls were randomly selected from California birth records and frequency matched 20:1 to all childhood cancer cases by birth year. To more specifically characterize traffic-related pollution, we restricted the study population to Los Angeles County, a densely urbanized region

with high roadway density and well-characterized mobile-source emissions.¹⁵⁵ Limiting the analysis to this setting reduces exposure misclassification by minimizing contributions from non-traffic sources, such as agriculture and wildfire, that may predominate in rural or less urbanized areas. This restriction is also expected to create a more homogeneous urban study sample concerning other unmeasured social and environmental factors that might otherwise confound these associations.

We excluded children with missing or nonviable birthweight (<500 g; n=95), nonviable gestational age (<20 weeks; n=60), missing sex (n=1), or missing covariate information (n=490). We excluded participants missing exposure data for criteria pollutants (n = 4,867) and air toxics (n = 5,053). The final analytic samples included 2,940 cases and 63,516 controls for criteria pollutants, and 2,933 cases and 63,337 controls for air toxics.

Criteria air pollutants

Maternal residential addresses recorded on the birth certificate were geocoded to obtain spatial coordinates for each individual.^{156,157} These coordinates were used to assign daily concentrations of PM_{2.5}, NO₂, and O₃ based on a LUR spatiotemporal modeling framework enhanced with advanced machine learning methods.¹⁵⁵ The exposure models utilized a deletion/substitution/addition (D/S/A) algorithm to estimate daily pollutant concentrations across California from 1998 to 2016; model development was conducted at a 30-meter spatial resolution and final exposure surfaces were produced at a 100-meter resolution. Pollutant exposures were then assigned at the residential address level using the 100-meter resolution surfaces.^{158,159}

Daily concentrations of NO₂, PM_{2.5}, and O₃ were estimated using LUR models that incorporated government-regulatory fixed-site monitoring data, fixed-site research saturation observations, and Google Streetcar-based mobile measurements for NO₂ and O₃, and government-regulatory monitoring plus Google Streetcar-based mobile measurements for PM_{2.5}. The modeling framework, including development, validation, and historical reconstruction, has been described in detail previously.¹⁵⁵ Predictors included daily vehicle miles traveled, satellite-derived measures of NO₂ and aerosol optical depth (AOD), biweekly vegetation indices, daily meteorological variables, and land use and land cover data collected at 2-4 year intervals between 2001 and 2021. To reduce overfitting and improve prediction in areas without direct measurements, models were developed using V-fold cross-validation and enhanced with machine learning techniques. For years with incomplete predictor data, key inputs, including traffic volume, vegetation indices, AOD, and satellite-derived pollutant measures, were reconstructed using regression-based approaches to extend daily exposure estimates back to 1989. The final models achieved prediction accuracies of 84% for NO₂, 65% for PM_{2.5}, and 92% for O₃.

Traffic-related air toxics

In addition to criteria air pollutants, we modeled five traffic-related air toxics (1,3-butadiene, benzene as markers of traffic exhaust; chromium, lead, and nickel as markers of brake and tire wear) selected for their known health risks and strong association with traffic and industrial emissions. Annual concentration surfaces for these pollutants were generated across California at a 100-meter spatial resolution over a 30-year period using LUR models enhanced with machine learning, similar to those developed for criteria pollutants. Data inputs included California Air Resources Board (CARB) speciation data (1996-2021), emission estimates from the California

Toxics Inventory (CTI) covering stationary sources reported under the Air Toxics “Hot Spots” Program, traffic information, land use and land cover, meteorological conditions, and satellite-derived data such as Sentinel spectral bands. Long-term emission trends were incorporated to reconstruct concentrations for years without direct observations. The models achieved high predictive performance, with adjusted R^2 values of 0.81 for benzene, 0.62 for 1,3-butadiene, 0.76 for chromium, 0.70 for nickel, and 0.59 for lead, providing high-resolution insights into the spatial and temporal distribution of these pollutants for assessing long-term exposure risks.¹⁶⁰

To reduce the influence of extreme or potentially implausible values, the upper tail of each air toxic was winsorized at the 99th percentile within birth year. In addition, because zero values in the air toxics data may reflect concentrations below the limit of detection rather than true absence, we replaced zeros with one-half of the minimum observed non-zero value to improve the robustness of our analyses.

Statistical analysis

To examine associations between prenatal exposure to criteria air pollutants and traffic-related air toxics, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression models. Prenatal exposure to criteria pollutants was calculated as the average of daily concentrations between the first day of the last menstrual period and the date of birth. For air toxics, which were available only as annual estimates, prenatal exposure was calculated as a weighted average based on the proportion of days in the pregnancy window overlapping each calendar year.

Cancer outcomes were classified a priori as primary or secondary based on the existing epidemiologic literature. Primary outcomes were those previously positively associated with

ambient air pollution or traffic-related exposures, regardless of the specific pollutant or exposure window examined. Outcomes with no previously reported positive association, whether unstudied or previously null, were classified as secondary. Findings for secondary outcomes were considered hypothesis-generating because they arose from exploratory analyses across multiple pollutant-cancer pairs.

All models were adjusted for the matching variable, birth year, and additionally for maternal age, area-level socioeconomic status (SES), and maternal ethnicity (non-Hispanic White, Hispanic, Black, Asian/Pacific Islander, other) based on prior literature.^{161,162} Area-level SES was assessed using the index developed by Yost et al.¹⁰¹ Pollutants were scaled to the interquartile range (IQR) of prenatal exposures among controls across the full study period (1998-2016). Pearson correlation coefficients were calculated across pollutants to assess suitability for dual adjustment models; in cases of high correlation ($|r| > 0.7$), co-pollutants were included in multipollutant models.

Several sensitivity analyses were conducted to assess the robustness of findings across different exposure windows. For criteria pollutants, we examined trimester-specific exposures (T1: last menstrual period + 93 days; T2: day 94-186 or until birth; T3: day 187-birth). First-year-of-life exposures were also examined for both criteria pollutants and air toxics. These exposures were defined as the period from birth through 365 days of age; for cases diagnosed before age 1 year, exposure assessment was truncated at the date of diagnosis to ensure that only pre-diagnostic exposures were included.

Analyses were stratified by maternal race/ethnicity, age at diagnosis, and birth year. Due to sparse data, stratified results by age at diagnosis and birth year were imprecise and not reported.

To evaluate the combined effects of the air toxics mixture, we additionally applied quantile g-computation, which models the joint effect of all mixture components and estimates a single, overall effect on childhood cancer risk.¹⁶³

Finally, to evaluate the potential impact of live-birth selection bias on observed associations, we conducted a probabilistic bias analysis. Live-birth bias arises when prenatal exposures associated with fetal loss selectively remove the most vulnerable individuals from the study population; this selection can result in the underestimation or apparent reversal of the true effect among live births.¹³⁰ Prenatal exposure to each pollutant was dichotomized as the highest quartile (Q4) versus the lower three quartiles combined (Q1-Q3), based on the distribution among controls, as the closest available approximation to the continuous per-interquartile-range (IQR) exposure metric used in primary analyses. Supplemental Table 3-1 details the fetal survival parameters utilized in the 100,000 Monte Carlo replications to generate bias-adjusted median odds ratios and corresponding 2.5th and 97.5th simulation limits.¹⁶⁴

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The probabilistic bias analysis was conducted in R using the episensr package.

3.4 Results

Demographic characteristics of the study population are presented in Table 3-1. Compared to control mothers, mothers of cases were slightly older, more likely to be non-Hispanic White, and more likely to reside in higher SES geographic areas. Additionally, cases had a higher proportion of males compared with controls.

Summary statistics for criteria pollutants and air toxics are presented in Table 3-2. Mean pollutant concentrations were similar between cases and controls, with slightly higher 1,3-butadiene and lower chromium concentrations among cases. Correlations among full-term

exposures in controls are shown in Supplemental Table 3-2, with strong positive correlations between PM_{2.5} and NO₂, 1,3-butadiene and chromium, and benzene and chromium, and strong inverse correlations between benzene and lead and between chromium and lead.

Adjusted associations between full-term criteria pollutant exposure and childhood cancers are presented in Table 3-3. In the primary analyses, prenatal PM_{2.5} exposure was associated with increased risk of all cancers combined after adjustment for NO₂. Elevated point estimates with confidence intervals crossing the null were also observed for all cancers combined, CNS tumors, and ependymoma in single-pollutant PM_{2.5} models. In secondary, hypothesis-generating analyses, PM_{2.5} exposure was associated with rhabdomyosarcoma in both single- and two-pollutant models and with glioma after adjustment for NO₂. Associations with soft tissue sarcoma were also elevated but imprecise (Supplemental Table 3-3).

Associations between full-term air toxic exposures and childhood cancers are shown in Table 3-4. In the primary analyses, elevated risks were observed for all cancers combined with 1,3-butadiene exposure, ependymoma with benzene exposure, and NHL with chromium and lead exposures. Elevated point estimates with confidence intervals crossing the null were also observed for CNS tumors with lead exposure. Inverse associations were observed for germ cell tumors and teratoma with benzene exposure. In secondary analyses, 1,3-butadiene exposure was associated with soft tissue sarcoma and rhabdomyosarcoma, lead exposure with Wilms' tumor, and nickel exposure inversely with hepatoblastoma (Supplemental Table 3-4). Models co-adjusted for highly correlated air toxics yielded similar point estimates with overlapping confidence intervals and are not shown.

Results from air toxic mixture analyses using quantile g-computation are presented in Table 3-5. In the primary analyses, higher mixture exposure was associated with increased risk of all

cancers combined. In secondary analyses, higher mixture exposure was associated with ependymoma and soft tissue sarcoma, while the association with rhabdomyosarcoma was elevated but imprecise (Supplemental Table 3-5).

Trimester-specific associations are shown in Supplemental Table 3-6. PM_{2.5} exposure during the third trimester was associated with increased risk of all cancers combined and rhabdomyosarcoma, while second trimester PM_{2.5} exposure was associated with ependymoma. Second trimester O₃ exposure was associated with increased risk of Wilms' tumor, while second trimester NO₂ exposure was inversely associated with Hodgkin lymphoma. Third trimester NO₂ exposure was inversely associated with germ cell tumors, including teratoma and yolk sac tumor subtypes.

In first year of life analyses, NO₂ and PM_{2.5} exposure were associated with increased risk of retinoblastoma and O₃ exposure was associated with an increased risk of GCT (Supplemental Table 3-7). Among air toxics, first year exposure to chromium and lead were associated with increased risk of NHL, lead exposure was associated with increased risk of Wilms' tumor, and 1,3-butadiene exposure was associated with an increased risk of ependymoma, though the confidence interval is wide (Supplemental Table 3-8).

Results stratified by race/ethnicity are presented in Supplemental Tables 3-9 and 3-10 and are limited to non-Hispanic White and Hispanic children and to cancer types with at least 20 exposed cases in both groups. For criteria pollutants, PM_{2.5} exposure was associated with increased risk of CNS tumors among non-Hispanic White children and soft tissue sarcoma among Hispanic children. For NHL, NO₂ exposure was inversely associated among non-Hispanic White children but positively associated among Hispanic children (Supplemental Table 3-9). For air toxics, associations varied by ethnicity and cancer subtype and were most consistent among Hispanic

children, including positive associations of 1,3-butadiene with all cancers combined and CNS tumors, chromium and lead with NHL, and lead with Wilms' tumor (Supplemental Table 3-10).

In sensitivity analyses adjusting for systematic selection (live-birth) bias, crude positive associations moved away from the null while crude negative associations moved toward the null (Supplemental Tables 3-11, 3-12).

3.5 Discussion

In this urban population-based case-control study, we found evidence that prenatal exposure to certain traffic-related air pollutants may increase the risk of specific childhood cancers. These findings are particularly relevant in Los Angeles County, where high traffic density contributes substantially to ambient levels of both criteria air pollutants and hazardous air toxics,¹⁶⁵ and where the Hispanic pediatric population has one of the highest reported childhood cancer incidence rates globally.¹⁶⁶ In Los Angeles, many homes are situated near major roads and freeways, and air pollutants and dust from traffic can drift considerable distances into surrounding residential neighborhoods; this proximity raises concerns about ambient exposure during pregnancy.^{167,168}

We observed associations between prenatal exposure to PM_{2.5} and certain air toxics with increased risks of several childhood cancers, most notably specific CNS tumor subtypes (ependymoma, glioma), rhabdomyosarcoma, and NHL. Our findings regarding PM_{2.5} and CNS tumors support findings of recent large-scale studies in Korea and Texas, which reported elevated risks for ependymoma and all cancers combined with higher particulate matter exposure, although those studies evaluated exposure across early life rather than specifically the prenatal period.^{148,149} While much of the existing literature has focused on nitrogen oxides and benzene in relation to childhood leukemia, our results found more prominent associations between PM_{2.5}

and heavy metals, specifically chromium and lead, with risk of solid tumors and NHL. Additionally, our results regarding air toxics, including positive associations between 1,3-butadiene and soft tissue sarcoma, lead and chromium with NHL, and lead with Wilms' tumor, provide more specific insight than previous studies relying on broader categories of pollution. The existing literature remains heterogeneous, potentially due to a reliance on crude proxy measures, such as residential proximity to roadways or census-tract level data, which lack the spatial precision to capture individual-level exposure. Such methodological limitations may introduce non-differential exposure misclassification, potentially contributing to the inconsistent associations reported for childhood leukemias and other rare malignancies across geographic regions.

By leveraging high-resolution land-use regression models and machine learning, our study provides exposure estimates at a 100-meter resolution, offering greater precision than prior research that utilized annual or regional averages. Specifically, the availability of daily concentration estimates for criteria pollutants allowed us to evaluate associations within distinct trimesters of pregnancy, identifying specific windows of vulnerability that may have been previously obscured by temporally averaged data. For instance, our trimester-specific analyses suggest the third trimester may be a particularly sensitive window for PM_{2.5}-associated rhabdomyosarcoma, while second-trimester exposure was relevant for ependymoma. These findings align with the hypothesis that late-gestational exposures may coincide with critical periods of fetal cell proliferation and epigenetic programming.¹⁶⁹

Several biological pathways may explain the association between prenatal air pollution and childhood cancer risk. Components of particulate matter and heavy metals have both been shown to cross the placental barrier, facilitating direct fetal tissue exposure to pollutants.^{170,171}

Furthermore, maternal exposure to traffic-related emissions has been associated with increased levels of bulky DNA adducts and micronuclei in umbilical cord blood, indicating direct DNA damage and chromosomal instability within the fetal environment.⁴⁰ Beyond direct genotoxicity, prenatal air pollution exposure has been shown to increase oxidative stress and inflammation.^{38,39} These processes can establish a pro-tumorigenic environment, potentially altering critical cellular signaling pathways and increasing the susceptibility of developing fetal cells to malignant transformation.

When adjusting for NO₂ in the PM_{2.5} full-term models, associations remained elevated or strengthened for all cancers combined, glioma, GCT, and rhabdomyosarcoma. This persistence suggests that the observed risks may be associated with non-combustion components of PM_{2.5}, such as heavy metals and particulate matter derived from brake and tire wear, rather than exhaust-related gases alone. Previous research has highlighted that these non-exhaust particles possess unique physicochemical characteristics and oxidative potential, which may contribute to adverse health outcomes and early-life carcinogenesis.¹⁷² In contrast, the association for ependymoma was attenuated upon adjustment for NO₂, suggesting that combustion-related emissions may be more relevant to the etiology of this specific CNS subtype.

In our analysis of benzene and 1,3-butadiene, the results suggest the prenatal period may be a more sensitive window for exposure compared to the first year of life. This suggests that fetal development may be uniquely susceptible to these air toxics. Benzene is an established cause of adult leukemia and traffic-related benzene has been associated with childhood leukemia in several studies, but our study did not have the same findings.¹⁷³ This may be due to differences in the models used, geographic location, or exposure windows. In our analysis of chromium and lead, we observed nearly identical elevated risk estimates across both the prenatal and first year

of life exposure windows. The consistency of these associations may be related to the cumulative burden or the biological persistence of heavy metals. Heavy metals are characterized by their inability to be biodegraded, allowing them to remain in the environment and the body for extended periods.¹⁷⁴ Heavy metals may contribute to pediatric cancer risk through chronic, sustained mechanisms, such as prolonged oxidative stress or impaired DNA repair.

Our mixture analyses indicated that higher combined exposure to all five traffic-related air toxics was associated with increased risks of all cancers combined, ependymoma, and soft tissue sarcoma. These results suggest that these agents may act through common or synergistic biological pathways, where low-dose exposures to multiple pollutants collectively overwhelm fetal antioxidant defenses and DNA repair mechanisms.^{175,176}

We observed several inverse associations in our study with exposure to NO₂, benzene, and nickel. These may be attributable to chance, given the relatively low number of cases for the cancer subtypes involved. Alternatively, these inverse associations may reflect live-birth bias.¹³⁰ Our probabilistic bias analysis supports this possibility; adjusting for differential in-utero survival moved crude positive associations away from the null and crude negative associations toward the null, suggesting that the observed inverse associations may be driven in part by conditioning on fetal survival rather than true biological mechanisms. Because this analysis required a dichotomized exposure and could not adjust for birth year or other primary-model confounders, results are not directly comparable in magnitude to primary estimates and should be interpreted as evidence of the direction and pattern of live-birth selection bias rather than a quantitative correction.

In our stratified analyses, we observed disparities in the associations between air pollution and childhood cancer risk across racial and ethnic groups, most notably for the association between

NO₂ and NHL. While the association was inverse among non-Hispanic White children, it inverted to a positive association in Hispanic children. These varying risk patterns may reflect structural disparities in neighborhood clustering; in Southern California, minority and high-poverty neighborhoods bear over twice the level of traffic density compared to the rest of the region.¹⁷⁷

A primary strength of this study is the use of high-resolution exposure modeling, which generated individual-level residential exposure estimates. This approach improved precision compared with ZIP code or county-level metrics and enabled us to evaluate associations with criteria pollutants during specific trimesters of pregnancy. Furthermore, we investigated a broad range of air toxics rarely examined in childhood cancer epidemiology and utilized mixture-based modeling to assess cumulative effects. The use of birth records and census-linked variables allowed for robust confounding adjustment, while the statewide cancer registry ensured comprehensive case ascertainment.

However, several limitations warrant consideration. The reliance on annual air toxic estimates restricted our ability to examine exposures during narrower developmental windows, such as individual trimesters or early postnatal life. This limitation may lead to non-differential misclassification and attenuation of associations if critical periods are masked. Additionally, using residential addresses at birth may introduce exposure misclassification, as we could not account for residential mobility during pregnancy or exposure during commutes or at the workplace. Generalizability may be limited to regions with similar pollution sources and demographic profiles. Finally, limited case counts for rare cancer subtypes, particularly within stratified racial/ethnic groups, reduced statistical power to detect small effects and rendered results stratified by age and birth year too imprecise to report.

In conclusion, our results suggest that prenatal exposure to specific traffic-related air pollutants, including PM_{2.5}, 1,3-butadiene, benzene, lead and chromium is associated with an increased risk of specific childhood cancers. To our knowledge, this is the first study to utilize high-resolution spatial modeling to evaluate associations between residential exposure to these pollutants across such a broad range of childhood cancer types. These findings underscore the importance of moving beyond proximity-based proxies to evaluate pollutant-specific exposures and support the need for targeted policy interventions to reduce the disproportionate burden of air pollution in high-traffic urban corridors.

3.6 Tables and figures

Table 3-1. Demographic characteristics of analytical population (N = 66,456)

Characteristic n (%)	Case (N=2940)	Control (N=63516)
Maternal Age		
Mean (SD)	28.8 (6.54)	28.0 (6.41)
Median [Min, Max]	29.0 [14.0, 49.0]	28.0 [13.0, 99.0]
Sex		
Female	1,347 (45.8%)	31,274 (49.2%)
Maternal Race/ethnicity		
Non-Hispanic White	624 (21.2%)	11,590 (18.2%)
Hispanic of any race	1,874 (63.7%)	39,812 (62.7%)
Black	158 (5.4%)	5,016 (7.9%)
Asian/Pacific Islander	265 (9.0%)	6,705 (10.6%)
Other/refused	19 (0.6%)	393 (0.6%)
SES Quintile		
1 (Low)	1100 (37.4%)	25,873 (40.7%)
2	653 (22.2%)	14,956 (23.5%)
3	489 (16.6%)	9,482 (14.9%)
4	338 (11.5%)	7,122 (11.2%)
5 (High)	360 (12.2%)	6,083 (9.6%)

Table 3-2. Summary statistics of full-term criteria pollutants and air toxics across study period (1998-2016)

Criteria Pollutants	Cases (N=2,940)		Controls (N=63,516)	
	Mean (SD)	IQR	Mean (SD)	IQR
PM2.5 (ug/m3)	12.87 (1.51)	2.086	12.88 (1.49)	2.064
NO2 (ppb)	22.33 (4.50)	5.756	22.35 (4.50)	5.769
O3 (ppb)	37.31 (2.38)	2.980	37.31 (2.43)	3.120
Air Toxics*	Cases (N=2,933)		Controls (N=63,516)	
	Mean (SD)	IQR	Mean (SD)	IQR
1,3-Butadiene (ppb)	5.53 e+00 (9.09 e-01)	1.19 e+00	5.49 e+00 (9.03 e-01)	1.19 e+00
Benzene (ppb)	9.25 e-01 (1.65 e-01)	2.82 e-01	9.22 e-01 (1.64 e-01)	2.78 e-01
Chromium (ug/m3)	4.30 e-03 (8.11 e-04)	8.58 e-04	4.34 e-03 (8.26 e-04)	8.58 e-04
Lead (ug/m3)	5.33 e-03 (3.90 e-04)	4.96 e-04	5.33 e-03 (3.99 e-04)	4.83 e-04
Nickel (ug/m3)	1.52 e-03 (1.60 e-04)	2.55 e-04	1.52 e-03 (1.58 e-04)	2.50 e-04

*For air toxics exposures, zero values were replaced with 1/2 the minimum non-zero value and the upper tails were winsorized at the 99th percentile within each birth year

Table 3-3. Associations of full term criteria pollutant exposure and childhood cancer among offspring per 1 IQR increase; primary analysis (births 1998-2016, continuous exposure variable) (N = 66,456)

Cancer Type	Cases*	PM2.5 (IQR=2.064)		NO2 (IQR=5.769)	
		Single-pollutant OR ^a (95% CI)	PM2.5 Adjusted for NO2 OR ^b (95% CI)	Single-pollutant OR ^a (95% CI)	NO2 Adjusted for PM2.5 OR ^b (95% CI)
All cancers combined	2940	1.06 (0.99, 1.14)	1.11 (1.00, 1.23)	1.01 (0.96, 1.07)	0.95 (0.88, 1.03)
Acute lymphoblastic leukemia	800	0.99 (0.87, 1.13)	0.89 (0.73, 1.08)	1.05 (0.94, 1.17)	1.13 (0.96, 1.33)
Acute myeloid leukemia	147	0.89 (0.66, 1.19)	0.82 (0.52, 1.28)	0.97 (0.76, 1.24)	1.10 (0.76, 1.58)
Central nervous system tumors	615	1.10 (0.95, 1.28)	1.15 (0.93, 1.42)	1.03 (0.91, 1.16)	0.95 (0.80, 1.13)
Astrocytoma	185	1.09 (0.83, 1.43)	1.26 (0.87, 1.83)	0.97 (0.78, 1.20)	0.84 (0.62, 1.14)
Ependymoma	81	1.51 (0.99, 2.31)	1.38 (0.76, 2.50)	1.35 (0.95, 1.91)	1.11 (0.68, 1.82)
Medulloblastoma	76	1.12 (0.73, 1.72)	0.80 (0.42, 1.53)	1.27 (0.89, 1.82)	1.46 (0.85, 2.48)
Germ cell tumors	143	1.03 (0.75, 1.41)	1.59 (1.04, 2.44)	0.81 (0.63, 1.02)	0.62 (0.44, 0.86)
Teratoma	46	0.90 (0.53, 1.53)	1.40 (0.67, 2.90)	0.75 (0.50, 1.12)	0.62 (0.35, 1.09)
Yolk sac tumor	23	0.60 (0.29, 1.22)	0.91 (0.32, 2.62)	0.60 (0.34, 1.06)	0.63 (0.27, 1.50)
Lymphomas	197	1.07 (0.83, 1.39)	1.21 (0.83, 1.76)	0.98 (0.79, 1.20)	0.87 (0.65, 1.18)
Hodgkin lymphoma	74	1.01 (0.66, 1.55)	1.40 (0.78, 2.52)	0.84 (0.60, 1.16)	0.69 (0.44, 1.09)
Non-Hodgkin lymphoma	123	1.12 (0.80, 1.55)	1.09 (0.68, 1.77)	1.08 (0.83, 1.41)	1.02 (0.69, 1.52)
Neuroblastoma	150	1.10 (0.82, 1.49)	1.21 (0.80, 1.83)	1.01 (0.79, 1.28)	0.90 (0.64, 1.27)
Retinoblastoma	123	1.22 (0.87, 1.71)	1.25 (0.78, 2.00)	1.11 (0.84, 1.47)	0.97 (0.66, 1.44)

^aThis model was adjusted for birth year, maternal age, maternal race/ethnicity, and area-level SES (quintile)

^bThis model was adjusted for birth year, maternal age, maternal race/ethnicity, area-level SES (quintile), and highly correlated pollutants

*N Controls = 63,516

Table 3-4. Associations of full-term air toxic exposure and childhood cancer among offspring per 1 IQR increase; primary analysis (births 1998-2016, continuous exposure variable) (N = 66,270)

Cancer	Cases	1,3-Butadiene OR ^a (95% CI)	Benzene OR ^a (95% CI)	Chromium OR ^a (95% CI)	Lead OR ^a (95% CI)	Nickel OR ^a (95% CI)
All cancers combined	2933	1.15 (1.04, 1.27)	1.09 (0.95, 1.25)	1.00 (0.95, 1.04)	1.03 (0.98, 1.09)	0.97 (0.83, 1.13)
Acute lymphoblastic leukemia	800	1.08 (0.90, 1.31)	1.10 (0.84, 1.45)	0.99 (0.91, 1.07)	1.01 (0.91, 1.12)	0.99 (0.74, 1.33)
Acute myeloid leukemia	148	1.22 (0.78, 1.93)	0.70 (0.40, 1.22)	0.98 (0.82, 1.19)	0.85 (0.65, 1.10)	0.76 (0.39, 1.50)
Central nervous system tumors	614	1.17 (0.94, 1.46)	1.15 (0.85, 1.56)	1.01 (0.92, 1.10)	1.09 (0.97, 1.22)	0.95 (0.69, 1.31)
Astrocytoma	182	1.11 (0.75, 1.64)	1.19 (0.68, 2.08)	1.00 (0.85, 1.18)	1.03 (0.83, 1.28)	0.89 (0.49, 1.59)
Ependymoma	82	1.19 (0.63, 2.25)	3.35 (1.18, 9.53)	1.21 (0.95, 1.54)	1.24 (0.94, 1.65)	1.82 (0.71, 4.65)
Medulloblastoma	77	1.26 (0.71, 2.24)	1.23 (0.52, 2.94)	1.01 (0.78, 1.31)	1.06 (0.77, 1.45)	1.56 (0.61, 3.96)
Germ cell tumors	143	1.51 (0.94, 2.42)	0.51 (0.31, 0.84)	0.91 (0.75, 1.10)	0.84 (0.65, 1.09)	1.11 (0.56, 2.18)
Teratoma	46	1.13 (0.53, 2.37)	0.33 (0.16, 0.72)	0.98 (0.70, 1.36)	0.89 (0.56, 1.40)	1.14 (0.35, 3.71)
Yolk sac tumor	23	1.30 (0.36, 4.76)	0.40 (0.12, 1.33)	0.85 (0.52, 1.39)	0.96 (0.52, 1.78)	1.17 (0.20, 6.96)
Lymphomas	197	1.13 (0.77, 1.65)	1.08 (0.66, 1.79)	1.15 (0.98, 1.34)	1.12 (0.93, 1.36)	1.16 (0.66, 2.06)
Hodgkin lymphoma	74	1.58 (0.85, 2.95)	0.89 (0.41, 1.92)	0.96 (0.74, 1.25)	0.72 (0.50, 1.04)	0.71 (0.29, 1.75)
Non-Hodgkin lymphoma	123	0.92 (0.58, 1.47)	1.24 (0.64, 2.41)	1.27 (1.05, 1.54)	1.36 (1.10, 1.68)	1.60 (0.76, 3.37)
Neuroblastoma	149	0.84 (0.56, 1.26)	0.95 (0.52, 1.72)	0.99 (0.82, 1.18)	0.92 (0.72, 1.18)	0.85 (0.43, 1.68)
Retinoblastoma	122	0.97 (0.61, 1.53)	2.06 (0.93, 4.57)	0.99 (0.81, 1.22)	0.98 (0.75, 1.28)	1.20 (0.57, 2.55)

^aThis model was adjusted for birth year, maternal age, maternal race/ethnicity, and area-level SES (quintile)

*N Controls = 63,337

Table 3-5. Associations of full-term air toxic mixture exposure and childhood cancer among offspring; primary analysis (births 1998-2016, continuous exposure variable) (N = 66,270)

Cancer Type	Cases	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
All cancers combined	2933	1.00 (0.93, 1.09)	1.09 (1.00, 1.19)
Acute lymphoblastic leukemia	800	1.02 (0.87, 1.19)	1.09 (0.92, 1.28)
Acute myeloid leukemia	148	0.92 (0.65, 1.32)	0.96 (0.66, 1.39)
Central nervous system tumors	614	0.95 (0.80, 1.13)	1.13 (0.94, 1.35)
Astrocytoma	182	0.85 (0.62, 1.17)	1.11 (0.80, 1.56)
Medulloblastoma	77	1.13 (0.70, 1.81)	1.24 (0.76, 2.03)
Germ cell tumors	143	1.04 (0.74, 1.45)	0.99 (0.70, 1.39)
Teratoma	46	0.77 (0.43, 1.36)	0.77 (0.42, 1.40)
Yolk sac tumor	23	1.04 (0.42, 2.56)	0.86 (0.34, 2.17)
Lymphomas	197	1.07 (0.80, 1.44)	1.13 (0.83, 1.54)
Hodgkin lymphoma	74	1.07 (0.67, 1.71)	1.18 (0.72, 1.93)
Non-Hodgkin lymphoma	123	1.09 (0.75, 1.59)	1.13 (0.76, 1.67)
Neuroblastoma	149	0.75 (0.52, 1.09)	0.86 (0.59, 1.27)
Retinoblastoma	122	1.19 (0.81, 1.76)	1.18 (0.79, 1.77)

^a This model was adjusted for birth year

^b This model was adjusted for birth year, maternal age, maternal race/ethnicity, and neighborhood SES (quintile)

*N Controls = 63,337

3.7 Supplemental materials

Supplemental Table 3-1. Uniform Distribution Parameters for Live-Birth Selection Bias Modeling

Parameter	Value Range c(min, max) ^a
Selection probability among case exposed (S_{11})	c(0.40, 0.60)
Selection probability among case un-exposed (S_{01})	c(0.50, 0.70)
Selection probability among non-case exposed (S_{10})	c(0.60, 0.80)
Selection probability among non-case un-exposed (S_{00})	c(0.70, 0.90)

^aValues define the minimum and maximum boundaries of a uniform distribution from which parameter values were randomly sampled across 100,000 Monte Carlo iterations

*Distribution boundaries represent presumed values based on established live-birth selection bias modeling templates¹³⁰

Supplemental Table 3-2. Pearson correlation coefficients for full-term exposures among controls (1998-2016, N = 63,516)

Criteria Pollutants					
	PM2.5		NO2		O3
PM2.5	1.000		0.767		-0.505
NO2	0.767		1.000		-0.572
O3	-0.505		-0.572		1.000
Air Toxics					
	1,3-Butadiene	Benzene	Chromium	Lead	Nickel
1,3-Butadiene	1.000	0.590	0.694	-0.645	0.075
Benzene	0.590	1.000	0.843	-0.773	0.270
Chromium	0.694	0.843	1.000	-0.829	0.129
Lead	-0.645	-0.773	-0.829	1.000	-0.032
Nickel	0.075	0.270	0.129	-0.032	1.000

Supplemental Table 3-6. Associations of full term criteria pollutant exposure and childhood cancer among offspring per 1 IQR increase; secondary analysis (births 1998-2016, continuous exposure variable) (N = 66,456)

Cancer Type	Cases*	PM2.5 (IQR=2.064)		NO2 (IQR=5.769)	
		Single-pollutant	PM2.5 Adjusted for NO2	Single-pollutant	NO2 Adjusted for PM2.5
		OR ^a (95% CI)	OR ^b (95% CI)	OR ^a (95% CI)	OR ^b (95% CI)
Bone tumors	88	1.03 (0.70, 1.52)	1.22 (0.70, 2.11)	0.93 (0.68, 1.28)	0.83 (0.53, 1.31)
Osteosarcomas	47	0.86 (0.50, 1.47)	0.97 (0.44, 2.15)	0.86 (0.57, 1.32)	0.88 (0.47, 1.66)
Ependymoma	81	1.51 (0.99, 2.31)	1.38 (0.76, 2.50)	1.35 (0.95, 1.91)	1.11 (0.68, 1.82)
Ewing sarcoma	34	1.16 (0.65, 2.08)	1.44 (0.64, 3.20)	0.96 (0.58, 1.59)	0.77 (0.38, 1.54)
Glioma	351	1.15 (0.94, 1.40)	1.34 (1.02, 1.77)	0.99 (0.84, 1.16)	0.83 (0.67, 1.04)
Hepatoblastoma	56	0.79 (0.49, 1.27)	0.72 (0.35, 1.49)	0.90 (0.60, 1.35)	1.10 (0.60, 2.02)
Soft tissue sarcoma	190	1.30 (0.98, 1.71)	1.45 (0.99, 2.11)	1.08 (0.87, 1.35)	0.88 (0.65, 1.19)
Rhabdomyosarcoma	94	1.59 (1.05, 2.40)	2.35 (1.42, 3.91)	0.99 (0.73, 1.35)	0.62 (0.42, 0.93)
Wilms' tumor	121	1.01 (0.73, 1.39)	1.09 (0.69, 1.73)	0.96 (0.74, 1.25)	0.91 (0.62, 1.33)

^aThis model was adjusted for birth year, maternal age, maternal race/ethnicity, and area-level SES (quintile)
^bThis model was adjusted for birth year, maternal age, maternal race/ethnicity, area-level SES (quintile), and highly correlated pollutants
*N Controls = 63,516

Supplemental Table 3-7. Associations of full-term air toxic exposure and childhood cancer among offspring per 1 IQR increase; secondary analysis (births 1998-2016, continuous exposure variable) (N = 66,270)

Cancer	Cases	1,3-Butadiene OR ^a (95% CI)	Benzene OR ^a (95% CI)	Chromium OR ^a (95% CI)	Lead OR ^a (95% CI)	Nickel OR ^a (95% CI)
Bone tumors	85	1.13 (0.64, 1.98)	1.26 (0.55, 2.87)	0.96 (0.75, 1.23)	1.09 (0.81, 1.48)	0.94 (0.39, 2.23)
Osteosarcomas	47	0.75 (0.39, 1.44)	1.49 (0.47, 4.73)	0.92 (0.66, 1.28)	1.23 (0.84, 1.79)	1.38 (0.43, 4.42)
Ependymoma	82	1.19 (0.63, 2.25)	3.35 (1.18, 9.53)	1.21 (0.95, 1.54)	1.24 (0.94, 1.65)	1.82 (0.71, 4.65)
Ewing sarcoma	31	2.06 (0.83, 5.11)	0.93 (0.25, 3.37)	0.95 (0.63, 1.42)	0.96 (0.56, 1.64)	0.58 (0.14, 2.40)
Glioma	351	1.09 (0.82, 1.45)	1.16 (0.78, 1.74)	1.01 (0.90, 1.14)	1.05 (0.91, 1.23)	0.93 (0.61, 1.43)
Hepatoblastoma	57	1.17 (0.58, 2.37)	1.32 (0.43, 4.06)	1.07 (0.79, 1.44)	0.79 (0.51, 1.20)	0.31 (0.10, 0.93)
Soft tissue sarcoma	189	1.71 (1.12, 2.61)	1.07 (0.63, 1.80)	0.91 (0.77, 1.07)	1.01 (0.82, 1.25)	1.69 (0.93, 3.06)
Rhabdomyosarcoma	93	1.89 (1.01, 3.54)	1.23 (0.58, 2.62)	0.86 (0.68, 1.08)	1.02 (0.76, 1.37)	1.60 (0.67, 3.79)
Wilms' tumor	121	1.06 (0.66, 1.70)	1.36 (0.66, 2.81)	1.03 (0.84, 1.26)	1.30 (1.03, 1.64)	0.50 (0.23, 1.06)

^a This model was adjusted for birth year, maternal age, maternal race/ethnicity, and area-level SES (quintile)

*N Controls = 63,337

Supplemental Table 3-8. Associations of full-term air toxic mixture exposure and childhood cancer among offspring; secondary analysis (births 1998-2016, continuous exposure variable) (N = 66,270)

Cancer Type	Cases	Crude OR ^a (95% CI)	Adjusted OR ^b (95% CI)
Bone tumors	85	0.91 (0.58, 1.41)	0.97 (0.61, 1.53)
Osteosarcomas	47	0.87 (0.47, 1.59)	0.94 (0.49, 1.78)
Ependymoma	82	1.79 (1.05, 3.07)	2.17 (1.23, 3.82)
Ewing sarcoma	31	0.82 (0.43, 1.59)	0.90 (0.45, 1.79)
Glioma	351	0.92 (0.73, 1.16)	1.10 (0.87, 1.41)
Hepatoblastoma	57	0.62 (0.35, 1.10)	0.69 (0.37, 1.26)
Soft tissue sarcoma	189	1.31 (0.95, 1.79)	1.41 (1.02, 1.96)
Rhabdomyosarcoma	93	1.57 (0.99, 2.49)	1.59 (0.98, 2.59)
Wilms' tumor	121	0.83 (0.55, 1.25)	0.92 (0.60, 1.41)

^aThis model was adjusted for birth year

^bThis model was adjusted for birth year, maternal age, maternal race/ethnicity, and neighborhood SES (quintile)

*N Controls = 63,337

Supplemental Table 3-6. Trimester-specific associations of criteria pollutant exposure and childhood cancer among offspring per 1 IQR increase (births 1998-2016, continuous exposure variable) (N = 66,456) (2940 Cases, 63516 Controls)

Cancer Type	Trimester	Cases	PM _{2.5}	NO ₂	O ₃
			OR ^a (95% CI)	OR ^a (95% CI)	OR ^a (95% CI)
All cancers combined	1	2940	1.02 (0.97, 1.08)	1.03 (0.97, 1.10)	1.01 (0.95, 1.07)
	2	2940	1.02 (0.97, 1.08)	0.99 (0.93, 1.05)	1.01 (0.95, 1.07)
	3	2931	1.07 (1.01, 1.13)	1.00 (0.94, 1.07)	0.96 (0.91, 1.02)
Acute lymphoblastic leukemia	1	800	1.03 (0.93, 1.15)	1.06 (0.94, 1.18)	0.97 (0.87, 1.09)
	2	800	0.99 (0.89, 1.10)	1.05 (0.94, 1.18)	0.97 (0.87, 1.09)
	3	796	0.98 (0.88, 1.10)	0.99 (0.89, 1.12)	0.96 (0.85, 1.08)
Acute myeloid leukemia	1	147	0.79 (0.62, 1.01)	0.94 (0.72, 1.23)	1.22 (0.95, 1.58)
	2	147	0.97 (0.76, 1.25)	1.02 (0.78, 1.33)	0.97 (0.74, 1.26)
	3	147	1.05 (0.81, 1.36)	0.94 (0.72, 1.24)	0.83 (0.64, 1.09)
Bone tumors	1	88	1.01 (0.74, 1.38)	0.86 (0.61, 1.22)	1.17 (0.84, 1.64)
	2	88	0.95 (0.69, 1.31)	0.90 (0.64, 1.27)	1.10 (0.79, 1.54)
	3	88	1.18 (0.85, 1.63)	1.13 (0.80, 1.59)	0.80 (0.57, 1.14)
Osteosarcomas	1	47	1.02 (0.65, 1.58)	1.01 (0.63, 1.61)	1.07 (0.67, 1.71)
	2	47	0.76 (0.48, 1.19)	0.78 (0.49, 1.26)	1.31 (0.83, 2.08)
	3	47	1.08 (0.68, 1.70)	0.95 (0.59, 1.53)	0.88 (0.55, 1.43)
Central nervous system tumors	1	615	1.02 (0.90, 1.15)	1.04 (0.92, 1.19)	0.93 (0.82, 1.06)
	2	615	1.06 (0.94, 1.20)	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)
	3	614	1.09 (0.96, 1.23)	1.02 (0.89, 1.16)	1.00 (0.88, 1.14)
Astrocytoma	1	185	1.07 (0.86, 1.33)	0.97 (0.76, 1.23)	0.95 (0.75, 1.21)
	2	185	1.06 (0.85, 1.33)	0.98 (0.78, 1.25)	1.03 (0.82, 1.31)
	3	184	1.02 (0.81, 1.27)	0.98 (0.77, 1.25)	1.02 (0.80, 1.29)
Ependymoma	1	81	1.10 (0.80, 1.52)	1.07 (0.75, 1.54)	1.06 (0.75, 1.50)
	2	81	1.38 (1.00, 1.89)	1.24 (0.87, 1.76)	0.84 (0.59, 1.20)
	3	81	1.35 (0.97, 1.88)	1.31 (0.92, 1.87)	0.88 (0.62, 1.26)
Glioma	1	351	1.05 (0.89, 1.23)	1.00 (0.84, 1.19)	0.97 (0.82, 1.16)
	2	351	1.10 (0.93, 1.29)	0.96 (0.81, 1.14)	1.04 (0.87, 1.23)
	3	350	1.10 (0.93, 1.29)	1.02 (0.85, 1.21)	1.04 (0.88, 1.23)
Medulloblastoma	1	76	1.10 (0.79, 1.55)	1.28 (0.88, 1.84)	0.73 (0.50, 1.07)
	2	76	1.00 (0.71, 1.42)	1.18 (0.82, 1.70)	0.99 (0.69, 1.42)
	3	76	1.13 (0.79, 1.60)	1.04 (0.72, 1.50)	1.03 (0.71, 1.49)
Ewing sarcoma	1	34	1.04 (0.66, 1.64)	0.73 (0.41, 1.27)	1.20 (0.71, 2.03)
	2	34	1.07 (0.67, 1.70)	0.95 (0.55, 1.65)	1.01 (0.60, 1.71)
	3	34	1.22 (0.74, 2.02)	1.31 (0.92, 1.87)	0.88 (0.62, 1.26)
Germ cell tumors	1	143	1.05 (0.82, 1.35)	1.01 (0.77, 1.32)	0.96 (0.73, 1.26)
	2	143	0.96 (0.75, 1.25)	0.85 (0.65, 1.12)	1.11 (0.85, 1.45)
	3	142	1.08 (0.84, 1.40)	0.70 (0.53, 0.93)	1.15 (0.88, 1.51)
Teratoma	1	46	0.93 (0.60, 1.45)	1.04 (0.65, 1.66)	0.81 (0.50, 1.31)

	2	46	0.94 (0.59, 1.48)	0.79 (0.49, 1.27)	0.90 (0.56, 1.44)
	3	45	0.92 (0.59, 1.45)	0.56 (0.34, 0.93)	1.21 (0.76, 1.93)
Yolk sac tumor	1	23	1.00 (0.51, 1.94)	1.65 (0.83, 3.25)	0.70 (0.34, 1.42)
	2	23	0.72 (0.37, 1.40)	0.58 (0.28, 1.18)	1.53 (0.79, 2.96)
	3	23	0.47 (0.26, 0.85)	0.26 (0.12, 0.59)	1.62 (0.85, 3.12)
Hepatoblastoma	1	56	0.85 (0.57, 1.28)	0.91 (0.58, 1.41)	1.07 (0.70, 1.65)
	2	56	0.95 (0.63, 1.45)	0.99 (0.65, 1.53)	0.94 (0.61, 1.43)
	3	55	0.74 (0.49, 1.14)	0.86 (0.55, 1.35)	1.08 (0.70, 1.66)
Lymphomas	1	197	1.00 (0.81,1.24)	1.05 (0.84,1.32)	1.22 (0.98,1.53)
	2	197	1.00 (0.81,1.24)	0.89 (0.71,1.12)	1.12 (0.89,1.40)
	3	196	1.14 (0.92,1.41)	1.00 (0.80, 1.26)	0.92 (0.73, 1.15)
Hodgkin lymphoma	1	74	0.93 (0.66, 1.33)	1.09 (0.75, 1.58)	1.14 (0.79, 1.65)
	2	74	0.92 (0.64, 1.32)	0.64 (0.44, 0.94)	1.18 (0.81, 1.71)
	3	73	1.12 (0.79, 1.60)	0.90 (0.62, 1.32)	0.97 (0.66, 1.42)
Non-Hodgkin lymphoma	1	123	1.04 (0.81, 1.35)	1.03 (0.77, 1.37)	1.27 (0.96, 1.68)
	2	123	1.05 (0.81, 1.37)	1.07 (0.80, 1.42)	1.09 (0.82, 1.44)
	3	123	1.15 (0.87, 1.51)	1.06 (0.80, 1.42)	0.89 (0.66, 1.19)
Neuroblastoma	1	150	1.06 (0.84, 1.35)	0.91 (0.69, 1.18)	1.02 (0.79, 1.32)
	2	150	1.03 (0.81, 1.31)	0.96 (0.74, 1.24)	1.11 (0.86, 1.43)
	3	150	1.06 (0.82, 1.36)	1.19 (0.92, 1.55)	0.96 (0.74, 1.24)
Retinoblastoma	1	123	1.07 (0.82, 1.39)	1.16 (0.87, 1.55)	1.14 (0.86, 1.52)
	2	123	1.01 (0.77, 1.31)	0.93 (0.69, 1.24)	1.15 (0.87, 1.53)
	3	123	1.29 (0.99, 1.68)	1.17 (0.88, 1.56)	0.85 (0.63, 1.15)
Soft tissue sarcoma	1	190	1.12 (0.90, 1.39)	1.01 (0.80, 1.28)	1.09 (0.87, 1.37)
	2	190	1.13 (0.91, 1.41)	1.07 (0.85, 1.35)	0.91 (0.72, 1.15)
	3	190	1.22 (0.98, 1.52)	1.07 (0.85, 1.36)	0.93 (0.73, 1.17)
Rhabdomyosarcomas	1	94	1.24 (0.92, 1.69)	1.14 (0.82, 1.59)	0.95 (0.69, 1.32)
	2	94	1.10 (0.81, 1.50)	0.85 (0.61, 1.19)	1.06 (0.77, 1.48)
	3	94	1.50 (1.10, 2.04)	0.98 (0.71, 1.37)	0.81 (0.58, 1.13)
Wilms' tumor	1	121	0.97 (0.74, 1.26)	1.18 (0.88, 1.58)	0.97 (0.73, 1.29)
	2	121	1.02 (0.78, 1.34)	0.87 (0.65, 1.17)	1.34 (1.02, 1.76)
	3	121	1.03 (0.78, 1.35)	0.89 (0.66, 1.19)	1.07 (0.81, 1.42)

*This model was adjusted for maternal age (continuous), maternal race/ethnicity, birthyear, and ses (quintile)

Supplemental Table 3-7. Associations of criteria pollutant exposure 1 year after birth and childhood cancer among offspring (births 1998-2016, quartile exposure variable) (N = 66,449)

Cancer Type	Cases*	PM _{2.5} OR ^a (95% CI)	NO ₂ OR ^a (95% CI)	O ₃ OR ^a (95% CI)
All cancers combined	2939	1.01 (0.94, 1.10)	1.04 (0.98, 1.11)	1.00 (0.95, 1.06)
Acute lymphoblastic leukemia	800	0.96 (0.83, 1.12)	1.07 (0.95, 1.21)	0.93 (0.83, 1.04)
Acute myeloid leukemia	147	0.84 (0.60, 1.18)	0.84 (0.65, 1.10)	1.21 (0.95, 1.56)
Bone tumors	88	1.01 (0.65, 1.56)	0.97 (0.69, 1.37)	0.97 (0.70, 1.33)
Osteosarcomas	47	0.98 (0.53, 1.80)	0.92 (0.57, 1.46)	0.99 (0.64, 1.54)
Central nervous system tumors	615	0.99 (0.84, 1.16)	1.04 (0.91, 1.19)	0.97 (0.86, 1.10)
Astrocytoma	185	1.05 (0.78, 1.41)	0.98 (0.77, 1.24)	0.98 (0.79, 1.21)
Ependymoma	81	1.35 (0.84, 2.18)	1.45 (0.97, 2.17)	0.87 (0.62, 1.22)
Glioma	351	1.01 (0.81, 1.25)	1.05 (0.88, 1.25)	1.01 (0.86, 1.19)
Medulloblastoma	76	1.01 (0.63, 1.62)	1.19 (0.80, 1.77)	0.87 (0.62, 1.22)
Ewing sarcoma	34	0.97 (0.50, 1.90)	1.00 (0.58, 1.73)	0.92 (0.56, 1.53)
Germ cell tumors	143	0.77 (0.56, 1.06)	0.70 (0.54, 0.89)	1.40 (1.09, 1.80)
Teratoma	46	0.69 (0.40, 1.19)	0.54 (0.37, 0.80)	1.51 (0.98, 2.33)
Yolk sac tumor	23	0.54 (0.26, 1.14)	0.60 (0.33, 1.10)	1.42 (0.75, 2.69)
Hepatoblastoma	56	0.96 (0.55, 1.68)	0.94 (0.60, 1.48)	1.08 (0.72, 1.62)
Lymphomas	197	1.06 (0.79, 1.41)	1.04 (0.83, 1.31)	1.13 (0.92, 1.40)
Hodgkin lymphoma	74	1.04 (0.65, 1.66)	0.99 (0.68, 1.44)	1.09 (0.77, 1.54)
Non-Hodgkin lymphoma	123	1.07 (0.74, 1.55)	1.08 (0.80, 1.45)	1.17 (0.89, 1.52)
Neuroblastoma	149	1.04 (0.74, 1.46)	1.02 (0.78, 1.33)	1.18 (0.93, 1.51)
Retinoblastoma	123	1.50 (1.00, 2.26)	1.88 (1.33, 2.66)	0.78 (0.59, 1.02)
Soft tissue sarcoma	190	1.14 (0.84, 1.54)	1.08 (0.85, 1.38)	1.12 (0.90, 1.39)
Rhabdomyosarcoma	94	1.14 (0.74, 1.76)	1.10 (0.78, 1.55)	0.87 (0.64, 1.18)
Wilms' tumor	121	1.16 (0.79, 1.70)	1.20 (0.88, 1.64)	0.99 (0.76, 1.29)

^aThis model was adjusted for birth year, maternal age, maternal race/ethnicity, and area-level SES (quintile)

*N Controls = 63,510

**Exposure was truncated at time of diagnosis for cases diagnosed before 1 year of life

Supplemental Table 3-8. Associations of air toxics exposure 1 year after birth and childhood cancer among offspring (births 1998-2016, continuous exposure variable) (N = 66,183)

Cancer Type	Cases*	1,3-Butadiene OR ^a (95% CI)	Benzene OR ^a (95% CI)	Chromium OR ^a (95% CI)	Lead OR ^a (95% CI)	Nickel OR ^a (95% CI)
All cancers combined	2912	1.02 (0.89, 1.18)	1.12 (0.96, 1.30)	1.00 (0.96, 1.04)	1.05 (0.99, 1.11)	0.98 (0.83, 1.15)
Acute lymphoblastic leukemia	799	0.99 (0.76, 1.30)	1.12 (0.83, 1.50)	0.99 (0.91, 1.07)	1.00 (0.90, 1.11)	0.97 (0.71, 1.33)
Acute myeloid leukemia	146	0.90 (0.52, 1.56)	0.61 (0.34, 1.07)	0.98 (0.81, 1.18)	0.88 (0.68, 1.14)	0.71 (0.35, 1.47)
Bone tumors	86	0.86 (0.48, 1.56)	1.24 (0.52, 2.95)	0.98 (0.77, 1.26)	1.12 (0.84, 1.51)	0.89 (0.35, 2.23)
Osteosarcomas	47	1.15 (0.41, 3.23)	1.32 (0.40, 4.39)	0.93 (0.67, 1.30)	1.21 (0.82, 1.77)	1.64 (0.47, 5.75)
Central nervous system tumors	611	0.95 (0.73, 1.22)	1.17 (0.84, 1.61)	1.01 (0.92, 1.11)	1.10 (0.98, 1.23)	0.98 (0.69, 1.39)
Astrocytoma	182	0.97 (0.62, 1.50)	1.19 (0.65, 2.16)	1.00 (0.85, 1.18)	1.03 (0.83, 1.28)	0.83 (0.44, 1.56)
Ependymoma	81	3.49 (1.00, 12.11)	2.91 (0.94, 9.08)	1.18 (0.93, 1.51)	1.21 (0.91, 1.63)	1.90 (0.69, 5.22)
Glioma	350	1.08 (0.72, 1.61)	1.17 (0.76, 1.81)	1.01 (0.89, 1.14)	1.05 (0.90, 1.23)	0.96 (0.61, 1.53)
Medulloblastoma	77	0.58 (0.40, 0.86)	1.15 (0.46, 2.85)	1.01 (0.78, 1.31)	1.09 (0.80, 1.49)	1.93 (0.70, 5.30)
Ewing sarcoma	32	0.64 (0.33, 1.26)	1.10 (0.27, 4.44)	1.00 (0.67, 1.49)	1.08 (0.66, 1.77)	0.43 (0.10, 1.89)
Germ cell tumors	135	1.22 (0.57, 2.61)	0.62 (0.35, 1.10)	0.94 (0.77, 1.15)	0.98 (0.76, 1.26)	1.19 (0.56, 2.52)
Teratoma	38	1.04 (0.32, 3.36)	0.57 (0.20, 1.57)	1.13 (0.78, 1.63)	1.36 (0.92, 2.01)	1.18 (0.29, 4.83)
Yolk sac tumor	23	0.62 (0.20, 1.96)	0.43 (0.11, 1.59)	0.85 (0.52, 1.39)	0.96 (0.52, 1.80)	1.56 (0.23, 10.53)
Hepatoblastoma	57	1.37 (0.36, 5.21)	1.22 (0.37, 3.99)	1.07 (0.79, 1.44)	0.74 (0.48, 1.14)	0.28 (0.09, 0.92)
Lymphomas	197	1.23 (0.67, 2.26)	1.05 (0.62, 1.78)	1.15 (0.98, 1.35)	1.15 (0.95, 1.39)	1.28 (0.69, 2.36)
Hodgkin lymphoma	74	1.24 (0.51, 3.04)	0.96 (0.42, 2.20)	0.96 (0.74, 1.25)	0.77 (0.53, 1.11)	0.83 (0.32, 2.17)
Non-Hodgkin lymphoma	123	1.24 (0.55, 2.84)	1.12 (0.56, 2.23)	1.27 (1.05, 1.54)	1.37 (1.11, 1.69)	1.70 (0.77, 3.77)
Neuroblastoma	147	1.18 (0.56, 2.50)	0.92 (0.49, 1.73)	1.00 (0.83, 1.20)	0.93 (0.73, 1.20)	0.92 (0.44, 1.90)
Retinoblastoma	120	1.03 (0.50, 2.16)	2.32 (0.94, 5.77)	0.97 (0.79, 1.20)	0.97 (0.74, 1.28)	1.12 (0.50, 2.51)
Soft tissue sarcoma	189	0.97 (0.59, 1.58)	1.04 (0.59, 1.82)	0.90 (0.77, 1.07)	1.02 (0.83, 1.26)	1.58 (0.84, 2.99)
Rhabdomyosarcoma	93	1.51 (0.53, 4.26)	1.25 (0.55, 2.83)	0.86 (0.68, 1.08)	1.02 (0.76, 1.37)	1.66 (0.66, 4.16)
Wilms' tumor	121	0.83 (0.46, 1.50)	1.78 (0.78, 4.06)	1.02 (0.83, 1.26)	1.30 (1.03, 1.64)	0.53 (0.24, 1.19)

^aThis model was adjusted for birth year, maternal age, maternal race/ethnicity, and area-level SES (quintile)

*N Controls = 63,271

**Exposure was truncated at time of diagnosis for cases diagnosed before 1 year of life

Supplemental Table 3-9. Associations of full term criteria pollutant exposure and childhood cancer among offspring per 1 IQR increase (births 1998-2016, continuous exposure variable) stratified by race/ethnicity

Cancer Type	Non-Hispanic White (N = 12,214)				Hispanic (N = 41,686)			
	Cases (N Controls=11,590)	PM _{2.5} OR ^a (95% CI)	NO ₂ OR ^a (95% CI)	O ₃ OR ^a (95% CI)	Cases (N Controls=39,812)	PM _{2.5} OR ^a (95% CI)	NO ₂ OR ^a (95% CI)	O ₃ OR ^a (95% CI)
All cancers combined	624	1.08 (0.94, 1.23)	1.02 (0.92, 1.14)	0.94 (0.85, 1.04)	1,874	1.06 (0.97, 1.16)	1.02 (0.95, 1.10)	1.00 (0.94, 1.07)
Acute lymphoblastic leukemia	139	0.99 (0.75, 1.30)	1.05 (0.82, 1.34)	0.85 (0.68, 1.05)	559	1.00 (0.85, 1.18)	1.06 (0.93, 1.22)	0.96 (0.86, 1.08)
Acute myeloid leukemia	27	0.83 (0.45, 1.53)	0.86 (0.53, 1.40)	0.86 (0.53, 1.39)	94	0.91 (0.62, 1.33)	1.08 (0.78, 1.50)	1.05 (0.79, 1.39)
Bone tumors	21	0.94 (0.47, 1.90)	0.78 (0.44, 1.38)	0.93 (0.54, 1.62)	55	1.06 (0.64, 1.75)	0.94 (0.62, 1.42)	1.19 (0.83, 1.71)
Central nervous system tumors	153	1.33 (1.01, 1.74)	1.16 (0.93, 1.46)	0.87 (0.71, 1.07)	372	1.06 (0.87, 1.30)	1.01 (0.86, 1.19)	1.01 (0.88, 1.17)
Astrocytoma	60	1.52 (0.98, 2.38)	1.16 (0.80, 1.69)	0.73 (0.53, 1.03)	97	1.01 (0.68, 1.50)	0.96 (0.70, 1.32)	1.13 (0.85, 1.49)
Glioma	95	1.33 (0.94, 1.88)	1.05 (0.80, 1.40)	0.88 (0.68, 1.14)	196	1.13 (0.85, 1.49)	1.01 (0.80, 1.26)	1.16 (0.95, 1.41)
Germ cell tumors	27	1.22 (0.65, 2.28)	0.79 (0.49, 1.29)	1.17 (0.74, 1.85)	97	0.85 (0.58, 1.25)	0.79 (0.58, 1.07)	1.12 (0.84, 1.49)
Lymphomas	49	0.74 (0.48, 1.14)	0.83 (0.58, 1.18)	1.40 (1.00, 1.96)	119	1.19 (0.83, 1.71)	0.98 (0.73, 1.30)	1.13 (0.88, 1.46)
Hodgkin lymphoma	21	0.90 (0.44, 1.86)	1.26 (0.69, 2.29)	1.00 (0.57, 1.75)	46	0.92 (0.52, 1.63)	0.58 (0.39, 0.88)	1.45 (0.98, 2.14)
Non-Hodgkin lymphoma	28	0.66 (0.38, 1.13)	0.65 (0.42, 1.01)	1.70 (1.12, 2.58)	73	1.40 (0.88, 2.24)	1.43 (0.97, 2.11)	0.97 (0.70, 1.34)
Neuroblastoma	43	1.38 (0.83, 2.30)	1.30 (0.85, 1.98)	0.80 (0.55, 1.17)	86	1.02 (0.68, 1.54)	0.91 (0.65, 1.27)	1.13 (0.84, 1.51)
Retinoblastoma	20	0.85 (0.43, 1.68)	0.86 (0.48, 1.54)	1.42 (0.85, 2.36)	78	1.30 (0.84, 2.02)	1.21 (0.84, 1.74)	0.90 (0.65, 1.23)
Soft tissue sarcoma	42	0.93 (0.57, 1.49)	0.90 (0.61, 1.34)	1.17 (0.81, 1.69)	113	1.67 (1.11, 2.50)	1.29 (0.95, 1.76)	0.77 (0.59, 1.01)
Wilms' tumor	27	1.30 (0.69, 2.46)	1.38 (0.80, 2.38)	0.92 (0.58, 1.46)	67	0.89 (0.57, 1.38)	0.83 (0.58, 1.20)	1.34 (0.98, 1.84)

^aThis model was adjusted for birth year, maternal age, and area-level SES (quintile)

*Displaying cancer types with >=20 cases in both race/ethnicity groups

Supplemental Table 3-10. Associations of full-term air toxic exposure and childhood cancer among offspring per 1 IQR increase (births 1998-2016, continuous exposure variable) stratified by maternal race/ethnicity

Cancer Type	Non-Hispanic White (N = 11,995)	Hispanic (N = 41,773)	1,3-Butadiene		Benzene		Chromium		Lead		Nickel	
	Cases	Cases	OR ^a (95% CI)		OR ^a (95% CI)		OR ^a (95% CI)		OR ^a (95% CI)		OR ^a (95% CI)	
	(N Controls=11,386)	(N Controls=39,890)	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic
All cancers combined	609	1,883	1.08 (0.89, 1.32)	1.18 (1.04, 1.35)	1.23 (0.94, 1.62)	1.01 (0.84, 1.22)	1.05 (0.97, 1.14)	0.95 (0.90, 1.01)	1.06 (0.94, 1.19)	1.03 (0.96, 1.10)	1.08 (0.80, 1.46)	0.94 (0.77, 1.15)
Acute lymphoblastic leukemia	135	562	0.91 (0.64, 1.29)	1.18 (0.93, 1.49)	1.36 (0.72, 2.59)	1.02 (0.73, 1.43)	1.06 (0.89, 1.26)	0.95 (0.86, 1.05)	1.20 (0.94, 1.53)	0.96 (0.85, 1.09)	1.10 (0.59, 2.05)	0.94 (0.65, 1.35)
Acute myeloid leukemia	27	95	2.51 (0.94, 6.72)	1.25 (0.68, 2.29)	0.63 (0.23, 1.75)	0.79 (0.37, 1.67)	1.10 (0.75, 1.62)	0.98 (0.76, 1.26)	1.29 (0.78, 2.13)	0.78 (0.56, 1.09)	0.57 (0.15, 2.12)	0.89 (0.36, 2.16)
Central nervous system tumor	150	375	1.09 (0.74, 1.60)	1.35 (1.01, 1.81)	1.56 (0.87, 2.77)	0.99 (0.67, 1.47)	1.09 (0.92, 1.29)	0.95 (0.84, 1.08)	1.20 (0.95, 1.51)	1.08 (0.93, 1.24)	1.35 (0.74, 2.45)	0.99 (0.64, 1.53)
Astrocytoma	57	97	1.15 (0.61, 2.18)	1.23 (0.70, 2.14)	2.63 (0.90, 7.70)	0.90 (0.42, 1.94)	1.27 (0.97, 1.67)	0.82 (0.64, 1.06)	1.45 (1.03, 2.06)	0.91 (0.67, 1.25)	1.13 (0.44, 2.93)	1.42 (0.59, 3.39)
Glioma	93	198	0.98 (0.61, 1.59)	1.30 (0.87, 1.92)	1.51 (0.74, 3.10)	1.03 (0.59, 1.80)	1.12 (0.91, 1.38)	0.92 (0.78, 1.10)	1.17 (0.87, 1.56)	1.05 (0.86, 1.29)	1.08 (0.51, 2.29)	1.14 (0.62, 2.10)
Germ cell	26	97	1.41 (0.50, 3.94)	1.27 (0.70, 2.29)	0.74 (0.24, 2.24)	0.45 (0.24, 0.82)	1.03 (0.70, 1.51)	0.83 (0.64, 1.06)	0.93 (0.53, 1.64)	0.88 (0.64, 1.20)	0.68 (0.17, 2.70)	1.19 (0.50, 2.82)
Lymphomas	48	120	1.02 (0.53, 1.98)	1.24 (0.75, 2.05)	0.82 (0.38, 1.80)	1.26 (0.61, 2.63)	0.99 (0.75, 1.31)	1.11 (0.89, 1.37)	0.66 (0.43, 1.01)	1.23 (0.98, 1.54)	0.98 (0.36, 2.66)	1.13 (0.52, 2.46)
Hodgkin lymphoma	20	47	1.81 (0.54, 6.07)	1.58 (0.71, 3.51)	1.14 (0.29, 4.54)	0.62 (0.24, 1.62)	1.01 (0.64, 1.58)	0.82 (0.57, 1.18)	0.72 (0.37, 1.37)	0.67 (0.41, 1.10)	1.46 (0.31, 6.79)	0.40 (0.12, 1.33)
Non-Hodgkin lymphoma	28	73	0.79 (0.40, 1.55)	1.07 (0.56, 2.03)	0.69 (0.27, 1.77)	2.45 (0.82, 7.32)	0.98 (0.68, 1.40)	1.30 (1.01, 1.67)	0.62 (0.35, 1.08)	1.54 (1.21, 1.95)	0.72 (0.19, 2.69)	2.32 (0.83, 6.49)
Neuroblastoma	42	86	0.76 (0.44, 1.31)	0.88 (0.47, 1.67)	1.90 (0.63, 5.75)	0.69 (0.32, 1.52)	1.12 (0.83, 1.53)	0.88 (0.67, 1.14)	0.92 (0.59, 1.45)	0.89 (0.64, 1.24)	0.83 (0.27, 2.58)	0.87 (0.34, 2.24)
Soft tissue sarcoma	42	112	2.09 (0.87, 5.01)	1.40 (0.79, 2.46)	0.93 (0.36, 2.36)	1.07 (0.52, 2.21)	1.00 (0.74, 1.36)	0.89 (0.71, 1.13)	0.83 (0.52, 1.33)	1.13 (0.88, 1.46)	1.41 (0.45, 4.39)	1.89 (0.84, 4.29)
Wilms' tumor	27	67	0.97 (0.36, 2.57)	1.16 (0.61, 2.20)	1.49 (0.36, 6.16)	1.23 (0.45, 3.31)	0.99 (0.67, 1.44)	1.05 (0.79, 1.40)	1.12 (0.63, 1.99)	1.40 (1.06, 1.86)	0.65 (0.14, 3.05)	0.50 (0.18, 1.39)

^aThis model was adjusted for birth year, maternal age, and area-level SES (quintile)

*Displaying cancer types with >=20 cases in both race/ethnicity groups

Supplemental Table 3-11. Probabilistic bias analysis estimates and 95% simulation intervals for the association between prenatal exposure to criteria air pollutants and childhood cancer risk, comparing the highest quartile of exposure to the lower three quartiles combined (Q4vs. Q1-Q3) (births 1998-2016) (N = 66,456)

Cancer Type	PM _{2.5}			NO ₂			O ₃		
	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)
All cancers combined	751	1.03 (0.95, 1.12)	1.08 (0.75, 1.55)	740	1.01 (0.93, 1.10)	1.06 (0.74, 1.52)	720	0.97 (0.89, 1.06)	1.02 (0.71, 1.47)
Acute lymphoblastic leukemia	190	0.93 (0.79, 1.10)	0.98 (0.69, 1.41)	186	0.91 (0.77, 1.07)	0.96 (0.67, 1.37)	184	0.90 (0.76, 1.06)	0.94 (0.66, 1.35)
Acute myeloid leukemia	32	0.83 (0.56, 1.24)	0.88 (0.61, 1.26)	36	0.97 (0.67, 1.42)	1.02 (0.71, 1.47)	34	0.90 (0.61, 1.32)	0.95 (0.66, 1.36)
Bone tumors	25	1.19 (0.75, 1.89)	1.25 (0.87, 1.80)	22	1.00 (0.62, 1.62)	1.05 (0.73, 1.51)	22	1.00 (0.62, 1.62)	1.05 (0.73, 1.51)
Central nervous system tumors	144	0.92 (0.76, 1.11)	0.96 (0.67, 1.38)	156	1.02 (0.85, 1.22)	1.07 (0.75, 1.54)	157	1.03 (0.86, 1.23)	1.08 (0.75, 1.55)
Astrocytoma	47	1.02 (0.73, 1.42)	1.07 (0.75, 1.54)	43	0.91 (0.65, 1.28)	0.96 (0.67, 1.37)	45	0.96 (0.69, 1.35)	1.01 (0.71, 1.45)
Ependymoma	21	1.05 (0.64, 1.73)	1.10 (0.77, 1.58)	23	1.19 (0.73, 1.93)	1.25 (0.87, 1.79)	24	1.26 (0.78, 2.04)	1.33 (0.93, 1.90)
Glioma	88	1.00 (0.79, 1.28)	1.06 (0.74, 1.51)	82	0.91 (0.71, 1.17)	0.96 (0.67, 1.38)	94	1.10 (0.87, 1.39)	1.15 (0.80, 1.65)
Medulloblastoma	17	--	--	22	1.22 (0.74, 2.01)	1.29 (0.90, 1.84)	23	1.30 (0.80, 2.12)	1.37 (0.95, 1.96)
Germ cell tumors	52	1.71 (1.22, 2.41)	1.80 (1.26, 2.58)	41	1.21 (0.84, 1.73)	1.27 (0.88, 1.82)	38	1.09 (0.75, 1.57)	1.14 (0.80, 1.64)
Hepatoblastoma	6	--	--	10	--	--	20	1.67 (0.96, 2.88)	1.75 (1.22, 2.51)
Lymphomas	56	1.19 (0.87, 1.62)	1.25 (0.87, 1.80)	53	1.10 (0.81, 1.51)	1.16 (0.81, 1.66)	52	1.08 (0.78, 1.48)	1.13 (0.79, 1.62)
Hodgkin lymphoma	19	--	--	18	--	--	20	1.11 (0.66, 1.86)	1.17 (0.81, 1.68)
Non-Hodgkin lymphoma	37	1.29 (0.88, 1.90)	1.36 (0.95, 1.95)	35	1.19 (0.81, 1.77)	1.25 (0.88, 1.80)	32	1.05 (0.70, 1.58)	1.11 (0.77, 1.59)
Neuroblastoma	32	0.81 (0.55, 1.20)	0.86 (0.60, 1.23)	27	0.66 (0.43, 1.00)	0.69 (0.48, 0.99)	46	1.33 (0.94, 1.88)	1.40 (0.97, 2.00)
Retinoblastoma	35	1.19 (0.81, 1.77)	1.25 (0.88, 1.80)	37	1.29 (0.88, 1.90)	1.36 (0.95, 1.95)	25	0.77 (0.49, 1.19)	0.80 (0.56, 1.15)
Soft tissue sarcoma	64	1.52 (1.13, 2.06)	1.60 (1.12, 2.30)	57	1.29 (0.94, 1.75)	1.35 (0.94, 1.94)	41	0.83 (0.58, 1.17)	0.87 (0.61, 1.24)
Rhabdomyosarcoma	35	1.78 (1.17, 2.70)	1.87 (1.31, 2.68)	27	1.21 (0.77, 1.89)	1.27 (0.89, 1.82)	18	--	--
Wilms' tumor	20	0.59 (0.37, 0.96)	0.62 (0.44, 0.90)	16	--	--	40	1.48 (1.01, 2.16)	1.56 (1.09, 2.23)

*N Cases = 2,940 N Controls = 63,516; N exposed Controls = 15,879

**CI=confidence interval; OR=odds ratio; SI=simulation interval

***Displaying cancer types with >= 20 exposed cases

Supplemental Table 3-12.Probabilistic bias analysis estimates and 95% simulation intervals for the association between prenatal exposure to air toxics and childhood cancer risk, comparing the highest quartile of exposure to the lower three quartiles combined (Q4 vs. Q1-Q3) (births 1998-2016) (N = 66,321)

Cancer Type	1,3-Butadiene			Benzene			Chromium			Lead			Nickel		
	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)	Exposed Cases	Crude OR (95% CI)	Selection Bias Adjusted OR (95% SI)
All cancers combined	789	1.10 (1.01, 1.20)	1.16 (0.81, 1.66)	752	1.03 (0.95, 1.12)	1.09 (0.76, 1.56)	672	0.89 (0.81, 0.97)	0.94 (0.65, 1.34)	759	1.04 (0.96, 1.14)	1.10 (0.77, 1.58)	796	1.11 (1.03, 1.21)	1.17 (0.82, 1.68)
Acute lymphoblastic leukemia	190	0.93 (0.79, 1.10)	0.98 (0.69, 1.41)	184	0.90 (0.76, 1.06)	0.94 (0.66, 1.35)	182	0.88 (0.75, 1.04)	0.93 (0.65, 1.33)	178	0.86 (0.73, 1.02)	0.90 (0.63, 1.29)	202	1.01 (0.86, 1.19)	1.07 (0.74, 1.53)
Acute myeloid leukemia	36	0.96 (0.66, 1.40)	1.01 (0.71, 1.45)	32	0.83 (0.56, 1.22)	0.87 (0.61, 1.25)	34	0.89 (0.61, 1.31)	0.94 (0.66, 1.35)	35	0.93 (0.64, 1.36)	0.98 (0.68, 1.40)	31	0.79 (0.53, 1.18)	0.84 (0.58, 1.20)
Bone tumors	28	1.42 (0.91, 2.23)	1.50 (1.04, 2.15)	26	1.28 (0.81, 2.02)	1.34 (0.94, 1.93)	17	--	--	26	1.28 (0.81, 2.02)	1.34 (0.94, 1.93)	25	1.21 (0.76, 1.93)	1.27 (0.89, 1.82)
Central nervous system tumors	178	1.22 (1.03, 1.46)	1.28 (0.90, 1.84)	158	1.04 (0.86, 1.24)	1.09 (0.76, 1.56)	128	0.79 (0.65, 0.96)	0.83 (0.58, 1.19)	166	1.11 (0.93, 1.33)	1.17 (0.81, 1.67)	170	1.15 (0.96, 1.37)	1.20 (0.84, 1.73)
Astrocytoma	57	1.36 (0.99, 1.86)	1.43 (1.00, 2.05)	37	0.76 (0.53, 1.09)	0.80 (0.56, 1.15)	34	0.68 (0.47, 0.99)	0.72 (0.50, 1.03)	42	0.89 (0.63, 1.26)	0.94 (0.66, 1.35)	48	1.07 (0.77, 1.48)	1.12 (0.78, 1.61)
Ependymoma	13	--	--	18	--	--	24	1.24 (0.77, 2.00)	1.31 (0.91, 1.87)	18	--	--	21	1.03 (0.63, 1.70)	1.09 (0.76, 1.56)
Glioma	98	1.16 (0.92, 1.46)	1.22 (0.85, 1.75)	76	0.83 (0.64, 1.07)	0.87 (0.61, 1.25)	75	0.81 (0.63, 1.05)	0.85 (0.60, 1.22)	83	0.93 (0.72, 1.18)	0.97 (0.68, 1.40)	93	1.08 (0.85, 1.37)	1.13 (0.79, 1.62)
Medulloblastoma	21	1.12 (0.68, 1.86)	1.18 (0.83, 1.70)	24	1.36 (0.84, 2.20)	1.43 (1.00, 2.05)	15	0.73 (0.41, 1.28)	0.76 (0.53, 1.09)	19	0.98 (0.59, 1.65)	1.03 (0.72, 1.48)	24	1.36 (0.84, 2.20)	1.43 (1.00, 2.05)
Germ cell tumors	46	1.42 (1.00, 2.02)	1.50 (1.04, 2.15)	50	1.61 (1.14, 2.28)	1.70 (1.18, 2.43)	30	0.80 (0.53, 1.19)	0.84 (0.58, 1.20)	47	1.47 (1.04, 2.08)	1.54 (1.08, 2.21)	49	1.56 (1.11, 2.21)	1.64 (1.15, 2.36)
Lymphomas	59	1.27 (0.94, 1.73)	1.34 (0.93, 1.92)	58	1.24 (0.91, 1.69)	1.31 (0.91, 1.87)	52	1.07 (0.78, 1.47)	1.12 (0.78, 1.61)	55	1.15 (0.85, 1.58)	1.21 (0.85, 1.74)	64	1.43 (1.06, 1.93)	1.51 (1.05, 2.16)
Hodgkin lymphoma	30	2.00 (1.26, 3.18)	2.10 (1.47, 3.02)	24	1.41 (0.87, 2.29)	1.48 (1.04, 2.13)	17	--	--	19	--	--	31	2.11 (1.33, 3.35)	2.22 (1.55, 3.19)
Non-Hodgkin lymphoma	29	0.93 (0.61, 1.40)	0.97 (0.68, 1.40)	34	1.15 (0.77, 1.70)	1.20 (0.84, 1.73)	35	1.19 (0.81, 1.77)	1.25 (0.88, 1.80)	36	1.24 (0.84, 1.83)	1.31 (0.91, 1.87)	33	1.10 (0.74, 1.64)	1.16 (0.81, 1.66)
Neuroblastoma	26	0.63 (0.42, 0.97)	0.67 (0.47, 0.96)	25	0.60 (0.39, 0.93)	0.64 (0.44, 0.91)	42	1.18 (0.82, 1.68)	1.24 (0.86, 1.78)	23	0.55 (0.35, 0.85)	0.58 (0.40, 0.83)	30	0.76 (0.51, 1.13)	0.80 (0.55, 1.14)
Retinoblastoma	27	0.85 (0.56, 1.31)	0.90 (0.63, 1.29)	25	0.77 (0.50, 1.20)	0.81 (0.57, 1.17)	27	0.85 (0.56, 1.31)	0.90 (0.63, 1.29)	36	1.26 (0.85, 1.85)	1.32 (0.92, 1.89)	30	0.98 (0.65, 1.48)	1.03 (0.72, 1.47)
Soft tissue sarcoma	58	1.33 (0.97, 1.81)	1.40 (0.97, 2.00)	56	1.26 (0.92, 1.73)	1.33 (0.93, 1.90)	42	0.86 (0.61, 1.21)	0.90 (0.63, 1.29)	59	1.36 (1.00, 1.85)	1.43 (1.00, 2.05)	61	1.43 (1.05, 1.94)	1.50 (1.05, 2.16)
Rhabdomyosarcoma	27	1.23 (0.78, 1.92)	1.29 (0.90, 1.85)	29	1.36 (0.88, 2.11)	1.43 (1.00, 2.05)	20	0.82 (0.50, 1.35)	0.86 (0.60, 1.24)	30	1.43 (0.92, 2.21)	1.50 (1.05, 2.15)	31	1.50 (0.97, 2.31)	1.58 (1.10, 2.26)
Wilms' tumor	17	--	--	21	0.63 (0.39, 1.01)	0.66 (0.46, 0.95)	28	0.90 (0.59, 1.38)	0.95 (0.66, 1.36)	22	0.67 (0.42, 1.06)	0.70 (0.49, 1.01)	15	--	--

*N Cases = 2,938 N Controls = 63,383; N exposed Controls = 15,846

**CI=confidence interval; OR=odds ratio; SI=simulation interval

***Displaying cancer types with >= 20 exposed cases

Chapter 4 Prenatal pesticide exposure and the neonatal blood spot metabolome in retinoblastoma

4.1 Abstract

Background: Prenatal pesticide exposure has been associated with increased retinoblastoma risk, but the biological pathways underlying these associations remain poorly understood. We investigated whether prenatal exposure to agricultural pesticides we identified as risk factors for retinoblastoma was associated with metabolic alterations at birth and differed between retinoblastoma cases and controls.

Methods: We conducted a population-based case-control study of California children born 1998-2011 using linked California birth records, the California Cancer Registry, and neonatal dried blood spots (226 retinoblastoma cases, 366 controls). Prenatal ambient agricultural pesticide exposure was estimated using California's Pesticide Use Reporting system linked with GIS-based land-use models. Pesticides associated with retinoblastoma were identified using unconditional logistic regression and semi-Bayesian hierarchical models and combined into a composite exposure score. Metabolome-wide association studies were conducted using high-resolution metabolomics to identify metabolic features and biological pathways associated with prenatal exposure to retinoblastoma-associated pesticides in the overall population and separately among retinoblastoma cases and controls.

Results: Prenatal exposure to two or more retinoblastoma-associated pesticides was associated with increased odds of retinoblastoma (aOR: 1.59; 95% CI: 1.11-2.26), with stronger associations observed for bilateral disease (aOR: 2.07; 95% CI: 1.27-3.36). Pesticide-associated metabolic responses differed between retinoblastoma cases and controls, with weak correlations between case- and control-specific metabolite effect estimates (C18: $r = 0.09$; HILIC: $r = 0.20$)

and broader pathway enrichment among cases. Enriched pathways included inflammatory lipid metabolism, central energy metabolism, amino acid metabolism, and oxidative stress-related pathways.

Conclusions: Prenatal exposure to retinoblastoma-associated pesticides was associated with distinct neonatal metabolic responses among children who developed retinoblastoma compared with controls. These findings suggest that inflammatory lipid metabolism and central energy metabolism may represent biological pathways linking prenatal pesticide exposure with retinoblastoma and provide hypotheses for future mechanistic and targeted metabolomic studies.

4.2 Introduction

Retinoblastoma, a tumor of the retina, is the most common extracranial solid tumor in children and accounts for 3% of all childhood cancer cases in the U.S., with 200-300 cases diagnosed annually.²³⁻²⁵ Retinoblastoma arises from the biallelic inactivation of the *RBI* tumor suppressor gene within a developing retinal cell, typically via a "two-hit" mechanism, and is usually diagnosed before 5 years of age.^{24,25} The early age of onset and two-hit mechanism support the hypothesis that prenatal exposures contribute to *RBI* mutation and subsequent tumor development.²⁶ Previous studies have identified increased retinoblastoma risk with several parental and environmental factors, including older parental age,^{29,30} maternal smoking,³¹ prenatal ambient air toxics,³² and parental residential pesticide exposure.^{27,28}

Pesticides are widely used in California, with 176 million pounds of active ingredients applied across 96 million acres in 2023.⁵⁰ The EPA has classified over 200 pesticides as possible or probable human carcinogens.⁵¹ Studies investigating occupational and residential pesticide exposure have generally reported positive, although inconsistent, associations with retinoblastoma, but many have been limited by small numbers of exposed cases and reliance on job titles or retrospective parental interview as exposure proxies.^{27,68,80,81} To our knowledge, only one study has evaluated retinoblastoma risk in relation to ambient exposure to specific agricultural pesticides using individual-level GIS-based exposure assessment and reported positive associations for several pesticides, including acephate, bromacil, captan, kresoxim-methyl, oxythioquinox, and pymetrozine.²⁸

High-resolution metabolomics (HRM), often applied through metabolome-wide association studies (MWAS), enables the untargeted characterization of thousands of endogenous and exogenous compounds in biological samples and has been used to identify metabolic signatures

of both pesticide exposure and disease risk.⁸² Targeted and untargeted metabolomic studies of prenatal and adult pesticide exposure have most consistently implicated disruptions in lipid metabolism, alterations in energy metabolism, and markers of oxidative stress, though findings have not been uniform across pesticide classes and populations.⁵²⁻⁵⁴ MWAS have also identified several biological pathways that may underlie pesticide toxicity. One study found that in-utero organochlorine pesticide exposure was associated with decreased lysophosphatidylcholine levels and alterations in phosphoethanolamine pathways linked to elevated serum lipids,⁵⁵ while another, conducted among older adults, identified fatty acid β -oxidation as a common pathway disrupted by organophosphate, organochlorine, and pyrethroid exposure.⁵⁶

Previous untargeted metabolomic studies of ex vivo retinoblastoma tumor tissue reported suggestive involvement of the taurine/hypotaurine and glycerophospholipid pathways, with greater tumor differentiation associated with higher taurine and greater necrosis associated with elevated lipid, taurine, creatine, hypotaurine, and choline-related metabolites.⁸⁴ Compared to medulloblastoma and neuroblastoma tissues, retinoblastoma had the highest concentrations of taurine, hypotaurine, and GABA, along with elevated succinate, a driver of retinal angiogenesis.⁸⁵ A MWAS of neonatal dried blood spots comparing retinoblastoma cases to healthy controls identified alterations in linoleate, pentose phosphate, pyrimidine, and lipid metabolism pathways among retinoblastoma cases.⁸⁶ These findings suggest that lipid and energy metabolism may represent shared biological processes in pesticide exposure and retinoblastoma.

To our knowledge, no previous study has applied metabolomics to investigate the biological pathways connecting specific pesticide exposures to retinoblastoma risk. To address this gap, we first used California's mandatory Pesticide Use Reports and GIS-based land-use modeling to

identify agricultural pesticides associated with retinoblastoma risk. We then conducted a metabolome-wide association study of neonatal dried blood spots to identify metabolic features and biological pathways associated with prenatal exposure to retinoblastoma-associated pesticides and to evaluate whether these associations differed between retinoblastoma cases and controls.

4.3 Methods

Study population

We used data from a population-based case-control study of childhood cancers among California children born 1983-2011 (ages ≤ 5 at diagnosis). Cases were identified through the California Cancer Registry, and controls were randomly selected from California birth rolls and frequency matched to cases 20:1 by birth year.²⁹ From this population, 1,400 children (501 retinoblastoma cases and 899 controls) were randomly selected for HRM analysis.

Neonatal blood spots were collected by the California Genetic Disease Screening Program, as previously described.⁸³ Demographic and gestational information was obtained from birth records. Because complete residential addresses were unavailable in the electronic birth certificate dataset prior to 1998, we limited the present analysis to births from 1998-2011.²⁸

Following Thompson et al., we restricted the study sample to mothers residing within 4,000 meters of a location where at least one pesticide (carcinogenic or non-carcinogenic) was agriculturally applied at any point during pregnancy, based on the residential address listed on the birth record. This restriction is intended to reduce potential exposure misclassification arising from county-level reporting of non-agricultural pesticide applications in urban areas and yield a more homogeneous rural study population with respect to unmeasured social and environmental factors.²⁸

After excluding samples identified as outliers based on metabolomic profiles (N=10), births prior to 1998 (N=669), and mothers without exposure within 4,000 meters of at least one agriculturally applied pesticide during pregnancy (N=129), the final analytic sample included 226 retinoblastoma cases and 366 controls (total N=592). This sample was used to identify retinoblastoma-associated pesticides via the single-pesticide models described below. After constructing the dichotomized retinoblastoma-associated pesticide exposure variable, mothers exposed to exactly one retinoblastoma-associated pesticide during pregnancy (N = 108) were excluded because the exposure variable compared no exposure with exposure to multiple retinoblastoma-associated pesticides

Pesticide exposure

Since 1990, California's Pesticide Use Reports (PUR) have mandated documentation of all agricultural pesticide applications, including the amount applied, application date and location, and crop treated. Our study's GIS-based Residential Ambient Pesticide Estimation System (GRAPES) maps PUR data onto the PLSS grid using land-use information from the California Department of Water Resources (CDWR), available in digitized form since 1986, to more accurately pinpoint pesticide applications and allow consistent exposure assessment across the study period.^{50,63}

We preselected 213 pesticides classified as possibly or probably carcinogenic by the Environmental Protection Agency or the International Agency for Research on Cancer (IARC).^{36,51,125,178,179} Of these, 103 pesticides had at least one exposed participant during the study period, and risk estimates were generated for 51 pesticides with at least twenty exposed retinoblastoma cases to avoid unstable estimates arising from sparse data.

Exposure was assigned using the maternal residential address recorded on the birth certificate and defined as agricultural pesticide applications within 4,000 meters of the residence. The 4,000-meter buffer was selected based on previous studies demonstrating strong correlations between PUR-reported pesticide applications and measured air concentrations up to 8,000 meters from treated fields.^{94-96,180} The pregnancy period was estimated from the date of last menstrual period to the date of birth.

High-Resolution Metabolomics (HRM)

Metabolomic profiling of neonatal blood spots was performed using liquid chromatography coupled with ultra-high resolution mass spectrometry (LC-HRMS; Thermo Scientific Fusion), consistent with previously established protocols.¹⁸¹ Each blood spot was sampled via a 5 mm hole punch and extracted in a 2:1 acetonitrile-to-water solution spiked with stable isotope-labeled internal standards. Extracts were agitated on a low-speed orbital shaker for 12 hours at 0-4°C, protected from light, then centrifuged to pellet particulate matter. Supernatants were run in triplicate across two complementary chromatographic platforms to maximize metabolite coverage: hydrophilic interaction liquid chromatography (HILIC) in positive electrospray ionization (ESI) mode, and C18 reversed-phase chromatography in negative ESI mode.¹⁸² Samples were processed in batches of 40, with pooled plasma reference samples analyzed alongside study samples and NIST 1950 standards run at the start and end of the analytical run. Feature extraction and cross-sample alignment of the resulting raw spectral data were carried out using apLCMS,¹⁸³ with additional refinement via xMSanalyzer;¹⁸⁴ each resulting metabolite feature was characterized by a unique mass-to-charge ratio (m/z), retention time, and signal intensity.

Prior to statistical analysis, features were batch corrected using wavelet analysis.¹⁸⁵ Features detected in >25% of samples, with a median coefficient of variation <30% across replicates and Pearson correlation >0.7, were retained. Replicate intensities collapsed to the median value and log2-transformed. Missing values were imputed with half of the smallest nonzero signal observed for that feature across the sample set.

Statistical analysis

Pesticides and retinoblastoma

We followed the analytic approach of a previous study by our group investigating associations between ambient agricultural pesticide exposure during pregnancy and retinoblastoma risk.²⁸ Briefly, we used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations between each selected pesticide and retinoblastoma (all types combined), adjusting for birth year, child's sex, maternal age, area-level socioeconomic status (SES), and maternal race/ethnicity based on prior literature.^{16,99,100} Area-level SES was measured using a composite index developed by Yost et al., which summarizes several census-group-level socioeconomic indicators into a single five-level variable.¹⁰¹

Single-pesticide models estimated the odds ratio (OR) and 95% confidence interval (CI) for each pesticide independently, without adjustment for co-exposure to other pesticides. To co-adjust for other selected pesticides and account for multiple comparisons, we then applied a semi-Bayesian hierarchical logistic regression model, following the approach of Momoli et al.,⁹⁸ with a pre-specified second-stage variance of 0.5, corresponding to a 16-fold prior uncertainty around the OR estimates. This approach assumes individual pesticide effect estimates follow separate prior normal distributions with group-specific means based on chemical class, as categorized by the

Pesticide Action Network (PAN) database: 2,6-dinitroaniline, amide, anilide, azole, dicarboximide, n-methyl carbamate, organochlorine, organophosphate, pyrethroid, substituted benzene, triazine, or urea.¹⁰³⁻¹⁰⁵

Pesticides associated with retinoblastoma in the adjusted single-pesticide models, defined as those with an OR ≥ 1.2 and a lower 95% CI ≥ 0.90 , were classified as retinoblastoma-associated pesticides (captan, diazinon, oxythioquinox, acephate, triforine, iprodione, fenoxycarb, and pymetrozine) and used in the composite exposure score. For each mother, we summed the number of these retinoblastoma-associated pesticides to which she was exposed at any point during pregnancy. To evaluate the association between the composite score and retinoblastoma risk, we fit logistic regression models treating the score as both a continuous exposure and as a series of dichotomous thresholds (≥ 2 , ≥ 3 , ≥ 4 , and ≥ 5 pesticides vs. none). The composite score was then dichotomized to define our primary exposure variable: mothers exposed to ≥ 2 retinoblastoma-associated pesticides during pregnancy were classified as exposed, mothers exposed to none were classified as unexposed, and mothers exposed to exactly 1 pesticide were not included in the MWAS analysis.

Metabolome-wise association study

We conducted a metabolome-wide association study (MWAS) to evaluate associations between prenatal exposure to retinoblastoma-associated pesticides and metabolic features. Analyses were conducted in the overall study population adjusting for case/control status as a covariate and then separately among retinoblastoma cases and controls. For each feature, we fit empirical Bayes-moderated linear regression models using the `lmFit` and `eBayes` functions in the *limma* R package, to estimate the association between prenatal exposure to ≥ 2 retinoblastoma-associated pesticides and feature intensity.¹⁸⁶ Minimally adjusted models were adjusted for the matching

variable birth year; fully adjusted models additionally included the same covariates adjusted for in the single-pesticide logistic regression models (child's sex, maternal age, maternal race/ethnicity, and area-level socioeconomic status).^{16,99-101} The MWAS in the overall population were additionally adjusted for retinoblastoma case/control status. P values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate (FDR) procedure.

To evaluate whether the association between pesticide exposure and metabolic features differed by case/control status, we conducted an exploratory interaction MWAS restricted to a subset of metabolic features selected from the case/control-stratified MWAS results. Among features reaching $p < 0.05$ in either stratum, we ranked features according to the absolute difference between case- and control-specific beta coefficients ($|\beta_{\text{case}} - \beta_{\text{control}}|$) and selected the 100 most discordant features per platform. We then fit empirical Bayes-moderated linear regression models including a pesticide exposure $\times$ retinoblastoma interaction term.

Additionally, we conducted two sensitivity analyses. First, to examine high-level exposure, we repeated the primary MWAS using a more stringent threshold requiring ever/never exposure to ≥ 4 (rather than ≥ 2) of the eight retinoblastoma-associated pesticides. Second, because glyphosate was the most prevalent pesticide exposure in the study population and was present among nearly all mothers exposed to multiple retinoblastoma-associated pesticides, yet was not included in the composite score, we repeated the MWAS using glyphosate as the exposure.

Annotation and pathway analysis

We annotated MWAS features using two sequential steps. First, features were matched to an in-house library of chemical standards previously characterized in the Emory laboratory, providing the strongest level of annotation confidence.^{181,187} Matching required agreement within 5 ppm for

m/z and 30 seconds for retention time; where a feature matched multiple library entries, the closest match by combined m/z and retention time difference was retained. Second, features that were not matched after Emory library annotation were annotated using *xMSannotator*, which matched accurate mass m/z for adducts formed under positive or negative electrospray ionization to the Human Metabolome Database (HMDB), with a mass error threshold of 10 ppm.¹⁸⁸ For each feature, we retained the best available annotation, prioritizing Emory library matches over *xMSannotator* matches when both were available.

Pathway enrichment was evaluated using *metapone*, which performs overrepresentation analysis (ORA) using a permutation-based weighted hypergeometric test with joint pathway analysis across positive- and negative-ionization mode data, avoiding double counting and accounting for multiple-matching uncertainty through a fractional weighting factor. *Metapone* uses a pathway database combining KEGG, Mummichog, and the Small Molecule Pathway Database (SMPDB).¹⁸⁹ Additionally, we conducted a sensitivity analysis using gene set enrichment analysis (GSEA), which evaluates enrichment across the ranked list of all metabolic features without requiring a significance threshold.

All statistical analyses were conducted using R Studio version 4.4.1 and SAS version 9.4.

4.4 Results

Study population characteristics

Demographic characteristics of retinoblastoma cases and controls are presented in Table 4-1.

Compared with controls, cases were more likely to be male, to be born to older mothers and fathers, to reside in lower socioeconomic status neighborhoods, and to have evidence of maternal smoking. Maternal race/ethnicity and education were similar between groups, with Hispanic

mothers representing approximately half of both. Birth weight and gestational age were also similar between groups.

Pesticide and retinoblastoma associations

The ORs and 95% CI for the single-pesticide and hierarchical logistic regression models are presented in Figure 1 and Supplemental Table 4-1. In the single-pesticide models, we observed increased risk of retinoblastoma with prenatal exposure to oxythioquinox and triforine and an inverse association with metam-sodium. Additionally, we observed elevated point estimates but with confidence intervals crossing the null for diazinon and fenoxycarb. In the hierarchical models, the positive association with triforine persisted as an elevated point estimate, though its confidence interval crossed the null. Inverse associations were observed for paraquat dichloride and kresoxim-methyl.

Pesticides meeting the predefined criteria for inclusion ($OR \geq 1.20$ and lower 95% CI ≥ 0.90) were classified as retinoblastoma-associated pesticides for the MWAS exposure score. These pesticides were captan, diazinon, oxythioquinox, acephate, triforine, iprodione, fenoxycarb, and pymetrozine. Across the full population (N=592), exposure to these pesticides ranged from 0-8 (median 2), with a similar distribution between cases (mean 2.6) and controls (mean 2.2). After excluding mothers exposed to exactly one pesticide, the resulting MWAS population (N=484) was classified as exposed (≥ 2 pesticides, 73.1%) or unexposed; exposure prevalence was higher among cases (79.1%) than controls (69.4%) and was associated with increased odds of retinoblastoma overall (aOR: 1.59; 95% CI: 1.11-2.26), more strongly for bilateral (aOR: 2.07; 95% CI: 1.27-3.36) than unilateral disease (aOR: 1.32; 95% CI: 0.85-2.06; Supplemental Table 4-2).

Metabolome-wide association study

The case/control-stratified MWAS included 10,937 C18 and 15,951 HILIC features. Among retinoblastoma cases, 650 C18 and 757 HILIC features reached $p < 0.05$, and one HILIC feature reached $FDR < 0.05$ but was unannotated. In contrast, no features reached $FDR < 0.05$ among controls. Beta-scatter plots (Figure 3) showed weak correlation between case- and control-specific regression coefficients ($r = 0.09$ - 0.20), whereas minimally and fully adjusted models were highly correlated ($r = 0.98$). Full summary statistics are in Supplemental Tables 4-3, 4-4.

In the overall MWAS adjusting for case/control status, two C18 and three HILIC features reached $p < 1 \times 10^{-4}$ (Figure 2; Supplemental Tables 4-5, 4-6).

Figure 2 shows volcano plots of the case/control-stratified and overall MWAS results, displaying $-\log_{10}(P\text{-value})$ against $\log_2$ fold-change for each metabolic feature.

Annotation and pathway enrichment analysis

Of the 15,951 HILIC and 10,937 C18 features analyzed, 86 (0.5%) and 60 (0.5%) HILIC and C18 features, respectively, were annotated using the in-house library of authenticated chemical standards, while an additional 4,626 (29.0%) HILIC and 3,559 (32.5%) C18 features were annotated using *xMSannotator*, for a total of 4,712 (29.5%) HILIC and 3,619 (33.1%) C18 features annotated overall (Supplemental Tables 4-3, 4-4, 4-5, 4-6).

Among retinoblastoma cases, 52 pathways were enriched at $p < 0.05$, of which 15 remained significant after FDR correction. The top enriched pathways included alanine, aspartate, and glutamate metabolism, the tricarboxylic acid (TCA) cycle, carbon metabolism, prostaglandin formation from arachidonate, and arginine biosynthesis. Among controls, 11 pathways were enriched with two remaining after FDR correction, aldosterone-regulated sodium reabsorption

and arginine biosynthesis. Arginine biosynthesis was the only pathway that remained significant after FDR correction in both cases and controls. Figure 4 shows an overview of the enriched pathways for cases and controls.

In the overall MWAS adjusting for retinoblastoma case/control status, 13 pathways were enriched at $p < 0.05$, of which two remained after FDR correction (arachidonic acid metabolism and eicosanoids). Complete pathway enrichment results are provided in Supplemental Table 4-7.

Sensitivity analyses

Using a more stringent exposure definition (≥ 4 retinoblastoma-associated pesticides), MWAS results were generally consistent with the primary analysis. No features reached $FDR < 0.05$ in the overall model, whereas one unannotated HILIC feature reached $FDR < 0.05$ in the control-stratified analysis. The numbers of features with $p < 0.05$ was similar to the primary analysis (C18: 746 in cases, 423 in controls; HILIC: 684 in cases, 925 in controls). Pathway enrichment also showed a similar pattern, with 12 pathways enriched in the overall model (3 $FDR < 0.05$), 65 among cases (29 $FDR < 0.05$), and 3 among controls (none at $FDR < 0.05$) (Supplemental Tables 4-8, 4-9, 4-10).

Results from the exploratory glyphosate MWAS are presented in Supplemental Tables 4-11, 4-12, 4-13. No metabolic features reached $FDR < 0.05$ in any model. Compared with the primary analysis, fewer metabolic features and enriched pathways were identified overall and within the case- and control-stratified analyses.

GSEA identified 39, 95, and 71 pathways at $p < 0.05$ in the overall, case-, and control-stratified analyses, respectively; none survived FDR correction (Supplemental Table 4-14).

*Pesticide * retinoblastoma interaction analysis*

Among the 100 preselected metabolic features per platform with the largest differences between cases and controls, most were positively associated with pesticide exposure in one group and negatively associated in the other (HILIC: 85/100; C18: 90/100). Because features were preselected based on differences between the case- and control-stratified MWAS results, formal significance testing of the interaction term was not performed. Interaction model results are presented descriptively in Supplemental Tables 4-15, 4-16.

4.5 Discussion

In this population-based study of California children, prenatal ambient exposure to a composite score of eight agricultural pesticides each individually increasing retinoblastoma risk (captan, diazinon, oxythioquinox, acephate, triforine, iprodione, fenoxycarb, and pymetrozine) was associated with an increased odds of retinoblastoma, with stronger associations observed for bilateral disease and with a higher number of concomitant pesticide exposure. We then used neonatal dried blood spots collected at birth to investigate whether prenatal pesticide exposure differentially influenced the neonatal metabolome of retinoblastoma cases compared with controls. Although few individual metabolic features survived multiple testing correction, pathway analyses consistently implicated inflammatory lipid metabolism, central energy metabolism, amino acid metabolism, and oxidative stress-related pathways. More importantly, pesticide-associated metabolic responses differed between cases and controls, suggesting that prenatal pesticide exposure may differentially influence the neonatal metabolome according to subsequent disease status. This extends previous epidemiologic evidence linking prenatal agricultural pesticide exposure with retinoblastoma and generates hypotheses regarding biological pathways contributing to these associations.

Our exposure assessment and analytic approach closely followed that of Thompson et al., using California's Pesticide Use Reports to estimate ambient agricultural pesticide exposure at the maternal residence during pregnancy and hierarchical logistic regression models to account for correlated pesticide exposures.²⁸ Similar to Thompson et al., several pesticides, including captan, diazinon, oxythioquinox, acephate, triforine, and pymetrozine, showed elevated associations with retinoblastoma in the single-pesticide models, and most of these point estimates remained elevated after hierarchical regression adjustment across both studies. Agreement with the previous study was weaker for a small subset of pesticides, most notably kresoxim-methyl, for which the hierarchical model estimate reversed direction between the two studies. Discrepancies may reflect variation in pesticide use patterns and co-exposure profiles across the two study populations. Although the two studies shared exposure assessment methods and were based on the same parent California case-control study, the current metabolomics study was conducted in a randomly selected subset of participants, and as a result, the geographic distribution of the selected participants is expected to differ somewhat from the full parent study. Because pesticide use varies across California by crop type and region, the distribution of pesticide exposures and co-exposure patterns therefore likely differed between studies. Given the relatively small number of exposed retinoblastoma cases for individual pesticides in both studies, limited statistical power may also have contributed to discrepancies. Overall, the consistency observed for several pesticides provides consistent support for an association between prenatal agricultural pesticide exposure and retinoblastoma.

The composite pesticide score demonstrated a stronger association with retinoblastoma than individual pesticides. Children exposed to two or more retinoblastoma-associated pesticides had increased odds of retinoblastoma, and associations strengthened with increasing exposure

thresholds. Because the composite score included pesticides from multiple chemical classes, this pattern suggests that cumulative pesticide exposures may be more relevant to retinoblastoma risk than exposure to any single pesticide. Consistent with previous findings, associations were stronger for bilateral than unilateral disease, suggesting that the two subtypes may differ in their susceptibility to prenatal pesticide exposure because of differences in their underlying etiology.^{28,190,191}

A key finding of this study is the observation that prenatal pesticide exposure was associated with different metabolic responses among retinoblastoma cases compared with controls. This was reflected by weak correlations between pesticide-associated metabolite effect estimates across the case- and control-stratified analyses, and broader pathway enrichment among retinoblastoma cases.

The broader pathway enrichment observed among cases was driven primarily by pathways involved in inflammatory lipid metabolism and central energy metabolism, including arachidonic acid metabolism, prostaglandin formation from arachidonate, eicosanoid metabolism, the tricarboxylic acid (TCA) cycle, pyruvate metabolism, carbon metabolism, and amino acid metabolism, several of which have been previously implicated in retinoblastoma pathogenesis. These pathways regulate inflammation, mitochondrial energy production, cellular biosynthesis, and maintenance of redox balance and are closely interconnected biologically,¹⁹² with arachidonic acid-derived eicosanoids shown to directly activate mitochondrial fatty acid oxidation and TCA cycle activity.¹⁹³ At a mechanistic level, oxidative stress can activate phospholipase A2, releasing arachidonic acid from membrane phospholipids for conversion into prostaglandins and leukotrienes, both proinflammatory mediators,¹⁹⁴ while disruption of amino acid pathways, including glycine, serine, and alanine metabolism, has been proposed as a marker

of antioxidative defense activation in response to pesticide-induced oxidative stress.⁵²

Experimental studies have also shown that many pesticides induce oxidative stress and mitochondrial dysfunction, processes that may contribute to these metabolic alterations.¹⁹⁵

Similar perturbations in inflammatory lipid and central energy metabolism have been reported across previous metabolome-wide association studies of pesticide exposure involving organophosphate, organochlorine, pyrethroid, and copper pesticides,^{56,196} suggesting that these pathways may represent common downstream biological responses to diverse pesticide classes despite differing primary mechanisms of toxicity.

These pathways may also be relevant to retinoblastoma biology, rather than reflecting a general response to pesticide exposure. Chronic inflammation has been shown to promote hyperphosphorylation of the Rb protein and activation of the transcription factor E2F1, resulting in loss of cell-cycle control in retinoblastoma tumorigenesis.¹⁹⁷ Therefore, it is plausible that pesticide-associated alterations in inflammatory lipid metabolism could influence the same molecular pathways disrupted by *RBI* inactivation. In addition, loss of functional Rb protein has been associated with altered tumor metabolism, including changes in glycolysis, oxidative phosphorylation, TCA cycle activity, and fatty acid oxidation in retinoblastoma tissue.¹⁹⁸ Our observation of enrichment in pathways related to the TCA cycle, pyruvate metabolism, and fatty acid metabolism is consistent with previously reported metabolic alterations in retinoblastoma tissue and suggests that prenatal pesticide exposure may influence biological processes involved in retinoblastoma development.

Our findings complement those of our group's previous MWAS of neonatal dried blood spots from retinoblastoma cases and controls. The prior study identified metabolic differences present at birth between retinoblastoma cases and controls, highlighting perturbations in linoleate

metabolism, pentose phosphate metabolism, fatty acid metabolism, and broader lipid metabolic pathways before diagnosis.⁸⁶ The authors proposed that alterations in fatty acid metabolism may reflect oxidative stress and inflammation arising from prenatal environmental exposures including pesticides. Consistent with this hypothesis, linoleate metabolism was enriched in our stratified pesticide exposure analysis among cases but not controls, and a feature annotated as linoleic acid trended higher among cases with exposure. Although these findings should be interpreted cautiously, they provide additional evidence that inflammatory lipid metabolism may be altered among neonates who later develop retinoblastoma following prenatal pesticide exposure. Similarly, metabolomic analyses of retinoblastoma tumor tissue have reported disruptions in glycerophospholipid metabolism, taurine and hypotaurine metabolism, and TCA cycle-related pathways.^{84,85} Although the specific pathways identified in blood spot and tumor tissue are not identical, they consistently implicate perturbations in inflammatory lipid metabolism and central energy metabolism before diagnosis or treatment.

The pathway enrichment observed among retinoblastoma cases was also broadly consistent in several secondary analyses. Increasing the pesticide exposure threshold yielded an even more pronounced case-concentrated pattern of pathway enrichment despite reduced sample sizes, suggesting that the observed biological pattern was not driven by a single exposure definition. Likewise, the exploratory interaction analysis identified metabolic features with differential associations between pesticide exposure and retinoblastoma status that largely reflected the case-control differences observed in the primary MWAS. Because these analyses were exploratory and the interaction features were selected based on the primary MWAS results, they should be considered hypothesis-generating and require replication in independent populations.

This study has several important strengths. To our knowledge, this is the first study to integrate GIS-based estimates of prenatal agricultural pesticide exposure with neonatal metabolomics to investigate biological pathways linking prenatal pesticide exposure with retinoblastoma. Ambient pesticide exposures were estimated using a validated GIS-based exposure model that links California's Pesticide Use Reports with land-use data to estimate residential exposure to individual agricultural pesticides, providing spatially and temporally refined exposure estimates while avoiding the recall bias inherent in studies relying on self-reported residential or occupational exposures.⁶⁴ In addition, neonatal dried blood spots were collected shortly after birth, allowing metabolic perturbations to be evaluated before cancer diagnosis or treatment. Finally, untargeted high-resolution metabolomics enabled the simultaneous evaluation of thousands of endogenous and exogenous metabolic features, providing a comprehensive assessment of metabolic responses associated with prenatal pesticide exposure.

Several limitations should also be considered. First, pesticide exposure was assigned using the maternal residential address recorded on the birth certificate. Although this approach captures the relevant prenatal exposure window, it assumes that maternal residence remained unchanged throughout pregnancy. Residential mobility during pregnancy may therefore have resulted in exposure misclassification, particularly for exposures occurring earlier in pregnancy.¹³² Second, total pesticide exposure may be underestimated as we were not able to account for exposure through occupation, diet, or residential use. Any resulting exposure misclassification would likely be nondifferential and would bias associations toward the null. Another limitation is the limited ability to confidently annotate many of the metabolic features detected through untargeted metabolomics. Consequently, inaccurate or incomplete feature identification may have influenced the interpretation of our results. Finally, although this is among the largest

metabolomic studies of retinoblastoma to date, the rarity of retinoblastoma and the high dimensionality of untargeted metabolomics limited statistical power to detect modest metabolite associations after correction for multiple testing.

Overall, this study extends previous epidemiologic evidence linking prenatal agricultural pesticide exposure with retinoblastoma by demonstrating that prenatal pesticide exposure is associated with distinct neonatal metabolic responses among children who later develop retinoblastoma compared with controls. The discordance between case- and control-specific metabolomic signatures, and the enrichment of inflammatory lipid metabolism and central energy metabolism among retinoblastoma cases, suggests that prenatal pesticide exposure may differentially influence biological processes during early development. This complements previous neonatal metabolomic studies of retinoblastoma by linking perturbations observed before diagnosis to a specific prenatal environmental exposure and generate new hypotheses regarding the biological pathways through which prenatal pesticide exposure may contribute to retinoblastoma development.

4.6 Tables and figures

Table 4-1. Demographic characteristics of the analytical population (N=484)

	Overall N = 484	Retinoblastoma Cases N = 187	Controls N = 297
Infant's sex, n (%)			
Female	293 (49.5%)	104 (46%)	189 (51.6%)
Male	299 (50.5%)	122 (54%)	177 (48.4%)
Birth Weight (g), mean (SD)	3379.8 (556.3)	3381.2 (559)	3378.9 (555.4)
Gestational Age (weeks), mean (SD)	38.9 (2.2)	38.9 (2.2)	38.9 (2.2)
Missing	21 (3.5%)	10 (4.4%)	11 (3%)
Maternal Age, mean (SD)	28.4 (6.3)	29 (6.3)	28 (6.2)
Paternal Age, mean (SD)	31.4 (7.2)	32.4 (7.5)	30.8 (7)
Area-Level SES index level, n (%)			
1 (Low)	139 (23.5%)	61 (27%)	78 (21.3%)
2	152 (25.7%)	50 (22.1%)	102 (27.9%)
3	112 (18.9%)	45 (19.9%)	67 (18.3%)
4	106 (17.9%)	38 (16.8%)	68 (18.6%)
5 (High)	83 (14%)	32 (14.2%)	51 (13.9%)
Maternal education, n (%)			
8 or less years	60 (10.1%)	18 (8%)	42 (11.5%)
9-11 years	103 (17.4%)	42 (18.6%)	61 (16.7%)
12 years	175 (29.6%)	65 (28.8%)	110 (30.1%)
13 to 15 years	114 (19.3%)	45 (19.9%)	69 (18.9%)
16 or more years	124 (20.9%)	48 (21.2%)	76 (20.8%)
Missing	16 (2.7%)	8 (3.5%)	8 (2.2%)
Maternal race/ethnicity, n (%)			
Asian/Pacific Islander	75 (12.7%)	27 (11.9%)	48 (13.1%)
Black	32 (5.4%)	12 (5.3%)	20 (5.5%)
Hispanic of any race	303 (51.2%)	116 (51.3%)	187 (51.1%)
Other	22 (3.7%)	9 (4%)	13 (3.6%)
White non-Hispanic	160 (27%)	62 (27.4%)	98 (26.8%)
Missing	29 (4.9%)	14 (6.2%)	15 (4.1%)
Maternal smoking ^a , n (%)			
Non-smoker	540 (91.2%)	201 (88.9%)	339 (92.6%)
Smoker	51 (8.6%)	25 (11.1%)	26 (7.1%)

^a Maternal smoking defined as any detectable cotinine, or hydroxycotinine intensity above the 86th percentile, in dried blood spot samples³¹

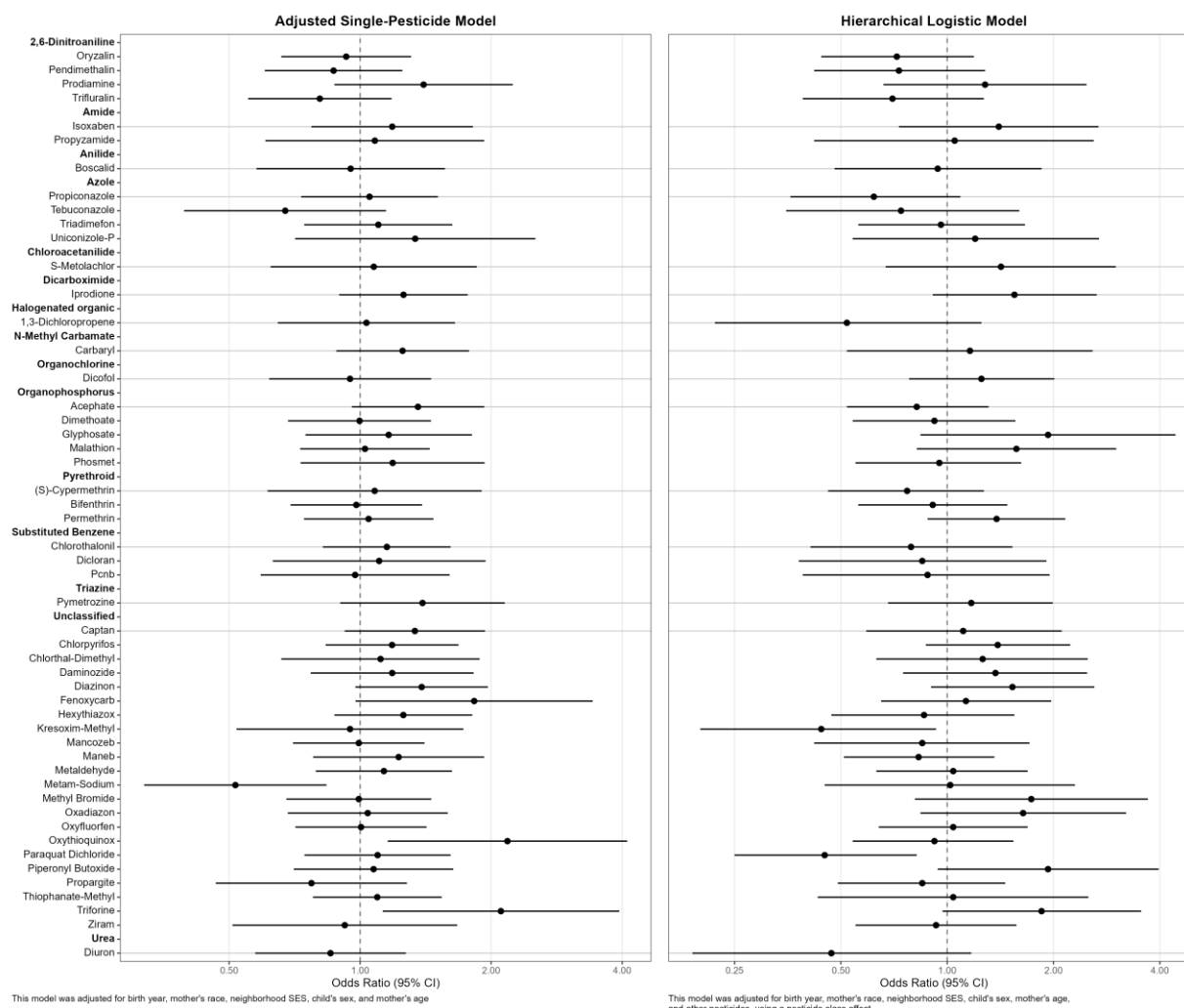


Figure 4-1. Associations between retinoblastoma and exposure to agricultural pesticide applications within 4000m of the residential address (N = 484)

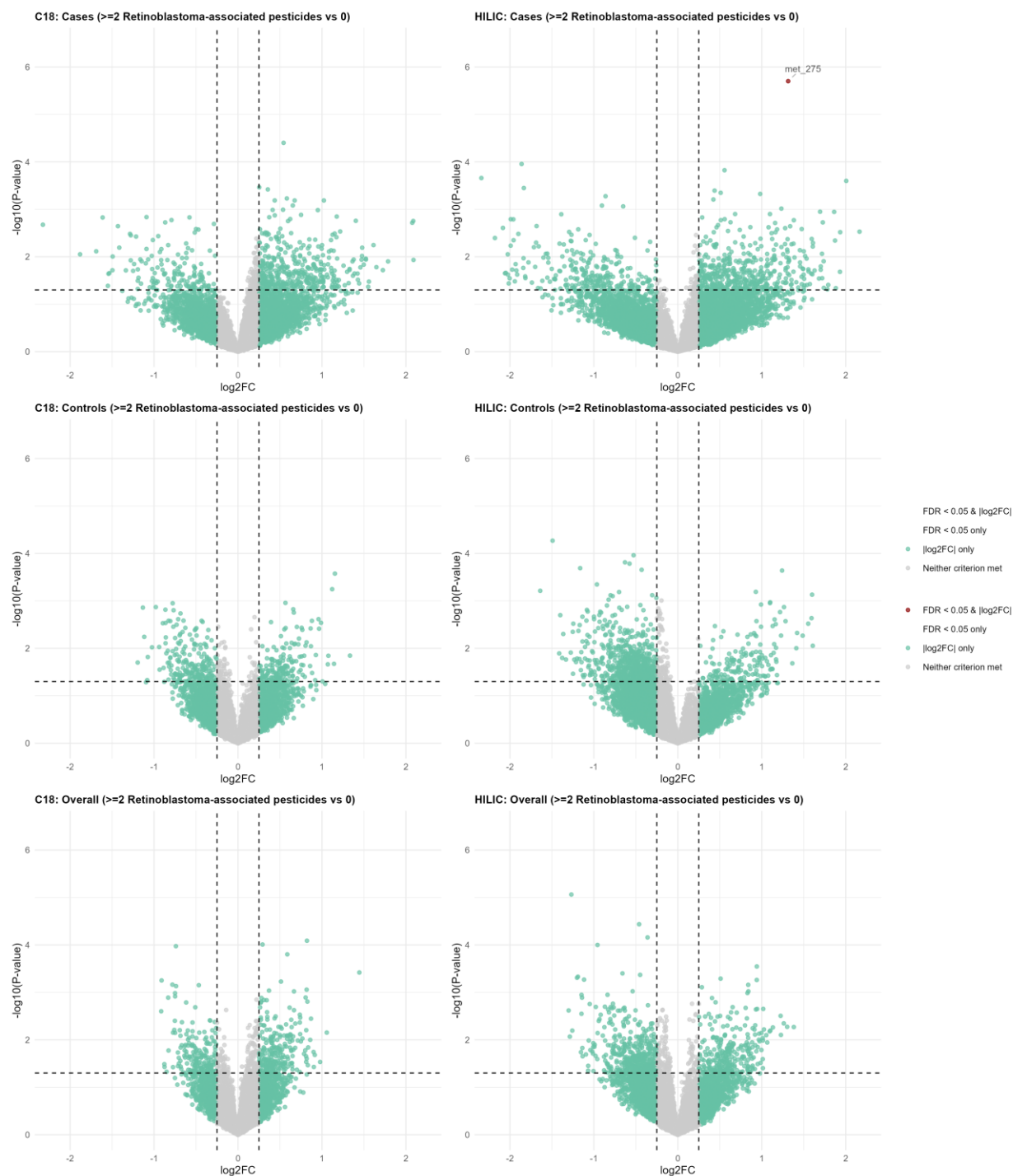


Figure 4-2. Volcano plots from the metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, by liquid chromatography platform and case/control stratum

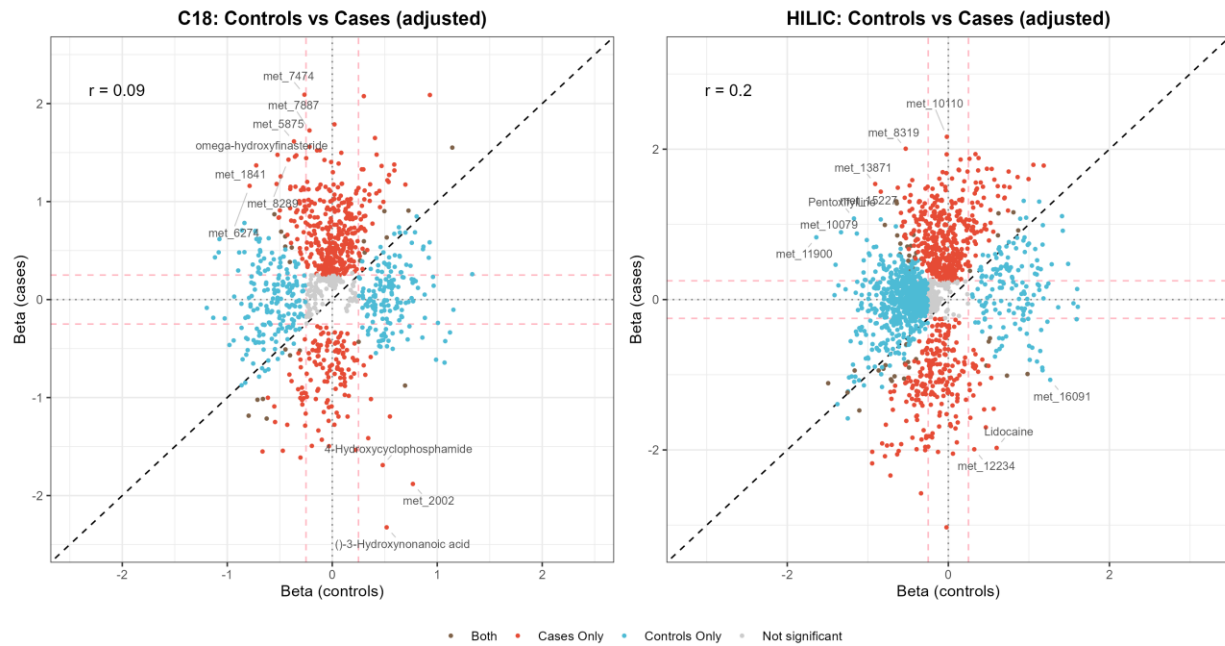


Figure 4-3. Comparison of case- and control-specific beta coefficients from the case/control-stratified MWAS (≥ 2 vs. 0 retinoblastoma-associated pesticides, fully adjusted), by platform (C18, HILIC)

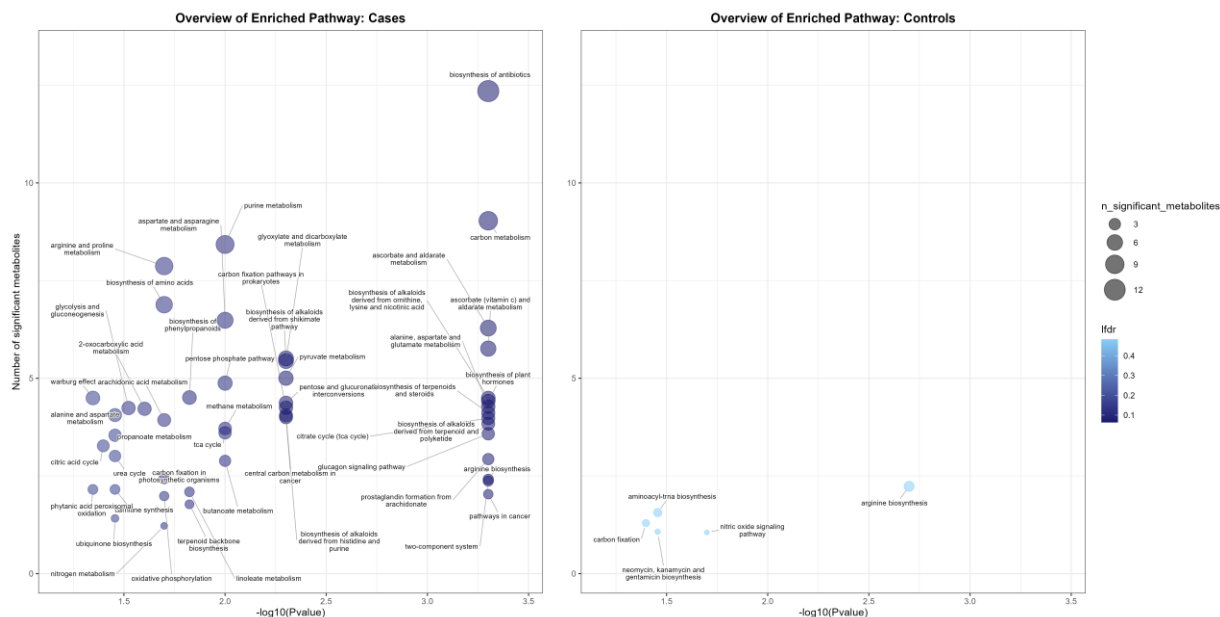


Figure 4-4. Overview of enriched pathway analysis, case/control-stratified. Based on pathway analysis of untargeted retinoblastoma-associated pesticide MWAS features using a permutation-based weighted hypergeometric test

4.7 Supplemental materials

Supplemental Table 4-1. Associations between retinoblastoma and exposure to agricultural pesticide applications within 4000m of the residential address (N = 592) (uploaded separately)

Supplemental Table 4-2. Associations between retinoblastoma and composite retinoblastoma-associated pesticide score (N=592)

Exposure Score	All Retinoblastoma			Unilateral Retinoblastoma RB (95% CI)			Bilateral Retinoblastoma aOR (95% CI) ^a		
	Exposed Cases	Exposed Controls	aOR (95% CI) ^a	Exposed Cases	Exposed Controls	aOR (95% CI) ^a	Exposed Cases	Exposed Controls	aOR (95% CI)
Continuous	226	366	1.14 (1.04, 1.25)	117	366	1.08 (0.96, 1.22)	109	366	1.21 (1.08, 1.37)
Dichotomous Exposures									
≥2 pesticides vs 0	148	206	1.79 (1.14, 2.82)	71	206	1.61 (0.91, 2.85)	77	206	2.22 (1.18, 4.18)
≥3 pesticides vs 0	111	150	1.85 (1.14, 2.99)	50	150	1.49 (0.81, 2.76)	61	150	2.58 (1.32, 5.07)
≥4 pesticides vs 0	75	97	1.98 (1.16, 3.38)	32	97	1.58 (0.79, 3.18)	43	97	2.98 (1.40, 6.37)
≥5 pesticides vs 0	39	48	2.28 (1.16, 4.47)	18	48	2.28 (0.92, 5.64)	21	48	2.75 (1.06, 7.16)

*Pesticides included in this score: captan, diazinon, oxythioquinox, acephate, triforine, iprodione, fenoxycarb, pymetrozine

**Retinoblastoma-associated pesticide defined as pesticides with OR ≥1.0 and lower 95% CI ≥0.90 in the fully adjusted single-pesticide logistic regression model

Supplemental Table 4-3. Full summary statistics from the case/control-stratified metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 vs. 0 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, HILIC platform (N=484) (uploaded separately)

Supplemental Table 4-4. Full summary statistics from the case/control-stratified metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 vs. 0 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, C18 platform (N=484) (uploaded separately)

Supplemental Table 4-5. Full summary statistics from the overall metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 vs. 0 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, C18 platform (N=484) (uploaded separately)

Supplemental Table 4-6. Full summary statistics from the overall metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 vs. 0 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, HILIC platform (N=484) (uploaded separately)

Supplemental Table 4-7. Full pathway over-representation analysis (ORA) results from the metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 vs. 0 retinoblastoma-associated pesticides, comparing the overall model (adjusted for case/control status), retinoblastoma cases, and controls, using metapone (uploaded separately)

Supplemental Table 4-8. Full summary statistics from the main-effects and case/control-stratified MWAS of prenatal exposure to ≥ 4 vs. 0 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, C18 platform (N=302) (uploaded separately)

Supplemental Table 4-9. Full summary statistics from the overall and case/control-stratified MWAS of prenatal exposure to ≥ 4 vs. 0 retinoblastoma-associated pesticides and the neonatal blood spot metabolome, HILIC platform (N=302) (uploaded separately)

Supplemental Table 4-10. Full pathway over-representation analysis (ORA) results from the metabolome-wide association study (MWAS) of prenatal exposure to ≥ 4 vs. 0 retinoblastoma-associated pesticides, comparing the overall model (adjusted for case/control status), retinoblastoma cases, and controls, using metapone (uploaded separately)

Supplemental Table 4-11. Full summary statistics from the main-effects and case/control-stratified MWAS of prenatal glyphosate exposure (ever vs. never) and the neonatal blood spot metabolome, C18 platform (N=592) (uploaded separately)

Supplemental Table 4-12. Full summary statistics from the main-effects and case/control-stratified MWAS of prenatal glyphosate exposure (ever vs. never) and the neonatal blood spot metabolome, HILIC platform (N=592) (uploaded separately)

Supplemental Table 4-13. Full pathway over-representation analysis (ORA) results from the metabolome-wide association study (MWAS) of prenatal glyphosate exposure (ever vs. never), comparing the overall model (adjusted for case/control status), retinoblastoma cases, and controls, using metapone (uploaded separately)

Supplemental Table 4-14. Full pathway gene set enrichment analysis (GSEA) results from the metabolome-wide association study (MWAS) of prenatal exposure to ≥ 2 vs. 0 retinoblastoma-associated pesticides,

comparing the overall model (adjusted for case/control status), retinoblastoma cases, and controls, using metapone (uploaded separately)

Supplemental Table 4-15. Top 100 discordant HILIC metabolic features by case/control beta difference ($\Delta\beta$), with case-stratified, control-stratified, and pesticide $\times$ retinoblastoma interaction model results (≥ 2 vs. 0 retinoblastoma-associated pesticides, fully adjusted for birth year, child sex, maternal age, maternal race/ethnicity, and area-level SES) (uploaded separately)

Supplemental Table 4-16. Top 100 discordant C18 metabolic features by case/control beta difference ($\Delta\beta$), with case-stratified, control-stratified, and pesticide $\times$ retinoblastoma interaction model results (≥ 2 vs. 0 retinoblastoma-associated pesticides, fully adjusted for birth year, child sex, maternal age, maternal race/ethnicity, and area-level SES) (uploaded separately)

Chapter 5 Conclusion and public health implications

This dissertation investigated prenatal agricultural pesticide and traffic-related air pollution exposures in relation to childhood cancer risk and explored metabolic pathways associated with prenatal pesticide exposure among children with retinoblastoma. Because many childhood cancers are believed to originate during fetal development, understanding environmental exposures during the prenatal period is essential for identifying opportunities for childhood cancer prevention.⁴¹⁻⁴³ Together, these studies provide new epidemiologic and mechanistic evidence regarding two of California's most prevalent environmental exposures and contribute to a growing understanding of childhood cancer etiology.

California applies more agricultural pesticides than any other state, often near homes, schools, and other populated areas.⁵⁰ Chapters 2 and 4 identified associations between prenatal exposure to specific agricultural pesticides and childhood cancer risk, extending previous studies that largely relied on occupational proxies or parental recall. The composite score findings from Chapter 4 further suggest that cumulative exposure to multiple pesticides may be relevant to childhood cancer risk and highlight the importance of considering both individual pesticides and pesticide mixtures in future epidemiologic studies and pesticide risk assessments.

Chapter 3 provides additional evidence that prenatal traffic-related air pollution may contribute to childhood cancer risk. Because traffic-related air pollution disproportionately affects lower-income and historically marginalized communities, reducing these exposures may also advance environmental health equity.^{165,199} Although combustion-related vehicle emissions continue to decline because of increasingly stringent emissions standards and the transition toward electric vehicles, non-combustion sources such as brake and tire wear are expected to contribute an increasing proportion of traffic-related particulate matter.¹³⁶⁻¹³⁸ As non-exhaust emissions

become a larger component of traffic-related air pollution, future air quality standards and exposure mitigation strategies may need to account for these sources in addition to traditional tailpipe emissions.

Chapter 4 illustrates how neonatal metabolomics can complement population-based epidemiologic studies to investigate biological mechanisms underlying environmental disease associations. We observed distinct metabolic responses to prenatal pesticide exposure among retinoblastoma cases and controls and identified inflammatory lipid metabolism, central energy metabolism, amino acid metabolism, and oxidative stress-related pathways as candidates for targeted mechanistic studies.

Collectively, these studies demonstrate the value of integrating advanced exposure assessment with molecular epidemiology to investigate childhood cancer etiology. By identifying environmental exposures associated with childhood cancer risk and generating hypotheses regarding the biological pathways through which they may influence disease development, this dissertation contributes to a growing body of evidence supporting the role of prenatal environmental exposures in childhood cancer etiology and provides a foundation for future mechanistic and epidemiologic research.

References

1. Siegel RL, Kratzer TB, Wagle NS, Sung H, Jemal A. Cancer statistics, 2026. *CA: A Cancer Journal for Clinicians*. 2026;76(1):e70043.
2. Kattner P, Strobel H, Khoshnevis N, et al. Compare and contrast: pediatric cancer versus adult malignancies. *Cancer Metastasis Rev*. 2019;38(4):673-682.
3. Howard J. *Minimum Latency & Types or Categories of Cancer* World Trade Center Health Program; November 7, 2014 2014.
4. Marsden HB. The classification of childhood tumours. *IARC Sci Publ*. 1988(87):9-16.
5. Grobner SN, Worst BC, Weischenfeldt J, et al. The landscape of genomic alterations across childhood cancers. *Nature*. 2018;555(7696):321-327.
6. Plon SE, Lupo PJ. Genetic Predisposition to Childhood Cancer in the Genomic Era. *Annu Rev Genomics Hum Genet*. 2019;20:241-263.
7. Bakhuizen JJ, Hopman SMJ, Bosscha MI, et al. Assessment of Cancer Predisposition Syndromes in a National Cohort of Children With a Neoplasm. *JAMA Netw Open*. 2023;6(2):e2254157.
8. International Agency for Research on Cancer [IARC]. *Radiation*. Vol 100D. Lyon, France: WHO Press; 2012.
9. Buser JM, Lake K, Ginier E. Environmental Risk Factors for Childhood Cancer in an Era of Global Climate Change: A Scoping Review. *J Pediatr Health Care*. 2022;36(1):46-56.
10. Geurten C, Geurten M, Rigo V, Dresse MF. Neonatal Cancer Epidemiology and Outcome: A Retrospective Study. *J Pediatr Hematol Oncol*. 2020;42(5):e286-e292.
11. Mahapatra S, Challagundla KB. Neuroblastoma. In: *StatPearls*. Treasure Island (FL) 2024.
12. Yan P, Qi F, Bian L, et al. Comparison of Incidence and Outcomes of Neuroblastoma in Children, Adolescents, and Adults in the United States: A Surveillance, Epidemiology, and End Results (SEER) Program Population Study. *Med Sci Monit*. 2020;26:e927218.
13. Brisse HJ, McCarville MB, Granata C, et al. Guidelines for imaging and staging of neuroblastic tumors: consensus report from the International Neuroblastoma Risk Group Project. *Radiology*. 2011;261(1):243-257.
14. American Cancer Society. Key Statistics About Neuroblastoma. 2021; <https://www.cancer.org/cancer/types/neuroblastoma/about/key-statistics.html>, 2024.
15. Matthay KK, Maris JM, Schleiermacher G, et al. Neuroblastoma. *Nat Rev Dis Primers*. 2016;2:16078.
16. Heck JE, Ritz B, Hung RJ, Hashibe M, Boffetta P. The epidemiology of neuroblastoma: a review. *Paediatr Perinat Epidemiol*. 2009;23(2):125-143.
17. Jung EM, Heck JE, Spector LG. The relative contributions of genetic and non-genetic factors to the risk of neuroblastoma. *Pediatr Investig*. 2025;9(1):82-93.

18. Sirirungreung A, Hansen J, He D, Huang X, Ritz B, Heck JE. Exposure to nitrosatable drugs during pregnancy and childhood cancer: A matched case-control study in Denmark, 1996-2016. *Pharmacoepidemiol Drug Saf.* 2023;32(4):496-505.
19. Olgun HN, Arayici ME, Cecen RE, Basbinar Y, Ellidokuz H. The association between birth weight and the risk of neuroblastoma: a meta-analysis of observational studies involving 4,361,141 participants. *Am J Cancer Res.* 2023;13(9):3854-3863.
20. Johnson KJ, Puumala SE, Soler JT, Spector LG. Perinatal characteristics and risk of neuroblastoma. *Int J Cancer.* 2008;123(5):1166-1172.
21. Bluhm EC, Daniels J, Pollock BH, Olshan AF, Children's Oncology G. Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States). *Cancer Causes Control.* 2006;17(5):663-669.
22. Westerveld ASR, Dalen ECV, Asogwa OA, et al. Neuroblastoma survivors at risk for developing subsequent neoplasms: A systematic review. *Cancer Treatment Reviews.* 2022;104.
23. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* 2024;74(1):12-49.
24. Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. *Nat Rev Dis Primers.* 2015;1:15021.
25. Yun J, Li Y, Xu CT, Pan BR. Epidemiology and Rb1 gene of retinoblastoma. *Int J Ophthalmol.* 2011;4(1):103-109.
26. Bunin GR, Meadows AT, Emanuel BS, Buckley JD, Woods WG, Hammond GD. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. *Cancer Res.* 1989;49(20):5730-5735.
27. Omidakhsh N, Ganguly A, Bunin GR, von Ehrenstein OS, Ritz B, Heck JE. Residential Pesticide Exposures in Pregnancy and the Risk of Sporadic Retinoblastoma: A Report From the Children's Oncology Group. *Am J Ophthalmol.* 2017;176:166-173.
28. Thompson S, Ritz B, Cockburn M, Heck JE. Prenatal ambient pesticide exposure and childhood retinoblastoma. *Int J Hyg Environ Health.* 2022;245:114025.
29. Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, Ritz B. Perinatal characteristics and retinoblastoma. *Cancer Causes Control.* 2012;23(9):1567-1575.
30. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol.* 2006;35(6):1495-1503.
31. He D, Huang X, Uppal K, et al. Biomarkers of Maternal Smoking and the Risk of Retinoblastoma in Offspring. *Retina.* 2023;43(3):481-489.
32. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. Retinoblastoma and ambient exposure to air toxics in the perinatal period. *J Expo Sci Environ Epidemiol.* 2015;25(2):182-186.
33. International Agency for Research on Cancer [IARC]. *Outdoor Air Pollution* Vol 109. Lyon, France: WHO Press; 2015.
34. International Agency for Research on Cancer [IARC]. *Benzene.* Vol 120. Lyon, France: WHO Press; 2018.
35. International Agency for Research on Cancer [IARC]. *Chemical Agents and Related Occupations: Volume.* Vol 100F. Lyon, France: WHO Press; 2012.

36. International Agency for Research on Cancer [IARC]. *Arsenic, Metals, Fibres, and Dusts*. Vol 100C. Lyon, France: WHO Press; 2012.
37. International Agency for Research on Cancer [IARC]. *Diesel and Gasoline Engine Exhausts and Some Nitroarenes*. Vol 105. Lyon, France: WHO Press; 2013.
38. Anderson SM, Naidoo RN, Ramkaran P, et al. The Effect of Nitric Oxide Pollution on Oxidative Stress in Pregnant Women Living in Durban, South Africa. *Arch Environ Contam Toxicol*. 2018;74(2):228-239.
39. Meng Q, Liu J, Shen J, et al. Ambient exposure to fine particulate matter with oxidative potential affects oxidative stress biomarkers in pregnancy. *Am J Epidemiol*. 2025;194(1):27-34.
40. Pedersen M, Wichmann J, Autrup H, et al. Increased micronuclei and bulky DNA adducts in cord blood after maternal exposures to traffic-related air pollution. *Environmental Research*. 2009;109(8):1012-1020.
41. Selevan SG, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. *Environ Health Perspect*. 2000;108 Suppl 3(Suppl 3):451-455.
42. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. *Nat Rev Cancer*. 2003;3(9):639-649.
43. Lafiura KM, Bielawski DM, Posecion NC, Jr., et al. Association between prenatal pesticide exposures and the generation of leukemia-associated T(8;21). *Pediatr Blood Cancer*. 2007;49(5):624-628.
44. Ghosh JK, Heck JE, Cockburn M, Su J, Jerrett M, Ritz B. Prenatal Exposure to Traffic-related Air Pollution and Risk of Early Childhood Cancers. *Am J Epidemiol*. 2013;178(8):1233-1239.
45. Heck JE, Wu J, Lombardi C, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. *Environ Health Perspect*. 2013;121(11-12):1385-1391.
46. Symanski E, Tee Lewis PG, Chen TY, Chan W, Lai D, Ma X. Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. *Environ Health*. 2016;15(1):70.
47. Lavigne E, Belair MA, Do MT, et al. Maternal exposure to ambient air pollution and risk of early childhood cancers: A population-based study in Ontario, Canada. *Environ Int*. 2017;100:139-147.
48. Hall C, Heck JE, Ritz B, Cockburn M, Escobedo LA, von Ehrenstein OS. Prenatal Exposure to Air Toxics and Malignant Germ Cell Tumors in Young Children. *J Occup Environ Med*. 2019;61(6):529-534.
49. Navarrete-Meneses MDP, Salas-Labadia C, Gomez-Chavez F, Perez-Vera P. Environmental Pollution and Risk of Childhood Cancer: A Scoping Review of Evidence from the Last Decade. *Int J Mol Sci*. 2024;25(6).
50. California Department of Pesticide Regulation. *Pesticide Use Annual Report 2023 Data Summary*. Sacramento, CA June 2025 2025.
51. US EPA Office of Pesticide Programs. *Annual Cancer Report 2022: Chemicals Evaluated for Carcinogenic Potential*. 2022.

52. Bonvallot N, Tremblay-Franco M, Chevrier C, et al. Metabolomics tools for describing complex pesticide exposure in pregnant women in Brittany (France). *PLoS One*. 2013;8(5):e64433.
53. Salihovic S, Ganna A, Fall T, et al. The metabolic fingerprint of p,p'-DDE and HCB exposure in humans. *Environ Int*. 2016;88:60-66.
54. Maitre L, Robinson O, Martinez D, et al. Urine Metabolic Signatures of Multiple Environmental Pollutants in Pregnant Women: An Exposome Approach. *Environ Sci Technol*. 2018;52(22):13469-13480.
55. Hu X, Li S, Cirillo P, et al. Metabolome Wide Association Study of serum DDT and DDE in Pregnancy and Early Postpartum. *Reprod Toxicol*. 2020;92:129-137.
56. Yan Q, Paul KC, Walker DI, et al. High-Resolution Metabolomic Assessment of Pesticide Exposure in Central Valley, California. *Chem Res Toxicol*. 2021;34(5):1337-1347.
57. Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood--a review. *Toxicol Appl Pharmacol*. 2004;199(2):118-131.
58. Tsubota S, Kadomatsu K. Origin and initiation mechanisms of neuroblastoma. *Cell Tissue Res*. 2018;372(2):211-221.
59. Park AS, Ritz B, Yu F, Cockburn M, Heck JE. Prenatal pesticide exposure and childhood leukemia - A California statewide case-control study. *Int J Hyg Environ Health*. 2020;226:113486.
60. Feulefack J, Khan A, Forastiere F, Sergi CM. Parental Pesticide Exposure and Childhood Brain Cancer: A Systematic Review and Meta-Analysis Confirming the IARC/WHO Monographs on Some Organophosphate Insecticides and Herbicides. *Children (Basel)*. 2021;8(12).
61. Karalexi MA, Tagkas CF, Markozannes G, et al. Exposure to pesticides and childhood leukemia risk: A systematic review and meta-analysis. *Environ Pollut*. 2021;285:117376.
62. Lombardi C, Thompson S, Ritz B, Cockburn M, Heck JE. Residential proximity to pesticide application as a risk factor for childhood central nervous system tumors. *Environ Res*. 2021;197:111078.
63. Cockburn M, Mills P, Zhang X, Zadnick J, Goldberg D, Ritz B. Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. *Am J Epidemiol*. 2011;173(11):1280-1288.
64. Rull RP, Ritz B. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. *Environ Health Perspect*. 2003;111(13):1582-1589.
65. Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. *Int J Cancer*. 1996;65(1):39-50.
66. Schuz J, Kaletsch U, Meinert R, Kaatsch P, Spix C, Michaelis J. Risk factors for neuroblastoma at different stages of disease. Results from a population-based case-control study in Germany. *J Clin Epidemiol*. 2001;54(7):702-709.
67. Olshan AF, De Roos AJ, Teschke K, et al. Neuroblastoma and parental occupation. *Cancer Causes Control*. 1999;10(6):539-549.

68. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect.* 2004;112(5):631-635.
69. Khan A, Feulefack J, Sergi CM. Pre-conceptional and prenatal exposure to pesticides and pediatric neuroblastoma. A meta-analysis of nine studies. *Environ Toxicol Pharmacol.* 2022;90:103790.
70. Hymel E, Degarege A, Fritch J, et al. Agricultural exposures and risk of childhood neuroblastoma: a systematic review and meta-analysis. *Environ Sci Pollut Res Int.* 2023;30(53):113193-113204.
71. Bunin GR, Ward E, Kramer S, Rhee CA, Meadows AT. Neuroblastoma and parental occupation. *Am J Epidemiol.* 1990;131(5):776-780.
72. Spitz MR, Johnson CC. Neuroblastoma and paternal occupation. A case-control analysis. *Am J Epidemiol.* 1985;121(6):924-929.
73. Wilkins JR, 3rd, Hundley VD. Paternal occupational exposure to electromagnetic fields and neuroblastoma in offspring. *Am J Epidemiol.* 1990;131(6):995-1008.
74. Daniels JL, Olshan AF, Teschke K, Hertz-Picciotto I, Savitz DA, Blatt J. Comparison of assessment methods for pesticide exposure in a case-control interview study. *Am J Epidemiol.* 2001;153(12):1227-1232.
75. Carozza SE, Li B, Wang Q, Horel S, Cooper S. Agricultural pesticides and risk of childhood cancers. *Int J Hyg Environ Health.* 2009;212(2):186-195.
76. Awounou D, Mancini M, Lacour B, et al. Residential proximity to vines and risk of childhood embryonal tumours in France - GEOCAP case-control study, 2006-2013. *Environ Res.* 2024;240(Pt 2):117417.
77. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. *Occup Environ Med.* 2003;60(10):798-801.
78. Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture: the role of pesticides. *Br J Cancer.* 1998;77(5):825-829.
79. Pearce MS, Hammal DM, Dorak MT, McNally RJ, Parker L. Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case-control study from the North of England. *Arch Environ Occup Health.* 2006;61(3):138-144.
80. MacCarthy A, Bunch KJ, Fear NT, King JC, Vincent TJ, Murphy MF. Paternal occupation and retinoblastoma: a case-control study based on data for Great Britain 1962-1999. *Occup Environ Med.* 2009;66(10):644-649.
81. Abdolahi A, van Wijngaarden E, McClean MD, et al. A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. *Occup Environ Med.* 2013;70(6):372-379.
82. Jones DP. Sequencing the exposome: A call to action. *Toxicol Rep.* 2016;3:29-45.
83. He D, Yan Q, Uppal K, et al. Metabolite Stability in Archived Neonatal Dried Blood Spots Used for Epidemiologic Research. *Am J Epidemiol.* 2023;192(10):1720-1730.
84. Kohe S, Brundler MA, Jenkinson H, et al. Metabolite profiling in retinoblastoma identifies novel clinicopathological subgroups. *Br J Cancer.* 2015;113(8):1216-1224.
85. Kohe SE, Bennett CD, Gill SK, Wilson M, McConville C, Peet AC. Metabolic profiling of the three neural derived embryonal pediatric tumors retinoblastoma,

- neuroblastoma and medulloblastoma, identifies distinct metabolic profiles. *Oncotarget*. 2018;9(13):11336-11351.
86. Yan Q, He D, Walker DI, et al. The neonatal blood spot metabolome in retinoblastoma. *EJC Paediatr Oncol*. 2023;2.
 87. California Department of Pesticide Regulation. *Pesticide Use Annual Report 2021 Data Summary*. 2023.
 88. Taiba J, Beseler C, Zahid M, Bartelt-Hunt S, Kolok A, Rogan E. Exploring the Joint Association Between Agrichemical Mixtures and Pediatric Cancer. *Geohealth*. 2025;9(2):e2024GH001236.
 89. Daniels JL, Olshan AF, Teschke K, et al. Residential pesticide exposure and neuroblastoma. *Epidemiology*. 2001;12(1):20-27.
 90. Rios P, Bailey HD, Lacour B, et al. Maternal use of household pesticides during pregnancy and risk of neuroblastoma in offspring. A pooled analysis of the ESTELLE and ESCALE French studies (SFCE). *Cancer Causes Control*. 2017;28(10):1125-1132.
 91. Michaelis J, Haaf HG, Zollner J, Kaatsch P, Krummenauer F, Berthold F. Case control study of neuroblastoma in west-Germany after the Chernobyl accident. *Klin Padiatr*. 1996;208(4):172-178.
 92. California Cancer Registry. About California Cancer Registry. 2018; <https://www.ccrca.org/learn-about-ccr/about-cancer-registries/>. Accessed 06 February 2024.
 93. Urayama KY, Von Behren J, Reynolds P, Hertz A, Does M, Buffler PA. Factors associated with residential mobility in children with leukemia: implications for assigning exposures. *Ann Epidemiol*. 2009;19(11):834-840.
 94. Curwin BD, Hein MJ, Sanderson WT, et al. Urinary and hand wipe pesticide levels among farmers and nonfarmers in Iowa. *J Expo Anal Environ Epidemiol*. 2005;15(6):500-508.
 95. Harnly M, McLaughlin R, Bradman A, Anderson M, Gunier R. Correlating agricultural use of organophosphates with outdoor air concentrations: a particular concern for children. *Environ Health Perspect*. 2005;113(9):1184-1189.
 96. Wofford P, Segawa R, Schreider J, Federighi V, Neal R, Brattesani M. Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year. *Environ Monit Assess*. 2014;186(3):1355-1370.
 97. Grimbuhler S, Viel JF. Bystander dermal exposure to drift during pesticide application in vineyards: An experimental factorial study. *Chemosphere*. 2024;369:143809.
 98. Momoli F, Abrahamowicz M, Parent ME, Krewski D, Siemiatycki J. Analysis of multiple exposures: an empirical comparison of results from conventional and semi-bayes modeling strategies. *Epidemiology*. 2010;21(1):144-151.
 99. Schraw JM, Rodriguez KB, Scheurer ME, Foster JH, Lupo PJ. Associations of demographic and perinatal factors with childhood neuroblastoma in Texas, 1995-2011. *Cancer Epidemiol*. 2022;78:102165.

100. Kehm RD, Spector LG, Poynter JN, Vock DM, Osypuk TL. Socioeconomic Status and Childhood Cancer Incidence: A Population-Based Multilevel Analysis. *Am J Epidemiol*. 2018;187(5):982-991.
101. Yost K, Perkins C, Cohen R, Morris C, Wright W. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Control*. 2001;12(8):703-711.
102. He D, Huang X, Arah OA, et al. A prediction model for classifying maternal pregnancy smoking using California state birth certificate information. *Paediatr Perinat Epidemiol*. 2024;38(2):102-110.
103. Greenland S. Hierarchical regression for epidemiologic analyses of multiple exposures. *Environ Health Perspect*. 1994;102 Suppl 8(Suppl 8):33-39.
104. Greenland S. A semi-Bayes approach to the analysis of correlated multiple associations, with an application to an occupational cancer-mortality study. *Stat Med*. 1992;11(2):219-230.
105. Pesticide Action Network. PAN Pesticide Database. 2021; <https://www.pesticideinfo.org/>, 2024.
106. Bennett DH, Sellen J, Moran R, Alaimo CP, Young TM. Personal air sampling for pesticides in the California San Joaquin Valley. *J Expo Sci Environ Epidemiol*. 2024.
107. Lee S, McLaughlin R, Harnly M, Gunier R, Kreutzer R. Community exposures to airborne agricultural pesticides in California: ranking of inhalation risks. *Environ Health Perspect*. 2002;110(12):1175-1184.
108. Gunier RB, Ward MH, Airola M, et al. Determinants of agricultural pesticide concentrations in carpet dust. *Environ Health Perspect*. 2011;119(7):970-976.
109. Coronado GD, Holte S, Vigoren E, et al. Organophosphate pesticide exposure and residential proximity to nearby fields: evidence for the drift pathway. *J Occup Environ Med*. 2011;53(8):884-891.
110. Insecticide Resistance Action Committee. IRAC Mode of Action Classification Scheme. 2025; <https://irac-online.org/documents/moa-classification/>, March 31, 2025.
111. U.S. Environmental Protection Agency [EPA]. Flonicamid. Human Health Risk Assessment for New Uses on Legume Vegetables, Subgroups 6A, 6B, and 6C; Add Directions for use on Greenhouse Grown Peppers and Increase the Tolerance for Residues on Fruiting Vegetables, Group 8-10; New Use on Citrus Fruits, Group 10-10; and a Tolerance without U.S. Registration for residues in/on Dried Tea. . In: U.S. Environmental Protection Agency, ed. Washington, DC: Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency; 2016.
112. Kara M, Oztas E, Ramazanogullari R, et al. Benomyl, a benzimidazole fungicide, induces oxidative stress and apoptosis in neural cells. *Toxicol Rep*. 2020;7:501-509.
113. U.S. Environmental Protection Agency [EPA]. Memorandum: Updated Human Health Assessment for Benomyl. In: U.S. Environmental Protection Agency, ed. Washington, DC: Office of Pesticide Programs, U.S. Environmental Protection Agency; 2001.

114. Ellis WG, Semple JL, Hoogenboom ER, Kavlock RJ, Zeman FJ. Benomyl-induced craniocerebral anomalies in fetuses of adequately nourished and protein-deprived rats. *Teratog Carcinog Mutagen*. 1987;7(4):357-375.
115. Zeman FJ, Hoogenboom ER, Kavlock RJ, Semple JL. Effects on the fetus of maternal benomyl exposure in the protein-deprived rat. *J Toxicol Environ Health*. 1986;17(4):405-417.
116. Carter SD, Hein JF, Rehnberg GL, Laskey JW. Effect of benomyl on the reproductive development of male rats. *J Toxicol Environ Health*. 1984;13(1):53-68.
117. Soderlund DM. Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. *Arch Toxicol*. 2012;86(2):165-181.
118. World Health Organization [WHO]. *Cypermethrin*. Vol 82. Geneva, CH1989.
119. U.S. Environmental Protection Agency [EPA]. *Reregistration Eligibility Decision (RED) Facts: Cypermethrin*. Washington, DC August 2009 2009. EPA 738-F-09-001.
120. Berrington de Gonzalez A, Masten SA, Bhatti P, et al. Advisory Group recommendations on priorities for the IARC Monographs. *Lancet Oncol*. 2024;25(5):546-548.
121. Nasuti C, Carloni M, Fedeli D, et al. Effects of early life permethrin exposure on spatial working memory and on monoamine levels in different brain areas of pre-senescent rats. *Toxicology*. 2013;303:162-168.
122. Ding G, Shi R, Gao Y, et al. Pyrethroid pesticide exposure and risk of childhood acute lymphocytic leukemia in Shanghai. *Environ Sci Technol*. 2012;46(24):13480-13487.
123. U.S. Department of Agriculture AaPHIS. *Final human health and ecological risk assessment for carbaryl: Rangeland grasshopper and Mormon cricket suppression applications*. Washington, DC: U.S. Department of Agriculture, Animal and Plant Health Inspection Service;2019.
124. Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect*. 2011;119(8):1189-1195.
125. International Agency for Research on Cancer [IARC]. *Some Organophosphate Insecticides and Herbicides*. Vol 112. Lyon, France WHO Press; 2018.
126. Alavanja MC, Dosemeci M, Samanic C, et al. Pesticides and lung cancer risk in the agricultural health study cohort. *Am J Epidemiol*. 2004;160(9):876-885.
127. Rusiecki JA, Hou L, Lee WJ, et al. Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study. *Int J Cancer*. 2006;118(12):3118-3123.
128. Silver SR, Bertke SJ, Hines CJ, et al. Cancer incidence and metolachlor use in the Agricultural Health Study: An update. *Int J Cancer*. 2015;137(11):2630-2643.
129. Assessment OoEHH. *Public Health Concentrations for Metolachlor and Metolachlor Degradates Ethanesulfonic Acid and Oxanilic Acid in Groundwater*. Sacramento. CA: California Environmental Protection Agency;2017.
130. Liew Z, Olsen J, Cui X, Ritz B, Arah OA. Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *Int J Epidemiol*. 2015;44(1):345-354.

131. Food Safety Commission of Japan. *Risk Assessment Report: Iprodione*. Tokyo, Japan 2013.
132. Ling C, Heck JE, Cockburn M, Liew Z, Marcotte E, Ritz B. Residential mobility in early childhood and the impact on misclassification in pesticide exposures. *Environ Res*. 2019;173:212-220.
133. Müller-Schulte E, Kurlemann G, Harder A. Tobacco, alcohol and illicit drugs during pregnancy and risk of neuroblastoma: systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(5):F467-f473.
134. Karalexi MA, Katsimpris A, Panagopoulou P, et al. Maternal lifestyle factors and risk of neuroblastoma in the offspring: A meta-analysis including Greek NARECHEM-ST primary data. *Cancer Epidemiol*. 2022;77:102055.
135. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA: A Cancer Journal for Clinicians*. 2025;75(1):10-45.
136. Mayer PM, Moran KD, Miller EL, et al. Where the rubber meets the road: Emerging environmental impacts of tire wear particles and their chemical cocktails. *Science of The Total Environment*. 2024;927:171153.
137. Grigoratos T, Martini G. Brake wear particle emissions: a review. *Environ Sci Pollut Res Int*. 2015;22(4):2491-2504.
138. Piscitello A, Bianco C, Casasso A, Sethi R. Non-exhaust traffic emissions: Sources, characterization, and mitigation measures. *Science of The Total Environment*. 2021;766:144440.
139. Kumar SV, Lupo PJ, Pompeii LA, Danysh HE. Maternal Residential Proximity to Major Roadways and Pediatric Embryonal Tumors in Offspring. *Int J Environ Res Public Health*. 2018;15(3).
140. Houot J, Marquant F, Goujon S, et al. Residential Proximity to Heavy-Traffic Roads, Benzene Exposure, and Childhood Leukemia-The GEOCAP Study, 2002-2007. *Am J Epidemiol*. 2015;182(8):685-693.
141. Magnani C, Ranucci A, Badaloni C, et al. Road Traffic Pollution and Childhood Leukemia: A Nationwide Case-control Study in Italy. *Arch Med Res*. 2016;47(8):694-705.
142. Brosselin P, Rudant J, Orsi L, et al. Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). *Occup Environ Med*. 2009;66(9):598-606.
143. Peckham-Gregory EC, Ton M, Rabin KR, Danysh HE, Scheurer ME, Lupo PJ. Maternal Residential Proximity to Major Roadways and the Risk of Childhood Acute Leukemia: A Population-Based Case-Control Study in Texas, 1995-2011. *Int J Environ Res Public Health*. 2019;16(11).
144. Badaloni C, Ranucci A, Cesaroni G, et al. Air pollution and childhood leukaemia: a nationwide case-control study in Italy. *Occup Environ Med*. 2013;70(12):876-883.
145. Janitz AE, Campbell JE, Magzamen S, Pate A, Stoner JA, Peck JD. Traffic-related air pollution and childhood acute leukemia in Oklahoma. *Environ Res*. 2016;148:102-111.
146. Mazzei A, Konstantinoudis G, Kreis C, et al. Childhood cancer and residential proximity to petrol stations: a nationwide registry-based case-control study in

- Switzerland and an updated meta-analysis. *Int Arch Occup Environ Health*. 2022;95(5):927-938.
147. Malavolti M, Malagoli C, Filippini T, et al. Residential proximity to petrol stations and risk of childhood leukemia. *Eur J Epidemiol*. 2023;38(7):771-782.
 148. Lee JM, Lee TH, Kim S, Song M, Bae S. Association between long-term exposure to particulate matter and childhood cancer: A retrospective cohort study. *Environ Res*. 2022;205:112418.
 149. Williams LA, Haynes D, Sample JM, et al. PM2.5, vegetation density, and childhood cancer: a case-control registry-based study from Texas 1995-2011. *J Natl Cancer Inst*. 2024;116(6):876-884.
 150. Raaschou-Nielsen O, Hvidtfeldt UA, Roswall N, Hertel O, Poulsen AH, Sorensen M. Ambient benzene at the residence and risk for subtypes of childhood leukemia, lymphoma and CNS tumor. *Int J Cancer*. 2018;143(6):1367-1373.
 151. von Ehrenstein OS, Heck JE, Park AS, Cockburn M, Escobedo L, Ritz B. In Utero and Early-Life Exposure to Ambient Air Toxics and Childhood Brain Tumors: A Population-Based Case-Control Study in California, USA. *Environ Health Perspect*. 2016;124(7):1093-1099.
 152. Janitz AE, Campbell JE, Magzamen S, Pate A, Stoner JA, Peck JD. Benzene and childhood acute leukemia in Oklahoma. *Environ Res*. 2017;158:167-173.
 153. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer*. 2005;103(7):1457-1467.
 154. Centers for Disease Control and Prevention. Link Plus. 2024; <https://www.cdc.gov/national-program-cancer-registries/registry-plus/link-plus.html>. Accessed December 17, 2025.
 155. Su JG, Shahriary E, Sage E, Jacobsen J, Park K, Mohegh A. Development of over 30-years of high spatiotemporal resolution air pollution models and surfaces for California. *Environ Int*. 2024;193:109100.
 156. Goldberg DW, Wilson JP, Knoblock CA, Ritz B, Cockburn MG. An effective and efficient approach for manually improving geocoded data. *Int J Health Geogr*. 2008;7:60.
 157. Texas A&M University GeoServices. TAMU GeoServices – Free Geocoding, Address Processing, and GIS Data Capture. 2022; <https://geoservices.tamu.edu/default.aspx>. Accessed December 17, 2025.
 158. Beckerman BS, Jerrett M, Serre M, et al. A hybrid approach to estimating national scale spatiotemporal variability of PM2.5 in the contiguous United States. *Environ Sci Technol*. 2013;47(13):7233-7241.
 159. Su JG, Hopke PK, Tian Y, et al. Modeling particulate matter concentrations measured through mobile monitoring in a deletion/substitution/addition approach. *Atmospheric Environment*. 2015;122:477-483.
 160. O'Sharkey K, Mitra S, Chow T, et al. Prenatal exposure to criteria air pollution and traffic-related air toxics and risk of autism spectrum disorder: A population-based cohort study of California births (1990–2018). *Environment International*. 2025;201:109562.

161. Houston D, Wu J, Ong P, Winer A. Structural Disparities of Urban Traffic in Southern California: Implications for Vehicle-Related Air Pollution Exposure in Minority and High-Poverty Neighborhoods. *Journal of Urban Affairs*. 2004;26(5):565-592.
162. Contreras ZA, Hansen J, Ritz B, Olsen J, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. *Cancer Epidemiol*. 2017;49:202-215.
163. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. *Environ Health Perspect*. 2020;128(4):47004.
164. Bedogni G. Applying Quantitative Bias Analysis to Epidemiologic Data. *Journal of the Royal Statistical Society Series A: Statistics in Society*. 2011;174(2):511-512.
165. District SCAQM. *MATES V: Multiple Air Toxics Exposure Study in the South Coast Air Basin*. Diamond Bar, CA: South Coast AQMD; August 2021 2021.
166. E. Steliarova-Foucher MC, L.A.G. Ries, F. Moreno, A. Dolya, H.Y. Shin, P. Hesselning, C.A. Stiller, ed *International Incidence of Childhood Cancer, Volume III*. Lyon: International Agency for Research on Cancer; 2025.
167. Hu S, Fruin S, Kozawa K, Mara S, Paulson SE, Winer AM. A Wide Area of Air Pollutant Impact Downwind of a Freeway during Pre-Sunrise Hours. *Atmos Environ (1994)*. 2009;43(16):2541-2549.
168. Gabbe CJ. Residential zoning and near-roadway air pollution: An analysis of Los Angeles. *Sustainable Cities and Society*. 2018;42:611-621.
169. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.
170. Bové H, Bongaerts E, Slenders E, et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun*. 2019;10(1):3866.
171. Gundacker C, Hengstschläger M. The role of the placenta in fetal exposure to heavy metals. *Wiener Medizinische Wochenschrift*. 2012;162(9):201-206.
172. Fussell JC, Franklin M, Green DC, et al. A Review of Road Traffic-Derived Non-Exhaust Particles: Emissions, Physicochemical Characteristics, Health Risks, and Mitigation Measures. *Environ Sci Technol*. 2022;56(11):6813-6835.
173. Carlos-Wallace FM, Zhang L, Smith MT, Rader G, Steinmaus C. Parental, In Utero, and Early-Life Exposure to Benzene and the Risk of Childhood Leukemia: A Meta-Analysis. *Am J Epidemiol*. 2016;183(1):1-14.
174. Briffa J, Sinagra E, Blundell R. Heavy metal pollution in the environment and their toxicological effects on humans. *Heliyon*. 2020;6(9):e04691.
175. Goodson WH, 3rd, Lowe L, Carpenter DO, et al. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead. *Carcinogenesis*. 2015;36 Suppl 1(Suppl 1):S254-296.
176. Valavanidis A, Vlachogianni T, Fiotakis K, Loridas S. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. *Int J Environ Res Public Health*. 2013;10(9):3886-3907.
177. Douglas Houston JW, Paul Ong, Arthur Winer. Structural Disparities of Urban Traffic in Southern California: Implications for Vehicle-Related Air Pollution Exposure in

- Minority and High-Poverty Neighborhoods. *Journal of Urban Affairs*. 2004;26(No. 5):565-592.
178. International Agency for Research on Cancer [IARC]. *DDT, Lindane, and 2,4-D*. Vol 113. Lyon, France: WHO Press; 2016.
 179. International Agency for Research on Cancer [IARC]. *IARC Monographs Volume 119: Some Chemicals That Cause Tumours of the Urinary Tract in Rodents*. Vol 119. Lyon, France: WHO Press; 2019.
 180. Madrigal JM, Gunier RB, Jones RR, et al. Contributions of nearby agricultural insecticide applications to indoor residential exposures. *Environ Int*. 2023;171:107657.
 181. Liu KH, Nellis M, Uppal K, et al. Reference Standardization for Quantification and Harmonization of Large-Scale Metabolomics. *Anal Chem*. 2020;92(13):8836-8844.
 182. Liang D, Moutinho JL, Golan R, et al. Use of high-resolution metabolomics for the identification of metabolic signals associated with traffic-related air pollution. *Environ Int*. 2018;120:145-154.
 183. Yu T, Park Y, Johnson JM, Jones DP. apLCMS--adaptive processing of high-resolution LC/MS data. *Bioinformatics*. 2009;25(15):1930-1936.
 184. Uppal K, Soltow QA, Strobel FH, et al. xMSanalyzer: automated pipeline for improved feature detection and downstream analysis of large-scale, non-targeted metabolomics data. *BMC Bioinformatics*. 2013;14:15.
 185. Deng K, Zhao F, Rong Z, et al. WavelCA 2.0: a novel batch effect removal method for untargeted metabolomics data without using batch information. *Metabolomics*. 2021;17(10):87.
 186. Smyth G. LIMMA: Linear models for microarray data. In: Vol .2005:397-420.
 187. Go YM, Walker DI, Liang Y, et al. Reference Standardization for Mass Spectrometry and High-resolution Metabolomics Applications to Exposome Research. *Toxicol Sci*. 2015;148(2):531-543.
 188. Uppal K, Walker DI, Jones DP. xMSannotator: An R Package for Network-Based Annotation of High-Resolution Metabolomics Data. *Anal Chem*. 2017;89(2):1063-1067.
 189. Tian L, Li Z, Ma G, et al. Metapone: a Bioconductor package for joint pathway testing for untargeted metabolomics data. *Bioinformatics*. 2022;38(14):3662-3664.
 190. Dyer MA. Mouse models of childhood cancer of the nervous system. *J Clin Pathol*. 2004;57(6):561-576.
 191. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971;68(4):820-823.
 192. Choi I, Son H, Baek JH. Tricarboxylic Acid (TCA) Cycle Intermediates: Regulators of Immune Responses. *Life (Basel)*. 2021;11(1).
 193. Tsai Y-T, Lo W-L, Chen P-Y, et al. Reprogramming of arachidonate metabolism confers temozolomide resistance to glioblastoma through enhancing mitochondrial activity in fatty acid oxidation. *Journal of Biomedical Science*. 2022;29.

194. Anthonymuthu TS, Kenny EM, Lamade AM, Kagan VE, Bayır H. Oxidized phospholipid signaling in traumatic brain injury. *Free Radic Biol Med.* 2018;124:493-503.
195. Karami-Mohajeri S, Abdollahi M. Toxic influence of organophosphate, carbamate, and organochlorine pesticides on cellular metabolism of lipids, proteins, and carbohydrates: a systematic review. *Hum Exp Toxicol.* 2011;30(9):1119-1140.
196. Gong Y, Paul KC, Lin Y, et al. Agricultural Copper Pesticide Exposure and Metabolic Profiles among Parkinson's Disease Cases and Community Controls in California. *Chem Res Toxicol.* 2026;39(1):20-30.
197. Ying L, Marino J, Hussain SP, et al. Chronic inflammation promotes retinoblastoma protein hyperphosphorylation and E2F1 activation. *Cancer Res.* 2005;65(20):9132-9136.
198. Suresh Babu V, Dudeja G, Sa D, et al. Lack of Retinoblastoma Protein Shifts Tumor Metabolism from Glycolysis to OXPHOS and Allows the Use of Alternate Fuels. *Cells.* 2022;11(20).
199. Houston D, Wu J, Ong P, Winer A. Structural Disparities of Urban Traffic in Southern California: Implications for Vehicle-Related Air Pollution Exposure in Minority and High-Poverty Neighborhoods. *Journal of urban affairs.* 2004;26(5):565-592.