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Analysis of Potential Right-of-Way Environmental Exposures and Childhood Leukemia: High Voltage Power Lines, Plant Nurseries, and Pesticides

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

Andrew Nguyen

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ABSTRACT OF THE DISSERTATION

Analysis of Potential Right-of-Way Environmental Exposures and Childhood Leukemia: High Voltage Power Lines, Plant Nurseries, and Pesticides

by

Andrew Nguyen

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2023

Professor Leeka I. Kheifets, Chair

Previous studies have observed consistent associations between magnetic fields exposure and childhood leukemia, and in children living close to high voltage overhead power lines. Biologic plausibility, changes over time and other methodologic issues connected with observed associations with magnetic fields exposure suggests that certain factors such as other associated exposures, confounding or interaction effects may play a role in observed childhood leukemia associations. In the US, high voltage overhead power lines are located in right-of-ways (ROW), which are often locations additionally for commercial plant nurseries, a potential source

of chronic pesticide exposures due to their close proximity to residencies. Pesticides are substances that are utilized to mitigate, repel, or kill unwanted pests. Pesticides are a potential childhood leukemia risk factor, due to their ability to cause molecular changes that are associated with cancer development.

We performed a large California state-wide records-based case-control study that consisted of childhood leukemia cases younger than 16 years of age that were diagnosed in California (1988-2008) obtained from the California Cancer Registry (CCR) and controls obtained from the California Birth Registry (CBR). Controls were randomly matched to cases based on their date of birth (± 6 months) and sex. We obtained commercial plant nursery and pesticide use information from the California Department of Food and Agriculture (CDFA) and the California Department of Pesticide Regulation (CDPR). We utilized CDFA reported locations for commercial plant nursery businesses that were classified as “producers,” which are plant nurseries that grow and sell a total of $1,000 or more of nursery stock annually. Additionally, we obtained Pesticide Use Reports (PUR) for pesticide applications that occurred at plant nurseries prior to 1990; for 1990 and onward, when more detailed pesticide information was available, we obtained pesticide applications for nursery plants grown in containers from the CDPR. Plant nurseries, pesticide applications and subject residences were then mapped with Geographic Information System (GIS) and then augmented with historic aerial satellite images to improve the obtained native data resolution of plant nursery/pesticide exposure information. Due to the unique size and shape footprint of plant nurseries, we selected subjects that resided within 600 m of a nursery for more detailed assessment. Additionally, many plant nurseries are located underneath high voltage power lines, therefore we selected subjects that

resided within 2000 m of such power lines to ensure that we captured all nurseries in proximity to these power lines. We observed that subjects that resided very close to commercial plant nurseries had elevated childhood leukemia risks. Subjects that resided within 75 m of a plant nursery had increased risk of childhood leukemia (OR 2.40, 95% CI 0.99-5.82); this increased risk was stronger for the acute lymphocytic leukemia subtype (OR 3.09, 95% CI 1.14-8.34).

We then explored the potential relationship of commercial outdoor plant nurseries as a confounder or effect modifier for observed childhood leukemia associations with magnetic fields exposure due to high voltage power lines. Power line information was based on GIS data from electric power companies, aerial satellite images and in-person site visits. Associations with childhood leukemia and calculated fields (OR 1.51, 95% CI 0.70-3.23) slightly attenuated after controlling for commercial outdoor plant nursery proximity (OR 1.43, 95% CI 0.65-3.16) or restricting analysis to study subjects residing far away (>300 m) from plant nurseries (OR 1.43, 95% CI 0.79-2.60); similar associations were observed between proximity to high voltage power lines and childhood leukemia after controlling and restricting subjects based on their proximity to plant nurseries. Observed associations for childhood leukemia and proximity to commercial plant nurseries remained elevated after excluding study subjects exposed to high calculated fields (OR 2.16, 95% CI 0.82-5.67) or close power line proximity (OR 2.15, 95% CI 0.82-5.64). Childhood leukemia associations with plant nurseries did not materially change after controlling for calculated fields or power line proximity. Our findings suggest that close residential proximity to plant nurseries is an independent risk factor and that plant nurseries do not explain observed childhood leukemia relationships with magnetic fields exposure or close power line proximity.

Finally, we followed up our study by examining childhood leukemia relationships with more detailed pesticide exposures, including specific intended pesticide use, pesticide chemical classes and active pesticide ingredients. Elevated childhood leukemia risks were observed for exposure to several active pesticide ingredients: permethrin (odds ratio (OR) 1.49, 95% confidence interval (CI) (0.83-2.67), chlorpyrifos (OR 1.29, 95% CI 0.89-1.87), dimethoate (OR 1.79, 95% CI 0.85-3.76), mancozeb (OR 1.41, 95% CI 0.85-2.33), oxyfluorfen (OR 1.41, 95% CI 0.75-2.66), oryzalin (OR 1.60, 95% CI 0.97-2.63), and pendimethalin (OR 1.82, 95% CI 0.81-1.25). Additionally, rodenticide (OR 1.42, 95% CI 0.78-2.66) and molluscicide (OR 1.22, 95% CI 0.82-1.81) exposure had elevated childhood leukemia risks. Observed childhood leukemia associations with calculated fields or power line proximity did not materially change after controlling for pesticide exposure. Our findings suggest that pesticide exposure is an independent risk factor for childhood leukemia and that pesticide exposure does not explain observed childhood leukemia associations with high magnetic fields exposure or nearby power line proximity.

The dissertation of Andrew Nguyen is approved.

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2023

DEDICATION

This dissertation is dedicated to my family, friends, and educators, who have supported me along my journey.

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CAPS	California Power Line Study
CBR	California Birth Registry
CCR	California Cancer Registry
CDFA	California Department of Food and Agriculture
CDPR	California Department of Pesticide Regulation
CF	Calculated Field
CI	Confidence interval
CLIC	Childhood Cancer & Leukemia International Consortium
DAG	Directed acyclic graph
ELF EMF	Extremely low frequency electromagnetic fields
EMF	Electromagnetic fields
ERR	Excess relative risk
GIS	Geographic Information System
Gy	Gray

IARC	International Agency for Research on Cancer
MF	Magnetic fields
OP	Organophosphorus
OR	Odds Ratio
PAN	Pesticide Action Network
PLSS	Public Land Survey System
PUR	Pesticide Use Reports
QS	Quality Score
ROW	Right-of-way
SES	Socioeconomic status

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Amoon, A. T., Crespi, C. M., **Nguyen, A.**, Zhao, X., Vergara, X., Arah, O. A., & Kheifets, L. (2020). The role of dwelling type when estimating the effect of magnetic fields on childhood leukemia in the California Power Line Study (CAPS). Cancer Causes & Control, 31(6), 559–567. https://doi.org/10.1007/s10552-020-01299-9

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Chapter 1. Introduction

1.1 Overview of Childhood Leukemia

1.1.1 Background

Cancer is the leading cause of death due to disease in children and second overall after accidents (American Cancer Society, 2021a; R. L. Siegel et al., 2021). Over 10,000 new cancer cases in children and adolescents (aged birth to 14 years) are estimated to occur in the United States in 2020 (World Health Organization, 2021a). Leukemia, cancer of the blood forming (hematopoietic) tissues, is the most common form of childhood cancer, accounting for approximately 25-30% of all childhood cancers (R. L. Siegel et al., 2021; World Health Organization, 2021a). Childhood leukemia consists of several different subtypes that are classified based on the level of cell differentiation (acute or chronic) and the predominant cell line involved (myeloid or lymphoid). Acute leukemias progress rapidly, affect less mature cells, and result in abnormal blood cells, known as blasts cells. These cells remain immature and overwhelm the normal cells in the bone marrow, preventing normal blood cell function. On the other hand, chronic leukemias progress slowly, resulting in more differentiated and functional cells. Lymphoid and Myeloid cells are both capable of developing into acute or chronic leukemias. Lymphoid cells include natural killer cells, B cells, and T cells. Myeloid cells include monocytes, macrophages, granulocytes (i.e., neutrophil, basophil, or eosinophil), platelets, and erythrocytes (Colby-Graham & Chordas, 2003; Lyengar & Shimanovsky, 2021).

Acute lymphocytic (or lymphoblastic) leukemia (ALL) is the most common form of childhood leukemia, making up approximately 75-80% of all childhood leukemias. ALL is more common in boys than in girls and children aged between 2 and 5 years. ALL is most common among Hispanic and white children (American Cancer Society, 2021b; National Cancer Institute, 2020; D. A. Siegel et al., 2014; Ward et al., 2014). Acute myeloid leukemia (AML) is the second most common form of childhood leukemia, accounting for approximately 20 to 25% of cases. AML is found in approximately equal numbers in boys and girls. AML has the highest incidence during the first 2 years and during the second decade of life (American Cancer Society, 2021b; Dores et al., 2012). Other types of leukemia include chronic myelogenous leukemia and chronic lymphocytic leukemia; chronic leukemias are more common in adults and very rare in children (Colby-Graham & Chordas, 2003; Ward et al., 2014).

1.1.2 Incidence and Mortality

In 2020, approximately 3,100 new cases of childhood leukemia occurred, making it the most common form of childhood cancer (World Health Organization, 2021a). The age-adjusted incidence rate for childhood leukemia (ages 0-14 years) is 5.2 per 100,000 children. The age-adjusted incidence rate has been increasing by 0.7% per year during 2013-2017 (National Cancer Institute, 2020). It is the second leading cause of childhood cancer deaths, after brain/central nervous system cancers. Approximately 329 childhood leukemia deaths occurred in 2020 in the United States (World Health Organization, 2021a). The age-adjusted death rate for childhood leukemia (ages 0-14 years) is 0.5 per 100,000 children and the median age at death is 11 years old. The age-adjusted death rate has been decreasing by 2.8% per year during 2013-2017 with a 5-year survival rate of approximately 85% (National Cancer Institute, 2020).

While advances in research and treatment have drastically improved the 5-year survival rate, leukemia remains a devastating disease and the most common childhood cancer with much of its etiology left unknown. Only a few risk factors have been well-established, including ionizing radiation and certain genetic syndromes such as Down syndrome, Fanconi anemia, Bloom syndrome, and neurofibromatosis (Belson et al., 2007; Kumar & De Jesus, 2021; Schüz & Erdmann, 2016a; Stieglitz & Loh, 2013; Whitehead et al., 2016; Wiemels, 2012; Ziegelberger et al., 2011). However, these only explain a small portion (less than 10%) of childhood leukemia cases and the potential causes for the majority of cases remain unclear (Buffler et al., 2005; Whitehead et al., 2016; Wiemels, 2012). Numerous possible risk factors have been studied such as infections (Arellano-Galindo et al., 2017; He et al., 2020; Hwee et al., 2018; Maia & Wünsch, 2013; Rudant et al., 2015), birth weight (Oksuzyan et al., 2012), magnetic fields (Amoon et al., 2022; Crespi et al., 2019a; Swanson et al., 2019), pesticides (Bailey, Infante-Rivard, et al., 2015; Chen et al., 2015a; Van Maele-Fabry et al., 2019; Vinson et al., 2011), parental age (Nybo Andersen & Urhoj, 2017; Sergentanis et al., 2015), pollution (Filippini et al., 2019), and smoking (Metayer et al., 2016).

1.1.3 Risk Factors

Genetic Susceptibility

A hypothesis about the development of childhood leukemia involves a multistep process that is initiated during fetal development and through subsequent events after birth that result in an accumulation of mutations and impaired immunological development (M Greaves, 1999, 2005; Wiemels, 2012). Potential mechanisms of childhood leukemia include aberrant DNA repair, cell regulation, and xenobiotic genes which may make an individual more susceptible to environmental exposures. DNA repair is vital in maintaining genomic stability and proper function of the body (Bhagavan & Ha, 2011). It involves actively repairing chromosomal breaks, crosslinks, and mutations that are due to endogenous metabolic processes as well as exogenous environmental exposures. Therefore, impaired DNA repair may result in genomic instability, a characteristic of most cancers (Negrini et al., 2010). Bloom syndrome and Fanconi anemia, both genetic syndromes resulting from defects in DNA repair mechanisms, have been highly associated with childhood leukemia.

Moreover, disorders in cell regulation mechanisms may result in abnormal proliferation of cells due to improper regulation of proto-oncogenes or tumor suppressor gene responses to environmental exposures, potentially leading to cancer (Barnum & O'Connell, 2014). For example, pesticides, smoking, and other exposures may increase childhood leukemia risk via faulty xenobiotic transport and metabolism. These harmful exogenous exposures gain access to target cells and are metabolically activated by xenobiotic system enzymes to cause genetic mutations (Chokkalingam et al., 2012). These genetic susceptibility factors may make individuals more susceptible to damage from exogeneous exposures, leading to the development of childhood leukemia.

Radiation

Ionizing radiation, defined as energy in the form of waves (X-rays or gamma) or particles (alpha, beta, or neurons), is one of the few established exogeneous risk factors for childhood leukemia. Ionizing radiation is capable of penetrating the human body and damaging cells and genetic material through inducing radioactivity which occurs when an unstable atom loses energy (World Health Organization, 2016). The extent of its effect on humans depends on the radiation source, radiation dosage, duration of exposure, as well as the genetic and epigenetic characteristics of the person (Reisz et al., 2014). Ionizing radiation is classified by the International Agency for Research on Cancer (IARC) as Group 1 (carcinogenic to humans) (IARC, 2012). Ionizing radiation may be due to natural sources or human-made sources. Examples of natural sources of ionizing radiation include Radon, which is a naturally occurring gas that may emanate from the soil and rocks. Human-made sources of ionizing radiation include certain medical imaging diagnostics and the generation of nuclear power (World Health Organization, 2016). A cohort study on Japanese survivors of the atomic bombings at Nagasaki and Hiroshima reported an excess of leukemia cases approximately 3 years after the bombings; Children that were approximately 10 years of age at the time of exposure had a peak excess relative risk (ERR) at 1 Gray (Gy) of about 70 for leukemia (Richardson et al., 2009). Individuals that were exposed at 30 or more years of age reported an ERR at 1 Gy of approximately 2 for leukemia. Children are potentially more susceptible to radiation exposure than adults as their organs and tissues are still developing (Khong et al., 2013). Non-ionizing radiation is a type of radiation that has less energy than ionizing radiation and not capable of causing ionization. Examples of non-ionizing radiation include electric and magnetic fields, microwaves, infrared, ultraviolet and radio waves (World Health Organization, 2021b). Though non-ionizing radiation has less energy than ionizing radiation, some forms of it have demonstrated the ability to cause biological effects (Reisz et al., 2014).

1.2 Magnetic Fields and Power Lines

Electric and magnetic fields, also known as electromagnetic fields (EMF), are ubiquitous in our environment. Electric fields are generated by voltage, which is the force that drives the movement of current. Magnetic fields are generated by moving electric charges. As a result, power lines are continuously generating magnetic fields, as current is always moving through them. As the distance from a magnetic field source increases, the strength of the magnetic field will decrease rapidly. Human tissue and air have the same permeability to magnetic fields, as a result, the human body does not appreciably perturb the field (International Commission on Non-Ionizing Radiation, 2010; World Health Organization, 2007). Possible sources of extremely low frequency electromagnetic fields (ELF EMFs) include electrical wiring, certain electrical appliances and power lines (Kheifets et al., 2005; National Cancer Institute, 2019). Children spend the majority of their time at home, as a result, high voltage power lines act as a significant contributor of ELF EMF exposure for children that live in close proximity to them (Friedman et al., 1996; Kheifets et al., 2005).

The study of the association between magnetic field exposure and childhood leukemia risks has been the subject of many epidemiological studies since the initial publication by Wertheimer & Leeper (1979). Epidemiological studies have utilized various EMF or surrogates for EMF exposure measurements: personal monitoring device measurements (Green et al., 1999; McBride et al., 1999), calculated magnetic field levels (Bunch et al., 2016; Feychting & Alhbom, 1993; Kheifets, Crespi, et al., 2017; Kroll et al., 2010), wiring configuration (Linet et al., 2009; London et al., 1991; Savitz et al., 1988), and measured magnetic fields inside residences

(Kabuto et al., 2006; Linet et al., 2009). Pooled analyses found elevated childhood leukemia risk associated with magnetic field levels greater than 0.3 or 0.4 µT (Ahlbom et al., 2000; Greenland et al., 2000; Kheifets et al., 2010). As such, ELF EMFs are classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) (IARC, 2007).

High voltage power lines may be a significant source of magnetic fields exposure for those living close to them; magnetic field levels are proportional to the size of the electric current moving through the power line. With high voltage power lines producing more magnetic fields than low voltage power lines. Additionally, magnetic field exposure from a power line decreases as distance increases (National Cancer Institute, 2019). A case-control study on childhood cancer and proximity to high voltage power lines among children (aged 0-14 years) born in England and Wales from 1962 to 1995 found increased risks among childhood leukemia subjects that were born <50 m from a high voltage power line compared to those born ≥600 m from a high voltage power line (Kroll et al., 2010). Elevated risks were observed for childhood leukemia up to 600 m from a high voltage power line. However, a study reported magnetic field levels should be insignificant after 200 m (Kaune & Zaffanella, 1992). A pooled analysis of 11 case-control studies reported small and imprecise elevated risk for childhood leukemia among residences less than 50 m of power lines 200 kV or higher, that could not be explained by high magnetic field exposure (Amoon, Crespi, et al., 2018a).

A recent study by Crespi et al. (2019) examining childhood leukemia risk and magnetic fields and proximity to power lines had interesting results. Elevated childhood leukemia risks (odds ratio (OR) 4.06, 95% confidence interval (CI) 1.16-14.3) were only observed among individuals that were both in close proximity (<50 m) to high voltage power lines 200 kV or higher and elevated calculated magnetic fields (≥0.4 µT). This increased risk was not observed among individuals that were only in close proximity to high voltage power lines or elevated calculated magnetic fields. This finding highlights a potential effect modification and/or interaction between proximity to high voltage power lines and elevated magnetic fields.

The amount of magnetic fields vary due to a variety of factors, such as distance from the source (i.e., the power line), voltage level, and spatial configuration of the components. As magnetic field levels are strongly associated with distance, many studies that examine childhood leukemia risks with proximity to high voltage power lines found similar relationships to those obtained with high magnetic field levels (Crespi et al., 2016a; Sermage-Faure et al., 2013). Increased risks (OR 3.02, 95% CI 1.09-8.36) were observed among subjects exposed to high magnetic fields (≥0.4 µT) living near high voltage power lines (>200 kV), but not observed among subjects (OR 0.31, 95% CI 0.06-1.54) exposed to high magnetic fields (≥0.4 µT) living near low voltage power lines (<200 kV) (Crespi et al., 2019a). If increased childhood leukemia risks are due to magnetic fields alone, then the childhood leukemia association with high magnetic fields exposure due to low or high voltage power lines should be similar; thus, it is possible that certain attributes associated with proximity to high voltage power lines may play a role in the development of childhood leukemia. Several potential factors have been hypothesized such as SES, dwelling type, and pesticides (Amoon, Crespi, et al., 2018a; Vinson et al., 2011). Power lines are located in right-of-way (ROW), which is a piece of land used for various reasons, including transmission lines, communication sites and other projects (U.S. Department of the Interior Bureau of Land Management, n.d.). Commercial plant nurseries, a potential source of chronic pesticide exposure, are often found under or in close proximity to high voltage power lines and ROWs.

1.3 Pesticides

Pesticides are substances or mixtures of substances intended to mitigate, repel, or kill unwanted plants or animals. Pesticides can be categorized by their intended target, with the most well-known pesticides being insecticides, herbicides, rodenticides and fungicides (National Institute of Environmental Health Sciences, 2021; US EPA, 2013). The use of pesticides has dated back many centuries, with records of their use during the eighth century BC (Mason, 1928). During World War II, the use of Dichlorodiphenyl trichloroethane (DDT), a synthetic pesticide, was quickly adopted due to being a very effective insecticide. Following the war, the use of synthetic pesticides became more widespread in the United States (Russell, 1999). More than 300 million pounds of pesticides were produced annually during the 1950s, in comparison with 100 million pounds in 1945 (Finegan, 1989). It is estimated that over 1.1 billion pounds of pesticides are annually used for agricultural purposes in the United States (Atwood & Paisley-Jones, 2017). The widespread use of pesticides is a public health concern, as pesticide exposure may result in molecular changes linked to cancer development, such as chromosomal anomalies, disruption of cell signaling, oxidative stress, or DNA damage (Hernández & Menéndez, 2016). Pesticides have been shown to be associated with numerous health effects (Kim et al., 2017) and various childhood cancers, including leukemia (Chen et al., 2015a; Turner et al., 2011; Van Maele-Fabry et al., 2019; Vinson et al., 2011; Wigle et al., 2009a).

Children are particularly susceptible to the effects of pesticides for several reasons, including their anatomy, behavior, and development. Exposure to pesticides may occur though inhalation, ingestion, or dermal contact. Children may have higher levels of exposure, as they consume a larger amount of food or fluid as well as breathe more air per pound of body weight compared to adults (Moya et al., 2004). Childhood behaviors such as being active and exploring their environment, by playing or crawling on the ground, is potentially conducive to high levels of pesticide exposure (Fenske et al., 1990). Children also frequently put their hands as well as other objects in their mouths. This hand-to-mouth behavior may result in pesticide exposure through contact as well as ingestion (Freeman et al., 2005). Furthermore, children are still developing and their ability to distribute, metabolize and eliminate toxins are less advanced compared to adults, making them more susceptible to negative health outcomes after exposure (Moya et al., 2004).

Proximity of residences to pesticide treated areas is one way for exposure to occur. A study in an agricultural community in Washington reported that agricultural work households living in close proximity (<60 m) to a pesticide treated orchard had higher concentrations of pesticides (azinphos methyl and dimethyl organophosphate (OP)) in household dust compared to household dust in non-agricultural work households living away from orchards (>400 m). Children that lived in close proximity to a pesticide treated orchard also had elevated measured concentrations of pesticide metabolites (dimethylthiophosphate and dimethyl OP metabolite) compared to those who did not live by an orchard. The relationship between elevated pesticide levels of exposure and residing in close proximity to pesticide treated area was still observed when the sample was restricted to agricultural work families. Measurable dimethyl OP pesticide concentrations were detected from environmental wipes for 38 of the agricultural families, with 32 of the 38 (84%) samples belonging to agricultural families living in close proximity (<60 m) to a pesticide treated orchard. Among the 61 agricultural children, 10 had detectable concentrations of dimethyl OP pesticide from hand wipe samples; all 10 children lived in close proximity (<60 m) to a pesticide treated orchard (Lu et al., 2000a). Another study that examined OP concentrations in household carpet dust found elevated OP concentrations among both agricultural and non-agricultural households in close proximity (<25 m) to an agricultural field or orchard compared to homes located farther away (Dawson et al., 2018). Other studies have examined distance to pesticide treated land and measured pesticide levels in households and have also found elevated levels of pesticides with close proximity (Fenske et al., 2002; Simcox et al., 1995). Hence, spatial proximity models are possible accurate surrogates for captured pesticide exposure levels for children, especially as children spend the majority of their time at home.

Chronic exposure to pesticides, such as residential exposure, has been hypothesized to increase childhood leukemia risk. A recent systematic review and meta-analysis found significant elevated risks with residential pesticide exposure and all types of childhood leukemia: ALL (OR 1.42, 95% CI 1.13-1.8), AML (OR 1.9, 95% CI 1.35-2.67), and unspecified (OR 1.57, 95% CI 1.27-1.95); elevated risks were reported for ALL, AML and unspecified leukemia when restricted to prenatal indoor exposure, prenatal insecticide exposure, and during pregnancy (Van Maele-Fabry et al., 2019). Previous meta-analyses also reported elevated childhood leukemia risks and residential pesticide exposure during the prenatal and pregnancy period (Bailey, Infante-Rivard, et al., 2015; Turner et al., 2010a; Vinson et al., 2011). Prenatal exposure to insecticides had elevated risk for childhood leukemia for both the meta analyses by Bailey et al. (2015) and Turner et al. (2010). These trends were observed beyond the prenatal and pregnancy exposure periods, with indoor pesticide exposure during childhood also reporting increased risks for childhood leukemia (ALL, AML, and unspecified) (Chen et al., 2015a; Turner et al., 2010a; Van Maele-Fabry et al., 2019).

Chapter 2. Residential proximity to plant nurseries and risk of childhood leukemia

2.1 Abstract

Background

Pesticides are a potential risk factor for childhood leukemia. Studies evaluating the role of prenatal and/or early life exposure to pesticides in the development of childhood leukemia have produced a range of results. In addition to indoor use of pesticides, higher risks have been reported for children born near agricultural crops. No studies have looked at pesticide exposure based on proximity of birth residence to commercial plant nurseries, even though nurseries are located much closer to residences than agricultural crops and can potentially result in chronic year-round pesticide exposure.

Objectives

To evaluate whether risk of childhood leukemia is associated with pesticide use as determined by distance of residence at birth to commercial, outdoor plant nurseries.

Methods

We conducted a large statewide, record-based case-control study of childhood leukemia in California, which included 5788 childhood leukemia cases and an equal number of controls. Pesticide exposure was based on a spatial proximity model, which combined geographic information system data with aerial satellite imagery.

Results

Overall, the results supported an increased childhood leukemia risk only for birth residences very close to nurseries. For birth residences less than 75 meters from plant nurseries, we found an increased risk of childhood leukemia (odds ratio (OR) 2.40, 95% confidence interval (CI) 0.99-

5.82) that was stronger for acute lymphocytic leukemia (OR 3.09, 95% CI 1.14-8.34).

Discussion

The association was robust to choices of reference group, cut points and data quality. Our findings suggest that close proximity to plant nurseries may be a risk factor for childhood leukemia and that this relationship should be further evaluated.

2.2 Introduction

Childhood leukemia is the most commonly diagnosed type of cancer in children, comprising approximately one in three childhood cancer cases, with an age-adjusted incidence rate of 5.2 per 100,000 children (ages 0-14 years) in the United States (Howlader et al., 2020). Acute lymphocytic leukemia (ALL) is the most common childhood leukemia subtype, followed by acute myeloid leukemia (AML) (American Cancer Society, 2018). While the 5-year survival rate for childhood leukemia has improved significantly over the last four decades, with over 80 percent surviving, relatively little is known about its etiology (National Cancer Institute, 2020).

Pesticide exposure could result in molecular changes, including chromosomal anomalies, disruption of cell signaling, oxidative stress, or DNA damage (Hernandez & Menendez, 2016). Children are especially susceptible to pesticide exposure compared to adults because their nervous, immune and other systems are still developing (U.S. Environmental Protection Agency, 2017). Their enzymatic and metabolic systems may be less able to detoxify and excrete pesticides than those of adults. Children also breathe more air in relation to their body size than adults (U.S. Environmental Protection Agency, 2017). Moreover, childhood behaviors, such as playing outdoors, crawling on the floor, and frequent hand-to-mouth contact may increase their pesticide exposure.

Studies have examined the relationship between childhood leukemia and pesticide exposure, including the types of application and timing of parental exposure, for home and residential environmental exposures. Research evaluating the role of pesticides has reported an increased risk of childhood leukemia associated with residential exposure to pesticides, particularly maternal exposures during pregnancy (Daniels, Olshan, & Savitz, 1997; Ma et al., 2002; Turner, Wigle, & Krewski, 2011).

A meta-analysis of parental occupational pesticide exposure and childhood leukemia found prenatal maternal occupational exposure was associated with childhood leukemia (odds ratio (OR) 2.1, 95% confidence interval (CI) 1.5-2.9); associations with paternal occupational exposure were weaker and less consistent (Wigle, Turner, & Krewski, 2009). A pooled analysis of 13 case-control studies in the Childhood Leukemia International Consortium (CLIC) that investigated parental occupational pesticide exposure and childhood leukemia subtypes found different associations for ALL and AML subtypes. During pregnancy, maternal occupational pesticide exposure only had elevated risks with AML (OR 1.9, 95% CI 1.2-3.2), while paternal occupational pesticide exposure had slightly elevated risks for ALL (OR 1.2, 95% CI 1.1-1.4) (Bailey et al., 2014).

Home pesticide exposures (before conception, during pregnancy or after birth) and childhood ALL or AML risks were examined in a pooled analysis that included 12 CLIC studies (Bailey et al., 2015). They observed associations for ALL and home pesticide exposure before birth (OR 1.4, 95% CI 1.3-1.6), during pregnancy (OR 1.4, 95% CI 1.3-1.5), and after birth (OR 1.4, 95% CI 1.2-1.5). Elevated risks for AML were only observed for home pesticide exposures before birth (OR 1.5, 95% CI 1.0-2.2) and during pregnancy (OR 1.6, 95% CI 1.2-2.0). There was little difference in risks by type of pesticide used. Additionally, Van Maele-Fabry et al. (2011) found the highest childhood leukemia risks to be associated with exposures during pregnancy as compared to exposures after birth.

Living near crops treated with pesticides and the resulting drift could be another source of chronic pesticide exposure. Pesticide concentrations in ambient air and household dust measurements have been shown to be higher in communities and households near treated fields and crops (Fenske, Lu, Barr, & Needham, 2002; Lu, Fenske, Simcox, & Kalman, 2000; Simcox, Fenske, Wolz, Lee, & Kalman, 1995; Weppner et al., 2006). Therefore, residential proximity to pesticide treated crops and land are possible sources for pesticide exposure in residences, even in households not involved in agricultural work (Dereumeaux, Fillol, Quenel, & Denys, 2020).

A meta-analysis on pesticide exposure and childhood cancer risks did not find a significant risk of childhood leukemia and household proximity to agricultural areas (Vinson, Merhi, Baldi, Raynal, & Gamet-Payrastre, 2011). Other studies have evaluated agricultural pesticide exposures and found no clear elevated risk trends with childhood leukemia (Carozza, Li, Wang, Horel, & Cooper, 2009; Reynolds et al., 2002). In contrast, an ecological study demonstrated possible dose-response effects for childhood leukemia (ALL, AML, and combined) risk associations with residence at diagnosis in counties with medium to high agricultural activity level (Carozza, Li, Elgethun, & Whitworth, 2008). A recent geographic information system (GIS), population-based study on maternal agricultural pesticide exposure during pregnancy and childhood leukemia found that exposure to any carcinogenic pesticide had positive associations for ALL (OR 2.8, 95% CI 1.7-4.8) and AML (OR 3.8, 95% CI 1.0-11.6) (Park, Ritz, Yu, Cockburn, & Heck, 2020). Similarly, a study based on the Danish National Birth Cohort using distance of birth addresses to crop fields found that risk of childhood leukemia was associated with large crop area near homes (Patel et al., 2020).

Pesticides are commonly used in commercial plant nurseries (California Department of Pesticide Regulation, 2019), but no studies have looked at the relationship between residential pesticide exposure from commercial plant nurseries and childhood leukemia risk. Organophosphates are often used by nurseries to control insect pests. Weed control for most nurseries entails a preemergent herbicide combination, and then hand weeding and non-selective herbicides. Because nursery plants are grown year-round, there is constant need for maintaining healthy plant stock to be sold and the potential for year-round pesticide release to the surrounding community. We present an analysis of childhood leukemia risk associated with pesticide use as determined by distance of residence at birth to commercial, outdoor plant nurseries.

2.3 Methods

Case Ascertainment and Control Selection

This research was part of the California Power Line Study (CAPS). As previously described for CAPS (Kheifets et al., 2013), childhood leukemia cases younger than 16 years residing in and diagnosed in California between 1988 and 2008 were obtained from the California Cancer Registry (California Cancer Registry, 2020). Cases were linked to the California Birth Registry (CBR; California Department of Public Health, Vital Statistics Branch) and randomly matched by date of birth (±6 months) and sex to a control from the CBR. Linkage of subjects to birth records had births that encompassed the years 1986-2008. Controls were excluded if they had any type of cancer diagnosis in California before the matched case time of diagnosis.

Variables obtained for cases and controls from the CBR included date of birth, mother's residential address at time of birth, race/ethnicity of parents, sex, birth weight, maternal and paternal education, maternal and paternal ages, and payment source for delivery. Child race/ethnicity was classified as White if both parents were White, Black if one or both parents were Black, Asian if one or both parents were Asian, Hispanic if one or both parents were Hispanic and neither parent was Black or Asian, and Other otherwise. Variables representative of socioeconomic status (SES) collected by the CBR varied year by year, therefore, a binary SES variable (high or low) was developed, based hierarchically as available for each subject: the father's years of education (high if >12 years, low otherwise), mother's years of education (high if >12 years, low otherwise), payment method for hospital delivery (low if no coverage or government assisted payment, high otherwise) or community-based SES derived from US Census data for seven indicator variables at the census block level using principal components analysis (Yost, Perkins, Cohen, Morris, & Wright, 2001) (high if >60th percentile of the principal components score, low otherwise). Birth addresses of subjects were geocoded to latitude and longitude coordinates. More information on study methods has been previously described (Kheifets et al., 2013).

Exposure Assessment

Two sources of data were used to identify nurseries of interest, the California Department of Food and Agriculture (CDFA) and Pesticide Use Reporting (PUR) program of the California Department of Pesticide Regulation (California Department of Pesticide Regulation). From CDFA, a list of licensed plant nurseries and nursery stock dealers located in California and active between 1978 and 2008 was obtained. The CDFA database includes variables such as nursery address, type of nursery business, and type of plant stock. Plant nurseries are classified as several different types of businesses by the CDFA; we focused on nursery businesses classified as "producers," which are nurseries that grow and sell a total of $1,000 or more of nursery stock annually. Nursery business addresses were geocoded using ArcGIS (Version 10.6, ESRI, Redlands, CA). Under PUR, all agricultural pesticide use must be reported monthly. Reporting includes location information based on the COMTRS (county, meridian, township, range, section) system, with sections having a typical resolution of about one square mile, and commodity codes that describe the type of business or site at which the pesticides were applied. To capture nurseries that used pesticides, prior to 1990 we identified codes for plant nursery; for 1990 onward, more detailed information was available, so we selected codes that specified nursery plants grown in containers. For thus identified nurseries, the centroids of the identified geographic area of application were converted to latitude and longitude coordinates.

In the next step, an initial distance to closest nursery was determined from the geocoded birth address of a subject (blinded to case/control status) to one of the geocoded nursery points. Due to their unique shapes and sizes, these initial distance classifications provide only a rough approximation of distance from nurseries. For example, many nurseries have footprints that run along power line rights-of-way for many blocks (Figure 2.1) or have a unique size and shape (Figure 2.2). Thus as a next step, we selected subjects for a more refined exposure assessment that involved individual evaluation of aerial satellite imagery to determine the perimeter of each nursery and calculated the shortest distance from residence to nursery perimeter. We selected all subjects within a 600 m based on initial distance for detailed assessment. Additionally, because plant nurseries are often located underneath high voltage power lines, which could create error in the initial distance metric due to footprint characteristics (long or unique shape) and geocoded business addresses that do not reflect their actual footprint, we selected birth addresses located within 2000 m of such lines to ensure we captured all nurseries in proximity to power lines.

For all subjects selected for a more detailed review, Google Earth aerial satellite imagery was used to verify the presence of a plant nursery during the birth year of a particular subject and to calculate the distance to the closest plant nursery perimeter. When possible, historic Google Earth aerial satellite images were used, matched as closely as possible to the year of birth. For each nursery, we determined the perimeter of the facility and measured the closest distance from the residence to the nursery's footprint.

For some subjects, aerial satellite imagery directly confirmed that a particular nursery was present on the birth year of a subject. However, aerial imagery was not available for all birth years of interest. If an aerial image was unavailable for the year of interest, we recorded the range of years for which a Google Earth aerial satellite image visually confirmed that the nursery was present, and considered the nursery as present if imagery spanned the years of interest e.g., before and after. Conversely, we considered a nursery as not present for the year of interest if the nursery was not observed in aerial satellite imagery before and after the birth year of a subject. A quality score (QS) was developed for the availability of aerial satellite images of nurseries as it pertained to subject birth year. A quality score of 1 consists of nurseries identified on the birth year of a subject or within 2 years of the birth year, or nurseries with images confirming its existence before and after the birth year. A quality score of 2 has a range within 2 and 5 years of the birth year. A quality score of 3 has a range of over 5 years and/or the image quality is too poor to determine the presence of a nursery. If Google Earth did not have an aerial satellite image prior to the birth year, but an image that visually confirmed the nursery was present after the birth year, then we assumed the nursery existed for the birth year and classified the nursery according to the number of years that required extrapolation as above.

Statistical analysis

All main analyses were restricted to subjects whose addresses were geocoded at a high level of resolution (street segment or parcel level). Two sets of analyses were conducted. One set focused on subjects confirmed as within 600 meters of a nursery perimeter after individual distance evaluation. For these analyses, shortest distance to nurseries was categorized as 0-75, 75-150, 150-300, and ⩾300 m (referent), based on the distribution of distance among controls and focusing on highest exposure (approximately 5% of controls). A second set of analyses included all subjects and considered a greater range of distances. For these analyses, shortest distance to nurseries was categorized as 0-500, 500-1000, 1000-1500 and ⩾1500 m (referent), based on prior literature and approximate distribution among controls. Analyses were also performed with distance to nurseries categorized as 0-1000 and ⩾1000 m (referent). Additionally, we conducted subgroup analyses that were restricted to the ALL subtype.

Odds ratios were obtained using logistic regression models controlling for sex, age at diagnosis, SES and race/ethnicity. Sensitivity analyses included: using all subjects regardless of geocode accuracy; stratifying by quality score; stratifying by nursery data source (CDFA versus PUR) and time period (prior to 1990 and 1990 or after). Multiple imputation was conducted for missing data on SES and race/ethnicity. Analyses were conducted using SAS (Version 9.4, The SAS Institute, Cary, NC).

CAPS was reviewed and approved by University of California, Los Angeles Office for the Protection of Research Subjects and the State of California Committee for the Protection of Human Subjects.

2.4 Results

Of the 6,645 childhood leukemia cases identified from the California Cancer Registry, 87.1% (n=5,788) were successfully linked to the California Birth Registry; an equal number of controls were included in this study. Table 2.1 shows demographic characteristics of study subjects. The median age at diagnosis was approximately 3 years. Males comprised more than half of the cases (56%). About half of cases and controls were of Hispanic origin, and about 80% were White (Hispanic or non-Hispanic). Approximately 84% of study subjects were geocoded at the highest resolution (street segment or parcel level). Demographic characteristics of subjects within 600 m of a plant nursery, regardless of power line distance, were similar to those of all subjects, with some differences in ethnicity (fewer White non-Hispanic and more Hispanic cases and controls).

Proximity to nurseries

Childhood leukemia risk was associated with proximity to nurseries at close distances (Table 2.2): the OR for the highest exposure category (<75 m) was 2.40 (95% CI: 0.99-5.82). Results were stronger for ALL, with OR 3.09, 95% CI: 1.14-8.34). Additionally, we extended the reference group to beyond 600 meters and still observed elevated risk for subjects in the highest exposure category (<75 m) (Table 2.4). There was no exposure response relationship, with reduced risk for 75-150 meter distance category. Numbers for AML were too small for a meaningful analysis.

In analyses considering larger distance categories, childhood leukemia risk was not associated with proximity to nurseries (Table 2.3). The odds ratio for childhood leukemia associated with the highest category of exposure (<500 m of a nursery) was 0.99 (95% CI: 0.82-1.19). The OR estimates for other exposure categories did not materially differ from the null value. There was no substantial change in leukemia risk when proximity to nurseries was dichotomized as 0-1000 vs ≥1000 m (OR 1.02, 95% CI 0.94-1.10). Restricting analyses to ALL subtype did not substantially change the leukemia risk for any of the distance categories.

Sensitivity Analyses

Including all subjects regardless of geocoding accuracy resulted in almost identical risk estimates (Table 2.4). Our finding of an increased leukemia risk in children born in homes within 75 m of a plant nursery did not depend on the choice of comparison group (i.e., use of 300-600 m vs. >600 m as a reference). Risk was increased for both nursery data sources (CDFA versus PUR), albeit a bit stronger for PUR data. Higher quality score and more recent time period, which are both indicative of better quality of information on nurseries, and thus better estimates of exposure, resulted in higher risk estimates.

Figure 2.1: Example of plant nurseries and the closest distance to a mock residence - plant nursery that runs along power line rights-of-way

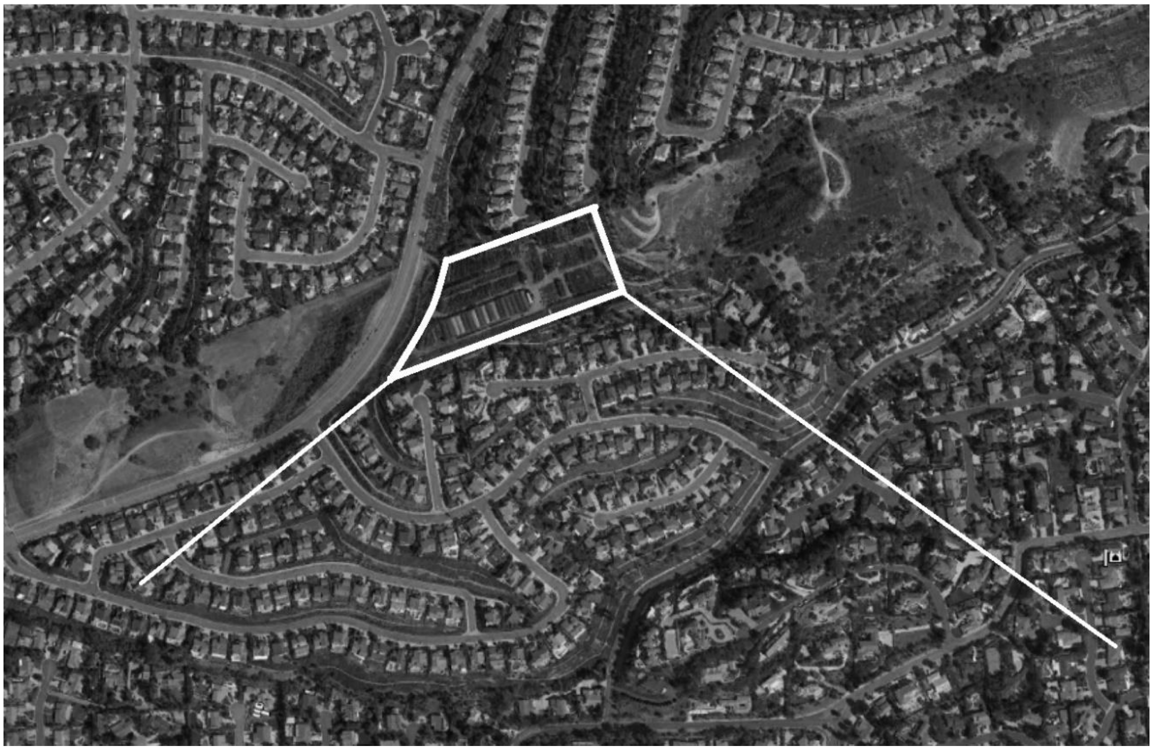

Figure 2.2: Example of plant nurseries and the closest distance to a mock residence – plant nursery with unique shape and size

Table 2.1: Demographic characteristics of study subjects, 1986-2008

All subjects			Subjects within 600 m of a plant nursery	
Characteristic	Cases (n=5788)	Controls (n=5788)	Cases (n=206)	Controls (n=210)
Sex				
Male	3231 (56%)	3231 (56%)	104 (50%)	106 (50%)
Female	2557 (44%)	2557 (44%)	102 (50%)	104 (50%)
Leukemia type				
ALL	4721 (85%)	4721 (85%)	156 (88%)	160 (85%)
AML	852 (15%)	852 (15%)	22 (12%)	28 (15%)
Age at diagnosis				
<2 year	2121 (37%)	2121 (37%)	72 (35%)	74 (35%)
3-4 year	1571 (27%)	1571 (27%)	59 (29%)	50 (24%)
5-6 year	751 (13%)	751 (13%)	29 (14%)	29 (14%)
7-15 year	1345 (23%)	1345 (23%)	46 (22%)	57 (27%)
Race/ethnicity[a, b]				
White	1697 (30%)	1799 (32%)	38 (19%)	60 (29%)
Black	290 (5%)	490 (9%)	14 (7%)	12 (6%)
Asian	614 (11%)	569 (10%)	24 (12%)	27 (13%)
Hispanic	2972 (52%)	2662 (47%)	125 (61%)	106 (51%)
Other	105 (2%)	109 (2%)	3 (1%)	2 (1%)
Socioeconomic Status indicator[c, d]				
High	1738 (31%)	1736 (31%)	55 (27%)	54 (26%)
Low	3900 (69%	3902 (69%)	151 (73%)	156 (74%)
Geocode geography matching feature				
Street segment or parcel	4879 (84%)	4835 (84%)	183 (89%)	194 (92%)
Other feature	909 (16%)	953 (16%)	23 (11%)	16 (8%)

m meters, ALL acute lymphocytic leukemia, AML acute myeloid leukemia

[a] Race/ethnicity was missing for 110 leukemia cases and 159 leukemia controls for all subjects.

[b] Race/ethnicity was missing for 2 leukemia cases and 3 leukemia controls for subjects within 600 m of a plant nursery.

[c] Socioeconomic status indicator was missing for 150 leukemia cases and 150 leukemia controls for all subjects.

[d] Socioeconomic status indicator was not missing for any leukemia cases and leukemia controls for subjects within 600 m of a plant nursery.

Table 2.2: Risk of childhood leukemia by proximity to nursery (≤ 600 m)*

	Leukemia		Acute lymphocytic leukemia	
Distance to nursery, m	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)
300-600	108/112	1.0 (ref)	90/95	1.0 (ref)
150-300	45/49	0.93 (0.57-1.50)	38/40	0.98 (0.58-1.67)
75-150	13/25	0.54 (0.26-1.11)	12/19	0.63 (0.29-1.38)
0-75	17/8	2.40 (0.99-5.82)	16/6	3.09 (1.14-8.34)

m meters

*All models adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputations for missing values

Table 2.3: Risk of childhood leukemia by proximity to nursery*

	Leukemia		Acute lymphocytic leukemia	
Distance to nursery, m	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)
≥ 1500	4341/4340	1.0 (ref)	3532/3545	1.0 (ref)
1000-1500	186/166	1.05 (0.88-1.25)	150/125	1.09 (0.90-1.33)
500-1000	205/189	1.01 (0.85-1.19)	164/152	0.98 (0.81-1.18)
0-500	147/140	0.99 (0.82-1.19)	128/117	1.00 (0.82-1.24)
≥ 1000	4527/4506	1.0 (ref)	3682/3670	1.0 (ref)
0-1000	352/329	1.02 (0.94-1.10)	292/269	1.03 (0.94-1.12)

m meters

*All models adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputations for missing values

Table 2.4: Sensitivity analysis of Risk of childhood leukemia by proximity to nursery*

Stratification	Distance to Pesticide/Nursery, m			
Quality Score[a]	300-600	150-300	75-150	0-75
Q1	1.0 (ref)	0.86 (0.48-1.52)	0.39 (0.17-0.92)	3.22 (1.01-10.28)
Q2	1.0 (ref)	1.87 (0.49-7.21)	Insufficient sample size	
Q3	1.0 (ref)	Insufficient sample size		
Data Source				
CDFA	1.0 (ref)	0.67 (0.33-1.36)	0.70 (0.27-1.81)	2.18 (0.60-7.92)
PUR	1.0 (ref)	1.37 (0.69-2.70)	0.36 (0.11-1.21)	2.86 (0.82-9.91)
Time Period				
<1990	1.0 (ref)	0.84 (0.23-3.08)	0.74 (0.11-5.12)	0.95 (0.05-16.89)
1990+	1.0 (ref)	0.95 (0.56-1.60)	0.52 (0.24-1.13)	2.63 (1.03-6.73)
Regardless of accuracy of birth residence geocoding	1.0 (ref)	0.98 (0.62-1.56)	0.63 (0.32-1.24)	2.39 (1.03-5.52)
Comparison group 600+m	0.94 (0.72-1.22)	0.87 (0.58-1.30)	0.51 (0.26-0.99)	2.24 (0.96-5.24)

m meters

[a] cells with less than 4 cases or controls were considered to have insufficient sample size

*All models adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputations for missing values

2.5 Discussion

We conducted a statewide, record-based case-control study of childhood leukemia in California. Overall, the results did not support an increased childhood leukemia risk associated with proximity to plant nurseries, except for residences very close to the nurseries. For birth residences <75 m to plant nurseries, we found an increased risk of childhood leukemia, which was stronger for ALL. Sensitivity analyses confirmed that our findings were not sensitive to quality of GIS coding for birth addresses or choice of comparison group. Higher risks were identified for subgroups with better information on nurseries, such as more accurate data source, more recent time period and high-quality score.

Approximately 13% of cases were not linked to the CBR. Sixteen and 8% of children (0-9 years of age) in California during 1990 and 2010 were born outside of California (Myers, 2013). Thus, it is likely that most of the unlinked cases were not born in California.

Only a few risk factors for childhood leukemia have been well-established, including ionizing radiation and certain genetic syndromes such as Down syndrome (Belson, Kingsley, & Holmes, 2007; Kumar & De Jesus, 2021; Stieglitz & Loh, 2013). Ionizing radiation is capable of inducing structural changes at the cellular and molecular level, which may result in cancer development (Kumar & De Jesus, 2021). Children with Down syndrome are at a 10 to 20-fold elevated risk of developing leukemia compared to children without Down syndrome (Xavier, Ge, & Taub, 2009). However, these only explain a small portion (less than 10%) of childhood leukemia cases and the potential causes for a majority of cases remain unclear (Buffler, Kwan, Reynolds, & Urayama, 2005; Whitehead, Metayer, Wiemels, Singer, & Miller, 2016; Wiemels, 2012)."

Previous results from studies of pesticide exposure and childhood leukemia risk have been inconsistent, particularly for exposure occurring outdoors. In a case-control study that evaluated household pesticide use and timing of exposure based on interviews, the authors reported that associations between outdoor pesticide exposure, during all time periods (3 months before pregnancy, during pregnancy, first year, second year, and third year), and childhood leukemia risk were small and all 95% CI included the null (Ma et al., 2002). A different case-control study of childhood leukemia, using interviews to assess pesticide exposure, found some increase in risk for the use of pesticides on farms (OR 1.5, 95% CI 1.0, 2.2), but no evidence of elevated risks for the use of pesticides in gardens (OR 1.0, 95% CI 0.8, 1.2) (Meinert, Schuz, Kaletsch, Kaatsch, & Michaelis, 2000). Another interview-based, case-control study found an elevated risk (OR 1.7, 95% CI 1.1-2.7) with garden pesticide use and childhood leukemia (Menegaux et al., 2006). Our results are broadly consistent with two recent studies, one in California (Park et al., 2020) and in Denmark (Patel et al., 2020) that showed an increased risk of childhood leukemia for children who lived in proximity of pesticide applications of crops, mainly occurring in rural environments, showing evidence pesticide exposure may reach beyond their intended application site and target.

This is the first childhood leukemia study to focus on proximity to commercial plant nurseries as a proxy for pesticide exposure. This study is important as a large amount of nursery producers in certain regions, such as in California, are situated in highly populated urban areas (Carman, 2011). This close proximity to urbanized areas may potentially result in increased pesticide exposure for individuals. Additionally, land use changes in urban environments may increase the number of persons living close to potential sources of pesticide. The strengths of our study include its large sample size, consisting of 5,788 childhood leukemia cases and 5,788 matched controls. Cases and controls were obtained from population-based registries with complete statewide registration of leukemia cases and births, which avoids participation bias. Other strengths are multi-stage exposure and confounder assessment blinded to case–control status to reduce information bias.

In this study, as in other studies of childhood leukemia, retrospective exposure assessment remains a challenge. We addressed accuracy, selection bias and validity issues identified as potential limitations of GIS based studies (Chang et al., 2014). To increase accuracy, our main analyses focused on cases and controls geocoded at the highest resolution. Theoretically, both the inclusion and exclusion of addresses with missing or poor-quality geocodes can introduce bias; however, in our sensitivity analyses, the results did not change when all subjects were included regardless of geocoding accuracy. To address validity, we focused on increasing specificity of exposure assessment for distance to nurseries, i.e., confirming that initial “close” distances were indeed close. Accurate current day distance measurements of subject’s residence in relation to plant nurseries may not reflect historic distances as the study spans a large time period and the footprint of some nurseries might have changed throughout the years, thus making the use of historic aerial images imperative. We used such images when available.

To ensure high sensitivity, distances to nurseries were obtained from two registries, the CDFA and PUR. PUR is considered to be the most comprehensive reporting system in the world, with mandatory reporting since 1990 (California Department of Pesticide Regulation, 2020). PUR data includes information such as the type of commodity usage, date of application, and chemicals used. Licensed plant nurseries and nursery stock dealers were obtained from the CDFA. The CDFA database does not contain details such as the exact years of operation or the facility footprint. Missing information about the nursery footprint is a potential limitation as nurseries can be of various shapes and sizes. For example, the operations of a nursery may extend for many blocks under a power line and the actual footprint boundary could be very close to a residence of interest, but the associated geographic coordinate may be in the center of the footprint, and as a result, far away from the residence of interest. PUR pesticide information does not contain exact coordinates of applications; the location of pesticide use information is approximately within a 1 mi^2 (2.59 km^2) area of where the application was performed. To address these limitations, the presence of a nursery as well as its actual footprint were confirmed with aerial satellite imagery. Focusing our attention on subjects close to nurseries improved distance classification accuracy by confirming exposure status and nursery presence.

A limitation of the study is qualitative and non-specific pesticide exposure based on a spatial proximity model. Spray drift patterns were not taken into account, as drift would be minimal from ground level applications used in commercial plant nurseries. Volatilization is a process whereby a chemical compound is transformed into a gas and may persist for days or months, resulting in atmospheric deposition and transfer to residences (Bedos, Cellier, Calvet, Barriuso, & Gabrielle, 2002). Several studies have examined the relationship between residential proximity to agricultural crops and pesticides by measuring organophosphates levels, which are carcinogenic and the most common chemical class of agricultural pesticides. Residences near agricultural crops have higher levels of pesticides in household dust, compared to residences further away (Butler-Dawson, Galvin, Thorne, & Rohlman, 2018; Fenske et al., 2002; Gunier et al., 2011; Lu et al., 2000; Quandt et al., 2004; Simcox et al., 1995). In a recent systematic review focused on non-occupational pesticide exposure for individuals that lived close to agricultural lands, the authors found homes near agricultural lands had higher measured pesticide concentrations in dust, indoor and outdoor air (Dereumeaux et al., 2020). Pesticide household concentrations decreased sharply as house distance to treated fields increased, as was observed in a meta-analysis (Deziel et al., 2017). Multiple studies have examined residential pesticide exposure of people living near treated lands using biological samples. Collection methods for biomonitoring data analysis were not only varied in their sample material collection (blood, urine, saliva, hair), but also the time and collection method (Babina, Dollard, Pilotto, & Edwards, 2012; Bradman et al., 2011; Chevrier et al., 2014; Galea et al., 2015; Lu et al., 2000; Mercadante, Polledri, Bertazzi, & Fustinoni, 2013; van Wendel de Joode et al., 2012). However, use of biomonitoring methods are very costly and require *a priori* knowledge of the type of pesticide being investigated for appropriate selection of sample media. It should be noted that limitations apply to more sophisticated and/or specific pesticide models as well. Exposure estimates depend on an ability to capture historical or retrospective exposure in a given residence based on measurements in that residence occurring years later, to model past exposure at a given residence based on historical information.

Another limitation of our study was the lack of individual-level data about occupational pesticide exposure and home pesticide use. Parents employed in occupations with potential pesticide exposures were not accounted for, potentially resulting in an underestimation of take-home pesticide exposure from residues on their skin, clothes and footwear. Moreover, home pesticide use was not available, possibly resulting in an underestimation of exposure. However, living in close proximity to commercial outdoor plant nurseries may act as a source for chronic pesticide exposure and may represent a significant exposure source. The observed higher levels of pesticides in household dust, as well as indoor and outdoor air, provide evidence for exposure among children in close proximity to pesticide treated areas. Thus spatial proximity models, such as the one used in this study, are capable of capturing pesticide exposure levels, and distance might be as good a surrogate as exposure estimates based on interviews or other exposure models. Additionally, it appears that studies based on distance to pesticide applications identify childhood leukemia risk more consistently than interview-based assessments of outdoor household pesticide use. One possible explanation is that pesticide applications to crops or nurseries result in higher and more consistent exposure with applications throughout the year than household exposures.

This study examined pesticide use in total rather than the use of particular pesticides. A wide variety of pesticides was used during the study period and, in practice, may be used on the intended target. On one hand, some studies address this by using multiple exposure surrogates by particular individual pesticides and pesticide classes while others target carcinogenic pesticides (Park et al., 2020). However, based on current literature, it is unclear which specific pesticides studies one should focus on. In a pooled individual level data analysis of 12 case–control studies, there was little difference observed by the type of pesticide used (Bailey et al., 2014).

Overall, our findings suggest that living in very close proximity to plant nurseries may be a potential risk factor for childhood leukemia, and that more moderate distances do not appear to be associated with elevated risk. Further research on the specific types of pesticides used at plant nurseries and childhood leukemia should be undertaken, as plant nurseries are possible sources of year-round pesticide exposure and are often located close to residences.

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Chapter 3. Commercial outdoor plant nurseries as a confounder for electromagnetic fields and childhood leukemia risk

3.1 Abstract

Background

Close residential proximity to power lines and high magnetic fields exposure may be associated with elevated childhood leukemia risks as reported by prior studies and pooled analyses. Magnetic fields exposure from high voltage power lines is associated with proximity to these power lines and consequently with any factor varying with distance. Areas underneath power lines in California may be sites for commercial plant nurseries that can use pesticides, a potential childhood leukemia risk factor.

Objectives

Assess if potential pesticide exposure from commercial plant nurseries is a confounder or interacts with proximity or magnetic fields exposure from high voltage power lines to increase childhood leukemia risk.

Methods

A comprehensive childhood leukemia record-based case-control study with 5,788 cases and 5,788 controls (born and diagnosed in California 1986-2008) was conducted. Pesticide, power line, and magnetic field exposure assessment utilized models that incorporated geographical information systems, aerial satellite images, site visits and other historical information.

Results

The relationship for calculated fields with childhood leukemia (odds ratio (OR) 1.51, 95% confidence interval (CI) 0.70-3.23) slightly attenuated when controlling for nursery proximity

(OR 1.43, 95% CI 0.65-3.16) or restricting analysis to subjects living far (>300 m) from nurseries (OR 1.43, 95% CI 0.79-2.60). Similar association pattern was observed between distance to high voltage power lines and childhood leukemia. The association between nursery proximity and childhood leukemia was unchanged or only slightly attenuated when controlling for calculated fields or power line distance; ORs remained above 2 when excluding subjects with high calculated fields or close power line proximity (OR 2.16, 95% CI 0.82-5.67 and OR 2.15, 95% CI 0.82-5.64, respectively). The observed relationships were robust to different time periods, reference categories, and cut points.

Discussion

Close residential proximity to nurseries is suggested as an independent childhood leukemia risk factor. Our results do not support plant nurseries as an explanation for observed childhood leukemia risks for power line proximity and magnetic fields exposure.

3.2 Introduction

Childhood leukemia accounts for approximately a third of all childhood cancer cases (Howlader et al., 2020). Few risk factors for childhood leukemia have been established, mainly ionizing radiation and certain genetic disorders like Down syndrome (Belson et al., 2007; Kumar & De Jesus, 2021; Schüz & Erdmann, 2016b; Stieglitz & Loh, 2013). However, these risk factors account for less than 10% of childhood leukemia cases (Buffler et al., 2005; Whitehead et al., 2016; Wiemels, 2012). Other suspected risk factors include pesticides, magnetic fields, pollution, and infections (Amoon et al., 2022; Arellano-Galindo et al., 2017; Bailey, Infante-Rivard, et al., 2015; Crespi et al., 2019b; Filippini et al., 2015; He et al., 2020; Kheifets et al., 2010; Talibov et al., 2019; Van Maele-Fabry et al., 2019). Living in close proximity to power lines and high magnetic fields (MF) exposure have been associated with elevated childhood leukemia risks in prior studies and pooled analyses (Ahlbom et al., 2000; Amoon, Crespi, et al., 2018a; Greenland et al., 2000; Kheifets et al., 2010). A most recent pooled analysis reported that risk has declined over time, but the reasons for that are not clear (Amoon et al., 2022). Electromagnetic fields exposure does not appear to be genotoxic, but biological evidence suggests that it might influence cellular function and proliferation. Therefore, it could act as a promoter, growth enhancer or co-carcinogen (Kheifets et al., 2018).

In a comprehensive records-based childhood leukemia case-control study, the California Power Line Study (CAPS), we observed elevated childhood leukemia risks associated with close high voltage power line proximity and high magnetic fields exposure, however neither close residential proximity (<50 meters (m)) to high voltage power lines (200+ kilovolts (kV)) alone nor high calculated MF (≥0.4 (µT)) exposure alone were robustly associated with increased risk of childhood leukemia (Crespi et al., 2016b; Kheifets, Crespi, et al., 2017). Instead, substantial increased risk was exclusive to subjects that were both in close proximity to high voltage power lines and exposed to high calculated MF (odds ratio (OR) 4.1, 95% confidence interval (CI) 1.2-14.3). Additionally, an increased risk was not observed for high calculated MF exposure attributable to lower voltage power lines (<200 kV); instead, it was observed only for high calculated MF due to high voltage power lines. These findings taken together indicate that other explanations are likely to play a role in explaining these associations (Crespi et al., 2019b).

The areas located beneath transmission lines, called right-of-ways (ROW), may serve multiple uses in California. Some ROW areas are leased to businesses. Commercial plant nurseries, located in ROWs may serve as a chronic exposure source for pesticides (California Department of Pesticide Regulation, 2019a). Further, pesticide applications are regularly utilized to maintain ROWs.

Human exposure to pesticides may be a potential risk factor for childhood leukemia. Exposure to pesticides may produce molecular changes associated with cancer development, such as abnormal cell signaling, DNA damage, oxidative stress or chromosomal abnormalities (Sabarwal et al., 2018). Children might be particularly vulnerable to environmental exposures, as their immune, nervous and other systems are not fully developed (Costa et al., 2004; Simon et al., 2015).

Further, behavior, anatomy and/or respiratory physiology in children may increase their relative exposure to pesticides compared to adults. Childhood behaviors like playing on the floor, exploring their environment (indoors and outdoors), and putting their hands in their mouth on a regular basis increase their potential for exposure to pesticides through contact, inhalation as well as ingestion (Carroquino et al., 2012; Freeman et al., 2005; Moya et al., 2004; Roberts & Karr, 2012). Unique anatomical and respiratory characteristics in children such as having thinner skin, a larger surface area to volume ratio, and higher respiratory rates than adults, may also result in higher levels of pesticide exposure (Moya et al., 2004; Weiss et al., 2004; World Health Organization, 2008).

Various aspects of the relationship between pesticide exposure and childhood leukemia have been explored, such as occupational exposures, residential exposures, exposure timing, and type of leukemia. Chronic exposures to pesticides, such as residential exposure, may be associated with increased childhood leukemia risks. A systematic review and meta-analysis observed increased risks between all types of childhood leukemia and residential pesticide exposure: acute lymphocytic leukemia (ALL) (OR 1.42, 95% CI 1.13-1.80), acute myeloid leukemia (AML) (OR 1.90, 95% CI 1.35-2.67), and unspecified (OR 1.57, 95% CI 1.27-1.95) (Van Maele-Fabry et al., 2019). More recently, in a meta-analysis, investigators found maternal exposure to pesticides during pregnancy resulted in elevated risks for childhood leukemia with an OR of 1.88 (95% CI 1.15-3.08), which was higher for ALL (OR 2.51, 95% CI 1.39-4.55) (Karalexi et al., 2021). Increased childhood leukemia risk associated with residential pesticide exposure during the prenatal period has also been reported in other research (Bailey, Infante-Rivard, et al., 2015; Daniels et al., 1997; Ma et al., 2002; Turner et al., 2010a; Vinson et al., 2011); association with parental occupational pesticide exposure has also been reported (Karalexi et al., 2021; Wigle et al., 2009a).

In a recent study focusing on plant nurseries, we evaluated childhood leukemia risk and residential pesticide exposure operationalized as distance to a nursery, determined by a spatial proximity model that combined data from geographic information system (GIS) and historic aerial satellite images (Nguyen et al., 2021). We observed elevated childhood leukemia risks (OR 2.40, 95% CI 0.99-5.82), with the ALL subtype having the highest risk (OR 3.09, 95% CI 1.14-8.34) for subjects with birth residences very close (<75 m) to plant nurseries.

Humans are often exposed to multiple environmental exposures concurrently; this is especially applicable for electromagnetic fields as they are ubiquitous in most countries. It has been hypothesized that the combination of non-ionizing electromagnetic fields and other exposures may result in synergistic effects on biological systems, thereby affecting cancer development, cellular mutations and teratogenicity (Kostoff & Lau, 2017). A meta-analysis of *in vitro* studies and short-term animal studies, suggests that magnetic fields do interact with other chemical and physical exposures, at least for exposures of 100 µT or higher (Juutilainen et al., 2006). Interactive effects for pesticides and extremely low frequency magnetic fields (EMF) have also been observed at lower exposure levels. Bee colonies co-exposed to both pesticides and EMF had worse health outcomes compared to colonies only exposed to pesticides in terms of colony survival, disease development, and aberrant behavior (Lupi et al., 2021). Other researchers have exposed peripubertal male rats to both MFs and a high dose of the herbicide atrazine, a widely used pesticide, and reported producing material difference in the total number of mast cells compared to a high dose atrazine exposure alone (Rajkovic et al., 2010). Mast cells are multipurpose immune cells that are most commonly associated with mediating inflammatory responses; however research has also reported that they may play a role in the pathogenesis of other disorders, such as cancer (da Silva et al., 2014; Rao & Brown, 2008). Further, a pooled analysis that focused on distance to power lines used individual level data from 11 case-control studies and reported small but imprecise elevated childhood leukemia risks for subjects within 50 m of high voltage (200+ kV) power lines that could not be explained by high magnetic fields exposure (Amoon, Crespi, et al., 2018a), pointing to a need for another explanation.

Pesticide use in commercial plant nurseries located underneath high voltage power lines may provide an alternative explanation for the reported associations between childhood leukemia and distance to power lines and/or magnetic fields or be synergistic. In this paper, we test these hypotheses and examine if potential pesticide exposure from nurseries located near residences explains or modifies the relationship between distance from high voltage power lines or calculated magnetic fields and childhood leukemia.

3.3 Methods

Case Ascertainment and Control Selection

Childhood leukemia cancer cases younger than the age of 16 years, born in and living in California at the time of diagnosis (1988-2008) were obtained from the California Cancer Registry (CCR) (California Cancer Registry, 2020). Cases were linked to California Birth Registry records (CBR; California Department of Public Health, Vital Statistics Branch) and randomly matched by sex and birthdate (± 6 months) to controls obtained from the CBR. Linkage of study subjects to birth records had births that consisted of years 1986–2008. Controls were excluded from the study if they received any form of cancer diagnosis within California prior to the time of diagnosis for their matched case. Six thousand six hundred forty-five childhood leukemia cancer cases satisfying our inclusion criteria were identified from the CCR. The majority were born in California, thus 87.1% (n=5,788) of identified childhood leukemia cancer cases were successfully linked to the CBR; an equal number of controls were included in this study.

The CBR provided several variables about cases and controls, which included birthdate, sex, mother's residential address at time of birth, parental race/ethnicity, birthweight, maternal and paternal education, ages of mother and father, payment method for delivery. During the study time period, certain variables (e.g., maternal education) collected by the CBR changed or were only collected in particular years. Child race/ethnicity was classified by us as White if both parents were White, Black if one or both parents were Black, Asian if one or both parents were Asian, Hispanic if one or both parents were Hispanic and neither parent was Black or Asian, and Other otherwise. A binary socioeconomic status (SES) indicator variable (high or low) was developed using father's education (high if greater than 12 years and low otherwise), mother's education (high if greater than 12 years and low otherwise), payment source for hospital delivery (low if no coverage or government assisted payment, high otherwise) or community-based SES information based on United States Census Bureau data, as available in the listed preferential order for each subject. Subject birth residences were geocoded to latitude and longitude coordinates. Multiple imputation was conducted for missing data on SES and race/ethnicity for analysis. Study methods have been described in previous publications (Kheifets et al., 2015; Oksuzyan et al., 2015a).

Exposure Assessment

Details on determining residential proximity to high voltage power lines and exposure to MF are given in previous publications (Kheifets et al., 2015; Vergara et al., 2015). Briefly, residential proximity to power lines were estimated using GIS data obtained from electric power companies, aerial satellite images, and in-person site visits for residences close enough to power lines to potentially have MF exposure levels elevated to background levels. For site-visited residences, we calculated MFs at birth residences using distance, historical load and phasing information (Vergara et al., 2015). Calculated MFs accounted for all power lines above 100 kV as well as some lower voltage power lines. MFs due to power lines for all other residential addresses were assumed to be <0.1 µT. Distance analysis focused on high voltage lines (200+ kV).

Identifying plant nurseries, determining residential proximity to nurseries and nursery presence has been described in detail in previous work (Nguyen et al., 2021). In short, identifying plant nurseries utilized two databases: the California Department of Pesticide Regulation Pesticide Use Reporting (PUR) and the California Department of Food and Agriculture (CDFA). Initial approximate residential proximity to plant nurseries from the subject's birth address in CAPS was calculated based on their geocoded birth address. All subjects within 2000 meters of both a nursery and a power line and all subjects within 600 meters of a nursery regardless of power line proximity were identified for more detailed assessment. For these subjects, Google Earth aerial satellite images matched as closely as possible to the subject's birthyear were used to confirm nursery presence as well as determine residential proximity to the nearest nursery footprint border. Exposure assessments were designed to ensure high sensitivity (through a multi-step process) and were completed blind to case-control status. The statistical analysis followed *a priori* developed plan.

Statistical Analysis

The analysis plan was based on the simplified directed acyclic graph (DAG) displayed in Figure 3.1.

The shortest distances between nurseries and subject residences were categorized as 0-75, 75-150, 150-300, and 300-600 m (referent), based on prior literature, the distribution of controls as well as focusing on the highest exposure (<75 m) group (approximately 5% of controls). The cut point of 600 m was chosen based on prior studies and to ensure an adequate distance to accurately capture exposure data. Additionally, as used in previous publications, the distances between power lines 200 kV or higher and subject residences were categorized as 0-50, 50-150, 150-300, and ⩾300 m (referent). We also performed analyses using ⩾600 m as a referent. Calculated magnetic fields (calculated fields) were categorized as ⩾0.4, 0.2-0.4, 0.1-0.2, and 0-0.1 µT (referent).

All main analyses for this study were conducted on subjects whose residential addresses were geocoded at a high resolution/accuracy, at the street segment or parcel level (n=9,714). Restriction of analyses to subjects geocoded at a high resolution required breaking matched subjects; thus, our main method of analysis was unconditional logistic regression controlling for matching variables (age and sex) and potential confounders, such as SES and race/ethnicity (White, Black, Asian, Hispanic, Other). Subgroup group analysis conducted focused on the acute lymphocytic leukemia (ALL) subtype, as it is the most common form and to ensure adequate subject count.

To examine whether residential proximity to nurseries was a confounder for the relationship between childhood leukemia and magnetic fields or power line proximity, we performed unconditional logistic regression with magnetic fields or power line proximity as the exposure and childhood leukemia as the outcome, both with and without adjustment for nursery proximity in the model along with other confounders, with the assumption of no uncontrolled confounding. Additionally, we examined the role of magnetic fields or power line proximity as possible confounders between childhood leukemia and residential proximity to nurseries by performing unconditional logistic regression with nursery proximity as the exposure and childhood leukemia as the outcome, both with and without adjustment for magnetic fields or power line proximity in the model alongside other confounders, with the assumption of no uncontrolled confounding. We conducted sensitivity analyses for our confounding analyses by assessing whether risk estimates were stable by restricting to subjects born in the year 1990 and onwards (when PUR data contained more details), stratifying by age at diagnosis (<5 years, ≥5 years), and restricting leukemia subtype to acute lymphocytic leukemia (ALL).

In order to assess whether nursery proximity, power line proximity and calculated fields are risk factors independent of each other, we performed unconditional logistic regression while excluding subjects that were categorized into the highest exposure category of one of the other exposures.

Because of small numbers, we were not able to fit models including interaction terms nor a full set of stratified models. Instead, as a preliminary assessment of whether the presence or absence of one exposure modified the risk associated with another exposure, we obtained risk estimates for each exposure restricted to subjects who were minimally exposed to another risk factor, for comparison with other estimates.

SAS (Version 9.4, The SAS Institute, Cary, NC) was used for the analyses. Approval for CAPS was received from University of California, Los Angeles Office for the Protection of Research Subjects and the State of California Committee for the Protection of Human Subjects.

3.4 Results

Details of study subject demographic characteristics are presented in previous publication (Nguyen et al., 2021). Initially 6,645 childhood leukemia cases were identified from CCR. Of these cases, 5,788 (87.1%) were linked successfully to the CBR; an equivalent number of controls were included in the study. The majority, approximately 85% of childhood leukemia cases consisted of the ALL subtype. Classification of race/ethnicity (missing for about 2% of cases and 3% of controls) and SES (missing for about 3% of cases and controls) was available for most subjects. Approximately 84% of cases and controls were geocoded at the highest level of accuracy (street segment or parcel level).

There was a strong correlation (r = 0.72) between distance to closest high voltage power line (200+ kV) and distance to closest plant nursery (Figure 3.2). Similarly, there was a strong relationship between high calculated fields and distance to nurseries (a Fisher exact test for the four categories of nursery distance versus the four categories of CF has p-value < 0.0001).

To disentangle the contributions of nurseries, calculated fields and distance to power lines on the risk of childhood leukemia, we performed a number of analyses. Table 3.1 shows confounder analyses for the relationship between childhood leukemia risk, proximity to nurseries, calculated fields and proximity to power lines. Results for distance to power lines and calculated fields were consistent with previous publications (Table 3.1); for childhood leukemia risk and calculated fields, the highest exposure level (≥0.4 μT) had an OR of 1.51 (95% CI 0.70-3.23), while for distance to high voltage power lines, the highest exposure category (<50 m) had an OR of 1.47 (95% CI 0.76-2.82). These ORs attenuated slightly when controlling for distance to nurseries (OR for calculated fields 1.43 (95% CI 0.65-3.16); OR for distance to power lines 1.38 (95% CI 0.71-2.69)). When we examined all subjects within 600 m of a nursery, regardless of power line distance, the OR for the highest exposure category (<75 m) was 2.40 (95% CI 0.99-5.82), which was consistent with previous publication (Table 3.1). Association with nurseries remained unchanged when adjusted for distance to power lines (OR 2.40, 95% CI 0.97-5.96), but attenuated slightly when adjusted for calculated fields (OR 2.31, 95% CI 0.94-5.71).

We further examined if the exposures are independent risk factors of each other by repeating analyses after excluding subjects with high exposures to the other putative risk factors, i.e., subjects closest (<50 m) to a high voltage power line, closest (<75 m) to a nursery, or exposed to high (≥0.4 μT) calculated fields (Table 3.2). While all of the associations attenuated when subjects highly exposed to another putative risk factor were removed, the associated risks between close proximity to nurseries and childhood leukemia remained elevated (ORs above 2), indicating that proximity to nurseries is a risk factor independent of calculated fields or distance to power lines. When subjects in close proximity (<75 m) to nurseries were excluded, the association between calculated magnetic fields (OR 1.27, 95% CI 0.55-2.92) or distance to high voltage power lines (OR 1.30, 95% CI 0.65-2.60) with childhood leukemia somewhat attenuated.

Table 3.2 also reports results when restricting analysis to subjects with low levels of other putative exposures, as a preliminary assessment of interaction effects (models with interaction terms or restricted to high levels of other putative exposures could not be fit due to small numbers). For subjects who had only background levels of magnetic fields exposure (below 0.1 μT), the OR for very close proximity to a plant nursery (<75 m) was 1.86 (95% CI 0.63-5.46). For subjects who lived far away from high voltage power lines (>300 m), the OR for close proximity to a plant nursery was 2.71 (95% CI 0.67-10.88). When restricting analysis to subjects living far (>300 m) from nurseries, the OR for calculated fields and close power line proximity were only slightly attenuated (OR 1.43 (95% CI 0.66-2.75) for calculated fields and OR 1.43 (95% CI 0.79-2.60) for high voltage power lines), suggesting no interaction.

Table 3.3 provides results from sensitivity analysis for confounding. Overall, the observed risks remained elevated (ORs above 3) when restricting analyses to the ALL subtype for distance to nursery, and were similar to overall childhood leukemia risks for calculated fields, and distance to power lines. Stratifying on age of diagnosis resulted in higher ORs for all exposures for younger subjects (<5 years) compared to not stratifying on age of diagnosis. The OR for nursery proximity (<75 m) increased to 3.47 (95% CI 1.00-12.07) after adjusting for power line proximity within the younger group. Additionally, we found higher ORs among younger subjects compared to older subjects (≥5 years), for nursery proximity (<75 m) (OR 2.98 vs OR 1.70), calculated fields (≥0.4 μT) (OR 2.04 vs OR 0.68), and power line proximity (<50 m) (OR 1.75 vs OR 0.97); this relationship trend was also observed after adjusting for other exposures. Supplementary Table 3.1 presents sensitivity analysis when all birth residences were included in analyses regardless of geocoding accuracy and when the reference group for power line proximity was increased to 600 m or higher. The adjusted and unadjusted ORs and 95% CI remained similar with no material differences from our main confounder analyses.

When restricting analyses to subjects with birth years from 1990 and on, the OR for the closest distance to nurseries increased to 2.63 (95% CI 1.03-6.74); adjusting for calculated fields resulted in associations of similar magnitude (OR 2.60, 95% CI 1.00-6.77), while adjusting for power line proximity increased risks slightly (OR 2.73, 95% CI 1.04-7.17). The observed associations for calculated fields and distance to power lines slightly attenuated when restricting to birth years from 1990 and on.

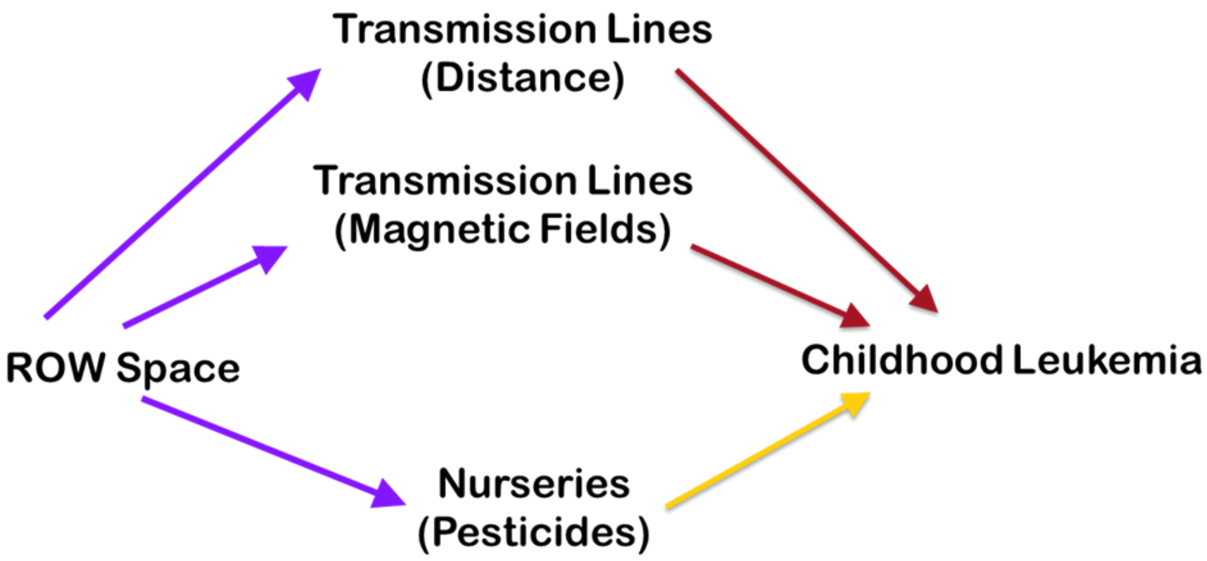

Figure 3.1: Simplified DAG to explore the association between Nurseries and ROW space and childhood leukemia

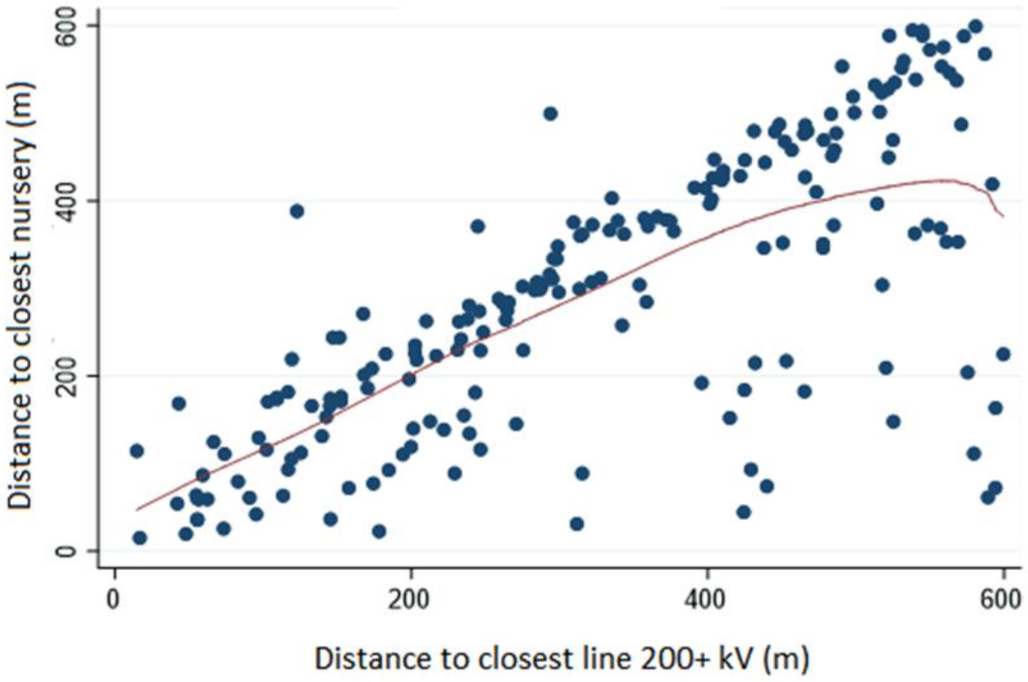

Figure 3.2: Scatterplot of distance to closest power line (200+ kV) and distance to closest nursery

Table 3.1: Logistic regression modeling of childhood leukemia risk as a function of distance to nurseries, distance to power lines 200+ kV, calculated fields, or a combination of exposures, California Power Line Study

	No adjustment[a]		Adjusting for	
			Distance to nursery	
Calculated fields, µT	Ca/Co	OR (95% CI)	OR (95% CI)	
<0.1	4,824/4,782	1.00 (ref)	1.00 (ref)	
0.1-.2	24/27	0.84 (0.48-1.46)	0.83 (0.47-1.45)	
0.2-.4	14/15	0.97 (0.47-2.02)	0.95 (0.46-1.99)	
≥0.4	17/11	1.51 (0.70-3.23)	1.43 (0.65-3.16)	
			Distance to nursery	
Distance to power lines, m	Ca/Co	OR (95% CI)	OR (95% CI)	
≥300	4,714/4,652	1.00 (ref)	1.00 (ref)	
150-300	92/110	0.82 (0.62-1.08)	0.85 (0.63-1.14)	
50-150	50/58	0.84 (0.58-1.24)	0.84 (0.56-1.25)	
0-50	23/15	1.47 (0.76-2.82)	1.38 (0.71-2.69)	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
300-600	108/112	1.00 (ref)	1.00 (ref)	1.00 (ref)
150-300	45/49	0.93 (0.57-1.50)	0.93 (0.57-1.51)	0.99 (0.60-1.62)
75-150	13/25	0.54 (0.26-1.11)	0.53 (0.26-1.10)	0.57 (0.27-1.18)
0-75	17/8	2.40 (0.99-5.82)	2.31 (0.94-5.71)	2.40 (0.97-5.96)

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values

m meters, µT microTesla, ca cases, co controls, OR odds ratio, CI confidence interval, ref reference

[a] No adjustment for other exposures

Table 3.2: Logistic regression modeling of childhood leukemia risk as a function of distance to nurseries, calculated fields and distance to power lines 200+ kV, with exclusions and restrictions on subjects based on other putative exposures, California Power Line Study

Subjects		Nursery (<75 m) (ref: 300-600 m)		CF (≥0.4 µT) (ref: <0.1 µT)		200+ kV Power line (<50m) (ref: >600 m)
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
No exclusion	17/8	2.40 (0.99-5.82)	17/11	1.51 (0.70-3.23)	23/15	1.47 (0.76-2.82)
Exclude if CF ≥0.4 µT	13/7	2.16 (0.82-5.67)				
Exclude if <50 m of 200+ kV power line	13/7	2.15 (0.82-5.64)				
Exclude if <75 m of nursery			13/10	1.27 (0.55-2.92)	19/14	1.30 (0.65-2.60)
Restrict to subjects with CF <0.1 µT	9/6	1.86 (0.63-5.46)				
Restrict to subjects >300 m from 200+ kV power lines	7/3	2.71 (0.67-10.88)				
Restrict to subjects >300 m from nurseries			12/8	1.43 (0.66-2.75)	18/12	1.43 (0.79-2.60)

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values

m meters, kV kilovolts, µT microTesla, ca cases, co controls, OR odds ratio, CI confidence interval, CF calculated fields, ref reference

Table 3.3: Sensitivity analysis for confounding of childhood leukemia risk for the highest exposure category for distance to pesticide/nursery applications, distance to power lines 200+ kV, calculated fields, or a combination of exposures, California Power Line Study

ALL subtype		No adjustment[a]	Adjusting for	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
0-75	16/6	3.09 (1.14-8.34)	3.03 (1.10-8.33)	3.32 (1.19-9.24)
Calculated fields, µT			Distance to nursery	
≥0.4	13/8	1.57 (0.65-3.80)	1.40 (0.56-3.51)	
Distance to power lines, m			Distance to nursery	
0-50	17/12	1.33 (0.63-2.79)	1.22 (0.57-2.61)	
Age of diagnosis <5 years		No adjustment[a]	Adjusting for	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
0-75	12/4	2.98 (0.90-9.81)	2.84 (0.84-9.66)	3.47 (1.00-12.07)
Calculated fields, µT			Distance to nursery	
≥0.4	14/7	2.04 (0.82-5.10)	1.77 (0.68-4.58)	
Distance to power lines, m			Distance to nursery	
0-50	18/10	1.75 (0.80-3.80)	1.49 (0.67-3.32)	

Age of diagnosis ≥5 years		No adjustment[a]	Adjusting for	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
0-75	5/4	1.70 (0.42-6.85)	1.72 (0.42-7.06)	1.54 (0.36-6.57)
Calculated fields, µT			Distance to nursery	
≥0.4	3/4	0.68 (0.15-3.07)	0.74 (0.15-3.53)	
Distance to power lines, m			Distance to nursery	
0-50	5/5	0.97 (0.28-3.39)	1.02 (0.28-3.70)	
Birth years ≥1990		No adjustment[a]	Adjusting for	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
0-75	16/7	2.63 (1.03-6.74)	2.60 (1.00-6.77)	2.73 (1.04-7.17)
Calculated fields, µT			Distance to nursery	
≥0.4	15/10	1.45 (0.65-3.24)	1.39 (0.60-3.21)	
Distance to power lines, m			Distance to nursery	
0-50	20/14	1.40 (0.71-2.79)	1.34 (0.66-2.70)	

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values

m meters, kV kilovolts, µT microTesla, ca cases, co controls, OR odds ratio, CI confidence interval, ALL acute lymphocytic leukemia

[a] No adjustment for other exposures

3.5 Discussion

In our case-control study in California, subjects living in close proximity (<75 m) to plant nurseries had an elevated risk of childhood leukemia, which was higher for the ALL subtype. Risk estimates of calculated MF or power line proximity and childhood leukemia were not explained by birth residence proximity to a plant nursery. Conversely, birth residence in close proximity to nurseries was associated with elevated childhood leukemia risk, independent of calculated MF exposure or proximity to high voltage power lines. Our findings were not sensitive to data quality issues or various assumptions.

Our findings observed increased risks for younger subjects compared to older subjects (≥5 years), for calculated fields (≥0.4 µT), power line proximity (<50 m), as well as nursery proximity (<75 m). There may be several reasons why elevated risks are observed for younger subjects. Younger children spend a large amount of time at home, thus their residential exposures are the most relevant. Younger children are more likely to learn about their environment by engaging in hand-to-mouth behavior. Since they may also play inside and outside, these behaviors may result in ingestion of pesticides from their environment. Pesticides that may be on various surfaces indoors and outdoors may cross over onto the hands of young children and then consumed during their mouthing behavior. Nondietary ingestion may result in higher levels of ingestion for containments compared to other ingestion routes (Weaver et al., 1998). Additionally, infants and young children have higher inhalation rates and thinner skin, which increases their relative exposure to pesticides compared to older children. Combined with the fact that young children have breathing zones closer to the floor than older children, higher levels of contaminant could be inhaled (Zhou et al., 2019). Further, children might be more susceptible to environmental exposures during some periods of development (Kheifets et al., 2005).

We observed that there was no material change in the relationship for either residential proximity to high voltage power lines or magnetic fields exposure and childhood leukemia when controlling for plant nursery proximity; thus our results do not support plant nurseries as a strong confounder; adjusting for plant nursery proximity did not remove additional bias beyond the already adjusted variables.

Our study on childhood leukemia is the first to focus on commercial plant nursery proximity to residencies as a pesticide exposure proxy and to examine pesticide exposure as a possible explanation for the association between magnetic fields and childhood leukemia. The strengths of this study are its large sample size, consisting of 5,788 childhood leukemia cases and an equal number of matched controls. Additionally, this study utilized population-based registries with complete registration of childhood leukemia cancer cases and births for the entire state of California for cases and controls, thus avoiding participation bias. Additional study strengths are reducing information bias by performing multi-stage exposure and confounder assessments blinded to the case and control status. High sensitivity for the identification of plant nurseries and their proximity to subjects was accomplished by utilizing two registries (CDFA and PUR). PUR is recognized as the most comprehensive reporting program in the world for pesticides (California Department of Pesticide Regulation, 2021). PUR collects comprehensive data on pesticide use such as the application date, chemicals applied, and the commodity usage type. The CDFA maintains a registry on licensed nurseries and nursery stock suppliers for the state of California (California Department of Food and Agriculture, 2021).

Historical exposure assessment is demanding for any childhood leukemia study, including this one. Potential exposure assessment issues specific to GIS-based studies (Chang et al., 2014), were addressed by incorporating multi-stage exposure assessment procedures. Additionally, cases and controls utilized in our main analyses were geocoded at the highest level of accuracy. Both the inclusion and exclusion of residential addresses with missing or poor-quality geocodes can theoretically result in bias; we explored whether this bias was present in our study. In our sensitivity analysis, we found that the risk estimates did not materially differ when all study subjects regardless of geocoding accuracy were included. Potential validity issues arising with GIS were addressed by increasing exposure assessment specificity for both nursery proximity and magnetic field exposure, accomplished by using historic data and site visits to accurately capture exposure to magnetic fields and residential proximity to nurseries and power lines.

Spatial proximity models, employed in this study, are capable of accurately capturing pesticide exposure levels: several studies have found that pesticide concentration levels are inversely associated with distance. A meta-analysis reported that house dust pesticide concentrations declined steeply as the distance to treated fields increased (Deziel et al., 2017). Previous studies on residential proximity to agricultural crops and measured household pesticide levels have found higher pesticide levels in residences located nearby agricultural crops compared to residences located further away (Dawson et al., 2018; Fenske et al., 2002; Gunier et al., 2011; Lu et al., 2000b; Quandt et al., 2004; Simcox et al., 1995). Additionally, a recent systematic review that focused on non-agricultural worker residents, reported that households located close to agricultural lands reported higher household concentrations of pesticides in the dust, indoor and outdoor air (Dereumeaux et al., 2020). As the CAPS study was interested in retrospective exposures, we utilized historic aerial satellite images to accurately determine subject distance to plant nurseries, as present-day measurements might not accurately capture nursery proximity. The present-day footprint of certain plant nurseries may not be reflective of historic exposures for those living near, as the footprint may have differed throughout the study period; it is crucial to use historic satellite imagery to ensure accurate distance and exposure assessments.

Possible study limitations were a lack of accounting for other sources of pesticide exposures using individual ambient pesticide or at home measurements, as this was a record-based study, which may have resulted in underestimating pesticide exposure for subjects. However, it is unlikely that pesticide exposure from plant nurseries is correlated with other sources of pesticide exposures. Other possible study limitations were that we had neither information for each footprint size for every nursery nor their years in business. These possible limitations were addressed by confirming nursery presence and the actual nursery footprint with historic aerial satellite images. Some nurseries have irregularly shaped land plots, that extend for a long distance or have unique shapes, using accurately dated satellite imagery was imperative to accurately capture subject exposure. Additionally, focusing on study subjects in close proximity to plant nurseries improved the accuracy of distance classification by confirming not only exposure status but also the presence of plant nurseries. Estimating magnetic fields exposure with geographically modeled distances can result in potentially larger errors at short distances, as field levels may vary substantially at close distances (Chang et al., 2014). We overcame this potential barrier by not relying exclusively on GIS, but rather supplemented our assessment with aerial satellite imagery and in-person site visits of residences with potentially elevated magnetic fields exposure due to their proximity to power lines. The site visits allowed us to precisely measure distances using a range finder. Another potential limitation of this study was having small numbers of subjects that were concurrently exposed to high magnetic fields, close power line proximity and plant nurseries; consequently, we were not able to fully assess potential confounding.

Since the early days of EMF research, investigators have searched for other possible factors to explain the observed associations with childhood leukemia. Hypothesized confounders of the relationship between magnetic fields and childhood leukemia include dwelling type, SES, viral exposures, residential mobility, exogeneous tobacco smoke, dietary components, and traffic related conditions (World Health Organization, 2007).

Residential mobility of subjects may have been a potential issue in this study and in other studies of similar design. Mobility can potentially result in selection bias, measurement error, confounding or could be a potential risk factor in itself (Kheifets, Swanson, et al., 2017). For cases to be included in this study they had to be born in and diagnosed with leukemia in California, while controls were only required to have been born in California, but did not have to be residing in California when the corresponding case was diagnosed. It is possible that some controls could have moved out of California and been subsequently diagnosed with leukemia in another state, but this is not likely, as the outcome is very rare. Further, we observed that mobility was not associated with proximity to the closest power line or calculated MFs in a case-only analysis (Amoon, Oksuzyan, et al., 2018). Similar results were obtained in a hybrid simulation study as well as an empirical analysis with the CAPS study (Amoon et al., 2019). Thus, mobility is unlikely to be an important confounder in this study.

In both individual studies and pooled analyses that focused on the possible effects of several other putative risk factors, such as mobility, dwelling type, traffic exposure, and SES, the authors found that associations with childhood leukemia did not materially change after adjustment for these risk factors (e.g. Amoon et al., 2018). Therefore, similar to our findings for distance to nurseries, none of these other variables confounded the association, although some have been identified as potential risk factors for childhood leukemia. Our study is the first to examine potential confounding by plant nurseries on the relationship between childhood leukemia and high voltage power line proximity or calculated fields in such detail. Land use patterns differ across geographic areas, and the use of land below power lines for commercial plant nurseries may be more prevalent in California compared to some other geographic areas, enabling us to conduct this study.

Overall, our findings did not support proximity to plant nurseries as an explanation for the MF and childhood leukemia association, however we were not able to fully assess possible confounding due to small numbers. Our findings suggest that close proximity to plant nurseries is an independent risk factor for childhood leukemia. Further research on the specific pesticide types applied at plant nurseries and childhood leukemia should be performed, as plant nurseries are potential sources of chronic pesticide exposure

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3.6 Appendix

Supplementary Table 3.1: Additional sensitivity analysis for confounding of childhood leukemia risk for the highest exposure category for distance to pesticide/nursery applications, distance to power lines 200+ kV, calculated fields, or a combination of exposures, California Power Line Study

Regardless of birth residence geocoding accuracy		No adjustment^{a}	Adjusting for	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
0-75	19/9	2.39 (1.03-5.52)	2.30 (0.98-5.40)	2.43 (1.03-5.75)
Calculated fields, µT			Distance to nursery	
≥0.4	17/11	1.53 (0.71-3.28)	1.42 (0.65-3.13)	
Distance to power lines, m			Distance to nursery	
0-50	23/15	1.48 (0.77-2.85)	1.38 (0.71-2.68)	
600 m or higher as power line proximity referent		No adjustment^{a}	Adjusting for	
			Calculated fields	Distance to power lines
Distance to nursery, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)
0-75	17/8	2.40 (0.99-5.82)	2.31 (0.94-5.71)	2.37 (0.95-5.90)
Calculated fields, µT			Distance to nursery	
≥0.4	17/11	1.51 (0.70-3.23)	1.43 (0.65-3.16)	
Distance to power lines, m			Distance to nursery	
0-50	23/15	1.47 (0.76-2.82)	1.39 (0.71-2.71)	

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values

m meters, µT microTesla, ca cases, co controls, OR odds ratio, CI confidence interval

[a] No adjustment for other exposures

Chapter 4. Pesticides as an independent childhood leukemia risk factor and as a confounder for electromagnetic fields exposure

4.1 Abstract

Background

Both pesticides and high magnetic fields are suspected to be childhood leukemia risk factors. Pesticides are utilized at commercial plant nurseries, which sometimes occupy the areas underneath high voltage power lines.

Objectives

To evaluate whether potential pesticide exposures (intended use, chemical class, active ingredient) utilized at plant nurseries act as an independent childhood leukemia risk factor or as a confounder for proximity to, or magnetic fields exposure from, high voltage power lines.

Methods

We conducted a state-wide records-based case-control study for California with 5,7888 childhood leukemia cases and 5,788 controls that examined specific pesticide use, magnetic field exposures and distances to both power lines and plant nurseries. Exposure assessment incorporated geographic information systems, aerial satellite images, and other historical information.

Results

Childhood leukemia risk was elevated for several active pesticide ingredients: permethrin (odds ratio (OR) 1.49, 95% confidence interval (CI) (0.83-2.67), chlorpyrifos (OR 1.29, 95% CI 0.89-1.87), dimethoate (OR 1.79, 95% CI 0.85-3.76), mancozeb (OR 1.41, 95% CI 0.85-2.33), oxyfluorfen (OR 1.41, 95% CI 0.75-2.66), oryzalin (OR 1.60, 95% CI 0.97-2.63), and

pendimethalin (OR 1.82, 95% CI 0.81-1.25). Rodenticide (OR 1.42, 95% CI 0.78-2.66) and molluscicide (OR 1.22, 95% CI 0.82-1.81) exposure also presented elevated childhood leukemia risks. Childhood leukemia associations with calculated fields or power line proximity did not materially change after adjusting for pesticide exposure. Childhood leukemia risks with power line proximity remained similar when pesticide exposures were excluded.

Discussion

Pesticide exposure may be an independent childhood leukemia risk factor. Childhood leukemia risks for power line proximity and magnetic fields exposure were not explained by pesticide exposure.

4.2 Introduction

Leukemia is the most common form of cancer in children, comprising 28% of childhood cancer cases (R. L. Siegel et al., 2022). Little is known about the etiology of childhood leukemia; ionizing radiation is the only established exposure risk factor. Various potential risk factors have been studied such as socioeconomic status (SES), dwelling type, and pesticides (Amoon, Crespi, et al., 2018b; Amoon et al., 2020; Karalexi et al., 2021). Previous studies and pooled analyses have provided evidence that close residential proximity to power lines and exposure to high magnetic fields (MF) may be a risk factor for childhood leukemia (Ahlbom et al., 2000; Amoon, Crespi, et al., 2018b; Amoon et al., 2022; Greenland et al., 2000; Kheifets et al., 2010). However, more recent pooled (Amoon et al., 2022) and meta-analyses (Swanson et al., 2019) found no association in more recent studies between MF and childhood leukemia.

Our group examined the relationship between childhood leukemia, living in close proximity (<50 m) to high voltage power lines (200+ kilovolts (kV)) and MF exposure with a California statewide records-based case-control study (California Power Line Study (CAPS)) and observed significant elevated childhood leukemia risk for subjects who were both in close residential proximity to high voltage power lines and exposed to high calculated MF (≥ 0.4 µT) attributable to high voltage power lines (odds ratio (OR) 4.1, 95% confidence interval (CI) 1.2-14.3) (Crespi et al., 2019b). Subjects who were only exposed to high calculated MF or only lived in close proximity to high voltage power lines did not present similar elevated risks (Crespi et al., 2016b; Kheifets, Crespi, et al., 2017). One possible explanation for the fact that robust childhood leukemia associations were only observed for subjects concurrently exposed to high

MF and residing in close proximity to high voltage power lines, is that another exposure is involved in these observed elevated risks.

Right-of-ways (ROW) are situated underneath high voltage power lines and may be utilized for commercial plant nurseries. These plant nurseries may routinely apply pesticides year-round and, similar to the power lines, may be located close to residences (California Department of Pesticide Regulation, 2019b). Pesticides consist of various chemicals that are intended to kill, keep away or control unwanted organisms. Exposure to pesticides has been hypothesized to be a risk factor for developing childhood leukemia (Bailey, Infante-Rivard, et al., 2015; Chen et al., 2015b; Karalexi et al., 2021; Turner et al., 2010b; Vinson et al., 2011; Wigle et al., 2009b).

Pesticides are often investigated based on their intended target (insecticides, herbicides, etc.), chemical class (organochlorines, carbamates, etc.) or the active ingredient (Lushchak et al., 2018). A systematic review and meta-analysis reported that maternal environmental exposure during pregnancy to insecticides (OR 1.60, 95% CI 1.11-2.29) and herbicides (OR 1.41, 95% CI 1.00-1.99) was associated with elevated childhood leukemia risks (Karalexi et al., 2021). Additionally, another meta-analysis observed increased risks for childhood leukemia associated with exposure to insecticides (OR 2.05, 95% CI 1.80-2.32) and herbicides (OR 1.61, 95% CI 1.20-2.16) during pregnancy and exposure to insecticides (OR 1.61, 95% CI 1.33-1.95) during childhood (Turner et al., 2010b). Different pesticide chemical classes have varying attributes that can allow them to bioaccumulate; for example, organochlorines have high lipophilicity and low water solubility. As a result, examining pesticides by their chemical classes is also important (Rull et al., 2009).

The ubiquitous nature of pesticide use in the maintenance of public areas and vegetation increases the likelihood of people being exposed, even if they are not personally involved in the pesticide applications. Studies have reported higher concentrations of pesticides in household dust and ambient air for those living near areas treated with pesticides (Fenske et al., 2002; Lu et al., 2000b; Simcox et al., 1995; Weppner et al., 2006). Thus, living near areas treated with pesticides may result in chronic pesticides exposure (Dereumeaux et al., 2020).

In a recent study based on CAPS, we examined childhood leukemia risk and pesticide exposure based on plant nursery proximity to subjects (Nguyen et al., 2021). Subjects who had birth residencies very close (<75 m) to nurseries had increased risk for childhood leukemia (OR 2.40, 95% CI 0.99-5.82) as well as for the acute lymphocytic leukemia (ALL) subtype (OR 3.09, 95% CI 1.14-8.34). The association between nursery proximity and childhood leukemia was unchanged or only slightly attenuated when controlling for calculated fields or power line distance (Nguyen et al., 2022).

Being exposed to multiple environmental exposures at the same time, such as MFs and pesticides, is likely throughout daily life. It is possible that concurrent human exposure to magnetic fields and other environmental exposures may produce a modified effect and as a result, affect cancer development (Kostoff & Lau, 2017). Animal studies have looked into this possible modified effect and have found that bee colonies exposed to both pesticides and extremely low frequency magnetic fields had worse colony survival, disease development and aberrant behavior outcomes (Lupi et al., 2021). Additionally, peripubertal male rats that were concurrently exposed to both MFs and high levels of the herbicide atrazine had significant differences in mast cell levels compared to peripubertal male rats solely exposed to high doses of atrazine (Rajkovic et al., 2010).

We extend our previous work by examining pesticide use types, pesticide chemical classes and specific pesticide active ingredients to elucidate their relationship with childhood leukemia as well as whether they modify previously observed associations between childhood leukemia and high voltage power lines or MF exposure.

4.3 Methods

Case and control selection

Childhood leukemia cases younger than 16 years of age that were diagnosed in the state of California (1988-2008) were retrieved from the California Cancer Registry (CCR) (California Cancer Registry, 2020). Obtained cases were randomly matched based on their date of birth (± 6 months) and sex to controls from the California Birth Registry records (CBR; California Department of Public Health, Vital Statistics Branch). Controls were excluded if they had any form of cancer diagnosed in California prior to the case's date of diagnosis. We identified 6,645 childhood leukemia cases from the CCR that satisfied our inclusion criteria. The bulk of retrieved childhood leukemia cases were born in California, resulting in 87.1% (n=5,788) of cases being linked to the CBR; controls were matched to cases 1:1.

Several variables utilized in analysis were obtained from the CBR including mother's residential address at the date of birth, birthdate, sex, maternal and paternal education, parental race/ethnicity, and form of payment for delivery. Socioeconomic status (SES) was categorized as a binary variable (high or low) based on available subject-level information listed in preferential order: father's education level (high if greater than 12 years, low if otherwise), mother's education level (high if greater than 12 years, low if otherwise), payment method for the hospital delivery (low if government assisted or no coverage, high if otherwise), or community-based SES information as determined by United States Census Bureau data. Case and control residences at birth were geocoded to latitude and longitude coordinates. Study methods have been previously described in detail (Kheifets et al., 2015; Oksuzyan et al., 2015b).

Exposure assessment

Proximity to high voltage power lines for subjects was determined by aerial satellite images, geographic information system (GIS) data from electric power companies as well as in-person visits to residences with potentially higher than background MF levels due to their proximity to power lines (Vergara et al., 2015). Distance, phasing information and historical load were utilized to determine calculated MF for subjects' birth residences. Study methods have been previously described in detail (Kheifets et al., 2015; Vergara et al., 2015).

To identify plant nurseries, we utilized two databases: the California Department of Food and Agriculture (CDFA) and the California Department of Pesticide Regulation Pesticide Use Reporting (PUR). Subject residential proximity to plant nurseries was determined based on their geocoded birth address. Pesticide usage was obtained from the PUR database. PUR pesticide applications that occurred at plant nurseries were mapped in GIS based on the California Public Land Survey System (PLSS) grid system. PUR provides pesticide application locations with an accuracy of approximately 1 mi^2. Subjects who resided where these pesticide application areas occurred within the PLSS grid system were selected for more detailed geospatial evaluation. We then combined historic aerial satellite images with PUR data to more accurately determine the location of nursery pesticide applications; this allowed us to determine pesticide applications within an area that was smaller than the approximate native 1 mi^2 PUR data. Google Earth aerial satellite images that were matched as closely as possible to subject birth year were utilized to confirm plant nursery presence as well as residential proximity to the closest nursery footprint border/pesticide application. For these analyses we focus on subjects who resided within 600 m of a nursery.

Intended pesticide use and chemical class were classified based on the Pesticide Action Network (PAN) Pesticide Info database (Pesticide Action Network, 2022). Pesticides were classified as Group 1/2A, carcinogenic or probably carcinogenic to humans, based on the International Agency for Research on Cancer (IARC) classifications (IARC, 2022). Additional study methods have been described previously (Nguyen et al., 2021). Exposure assessments were developed to ensure high sensitivity by utilizing a multi-step process. Additionally, all assessments were conducted blind to case-control status.

Statistical analysis

Distance between high voltage (200+ kV) power lines and subject residences was categorized as 0-50, 50-150, 150-300, or ⩾300 m (referent). Calculated magnetic fields exposure for subjects was categorized as ⩾0.4, 0.2–0.4, 0.1–0.2, and 0–0.1 µT (referent). Subjects within 600 meters of a PUR pesticide application were categorized as exposed and subjects not exposed to any PUR pesticide application were categorized as unexposed (referent). A buffer of 600 m was selected to ensure adequate distance to accurately capture pesticide exposure data as well as based on prior studies.

Main study analyses were performed on subjects with residential addresses that were geocoded at the highest accuracy/resolution, the street segment or parcel level (n = 9,714); this restriction resulted in breaking some matched subjects and lead to our use of unconditional rather than conditional logistic regression. We controlled for the matching variables (age and sex) as well as the potential confounders SES and race/ethnicity (White, Black, Hispanic, Asian, Other). Multiple imputation was conducted for missing data on race/ethnicity. Statistical analyses followed an *a priori* developed plan.

We examined the relationship between pesticide exposure and childhood leukemia risk by fitting unconditional logistic regression models with the outcome as case-control status and the exposure as pesticide type, chemical class, or specific active ingredient, controlling for age, sex, SES and race/ethnicity. The reference group was subjects not exposed to any type of PUR pesticide application.

To examine whether pesticide exposure was a confounder for the relationship between childhood leukemia and power line proximity or magnetic fields exposure, we conducted confounder analyses. These analyses used unconditional logistic regression modeling with the outcome as childhood leukemia and the exposure as power line proximity or magnetic fields; odds ratios were obtained without adjustment for pesticide exposure and with adjustment for specific pesticide exposures identified as risk factors in the previous analyses, for comparison; the models controlled for age, sex, SES and race/ethnicity. The confounder analyses were done under the assumption of no uncontrolled confounding.

We were not able to fit models with interaction terms in order to examine whether pesticide exposure was an effect modifier, due to small numbers. We therefore examined whether pesticide exposure modified the risk associated with high magnetic fields exposure or power line proximity by fitting models with the outcome as case-control status and the exposure as high magnetic fields exposure or power line proximity and examining whether the odds ratio for the association changed when the analysis was restricted to subjects minimally exposed to pesticides. These analyses were conducted for each pesticide exposure identified as a potential risk factor.

We performed sensitivity analyses by evaluating whether childhood leukemia risk estimates remained stable when restricting analyses to subjects born in the year 1990 and later (when PUR data contained more details), stratifying by age at diagnosis (<5 years, ≥5 years), and restricting childhood leukemia subtype to ALL.

SAS (Version 9.4, The SAS Institute, Cary, NC) was used for the analyses. Approval for CAPS was received from University of California, Los Angeles Office for the Protection of Research Subjects and the State of California Committee for the Protection of Human Subjects.

4.4 Results

Table 4.1 presents childhood leukemia associations with nursery pesticide applications, classified by their active ingredient, chemical class, and intended use. Classification of pesticide active ingredients by chemical class, intended use, and IARC grouping are presented in Supplemental Table 4.1.

Permethrin (OR 1.49, 95% CI 0.83-2.67), chlorpyrifos (OR 1.29, 95% CI 0.89-1.87), dimethoate (OR 1.79, 95% CI 0.85-3.76), mancozeb (OR 1.41, 95% CI 0.85-2.33), oxyfluorfen (OR 1.41, 95% CI 0.75-2.66), oryzalin (OR 1.60, 95% CI 0.97-2.63), and pendimethalin (OR 1.82, 95%

CI 0.81-1.25) all presented elevated childhood leukemia risks. In analyses focusing on pesticide chemical classes, organophosphorus (OR 1.14, 95% CI 0.73-1.78) and carbamate (OR 1.14, 95% CI 0.81-1.61) presented increased associations with childhood leukemia. Additionally, subjects exposed to rodenticides (OR 1.42, 95% CI 0.78-2.56) had increased childhood leukemia risks. Subjects who were exposed to pesticides classified by IARC as carcinogenic or probably carcinogenic to humans also had increased childhood leukemia risks (OR 1.41, 95% CI 0.82-2.45).

Table 4.2 presents confounder analyses for the association between childhood leukemia and selected pesticides, power line proximity and magnetic fields. Pesticides with an OR of ≥1.60 were selected for confounder analyses; these included dimethoate, oryzalin and pendimethalin. Associations for calculated magnetic fields and distance to power line were consistent with previous publications. Childhood leukemia relationships with calculated fields and distance to power lines remained virtually unchanged after adjusting for specific pesticide exposure.

Table 4.3 provides analyses for interaction effects by excluding and restricting subjects based on other putative risk factors, i.e., subjects that reside closest (<50 m) of a high voltage power line, exposed to high (≥0.4 μT) calculated fields, etc. Childhood leukemia associations for subjects exposed to high calculated fields (OR 1.52, 95% CI 0.70-3.24) remained similar when we excluded subjects exposed to dimethoate or pendimethalin, and somewhat attenuated when we excluded subjects exposed to oryzalin (OR 1.31, 95% CI 0.70-2.46). Associations for childhood leukemia and power line proximity remained similar when other putative risk factors were excluded.

Table 4.4 presents sensitivity analyses for childhood leukemia risks and pesticide exposures with sufficient subject count. We examined the relationship with the ALL subtype (the most common subtype of childhood leukemia), age of diagnosis <5 years and ≥5 years (peak incidence occurs between 2 and 5 years of age) and birth years from 1990 and on (when PUR reporting contained more details). Overall, childhood leukemia risks remained stable for analyses restricted to the ALL subtype and for birth years from 1990 and on. When we stratified on age of diagnosis, we observed higher ORs overall for age of diagnosis 5 years and older.

Table 4.1: Risk of childhood leukemia and nursery pesticide applications within 600 m of residences

	Exposed Cases	Exposed Controls	OR (95% CI)
Pesticide			
Glyphosate	51	45	1.15 (0.83-1.58)
Permethrin	15	9	1.49 (0.83-2.67)
Acephate	36	40	0.97 (0.68-1.37)
Abamectin	26	33	0.87 (0.59-1.29)
Chlorpyrifos	35	28	1.29 (0.89-1.87)
Diazinon	31	32	1.09 (0.75-1.57)
Iprodione	22	21	1.12 (0.72-1.74)
Metalaxyl	26	34	0.86 (0.59-1.25)
Thiophanate-Methyl	22	25	0.97 (0.63-1.49)
Imidacloprid	7	7	0.95 (0.46-1.97)
Dimethoate	10	5	1.79 (0.85-3.76)
Tau-Fluvalinate	25	32	0.89 (0.60-1.31)
Malathion	28	22	1.19 (0.79-1.79)
Fosetyl-Al	14	12	1.20 (0.69-2.09)
Dienochlor	20	24	0.91 (0.59-1.41)
Mancozeb	19	13	1.41 (0.85-2.33)
Oxyfluorfen	11	9	1.41 (0.75-2.66)
Oryzalin	22	12	1.60 (0.97-2.63)
Pendimethalin	9	4	1.82 (0.81-1.25)
Chemical Class			
Organophosphorus compounds	72	67	1.14 (0.73-1.78)
Carbamate	40	36	1.14 (0.81-1.61)
Pyrethroid	37	46	0.86 (0.61-1.20)
Organochlorine	33	38	0.93 (0.65-1.32)

Intended Use			
Insecticide	80	79	1.06 (0.76-1.46)
Herbicide	67	63	1.12 (0.83-1.53)
Fungicide	67	71	0.95 (0.70-1.29)
Acaracide	56	55	1.08 (0.79-1.47)
Plant growth regulator	15	15	1.12 (0.67-1.89)
Rodenticide	14	9	1.42 (0.78-2.56)
Molluscicide	30	25	1.22 (0.82-1.81)
IARC Classification			
Group 1/2A	68	57	1.41 (0.82-2.45)

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values.
m meters, OR odds ratio, CI confidence interval, IARC International Agency for Research on Cancer

Table 4.2: Childhood leukemia risk as a function of pesticide exposure, distance to power lines 200+ kV, magnetic fields, or a combination of exposures, California Power Line Study

		No Adjustment	Adjusting for Dimethoate	Adjusting for Oryzalin	Adjusting for Pendimethalin
Calculated fields, µT	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<0.1	4824/4782	Ref	Ref	Ref	Ref
0.1-0.2	24/27	0.84 (0.48-1.45)	0.84 (0.48-1.45)	0.84 (0.48-1.45)	0.84 (0.48-1.45)
0.2-0.4	14/15	0.97 (0.47-2.02)	0.95 (0.47-2.02)	0.97 (0.47-2.02)	0.97 (0.47-2.02)
≥0.4	17/11	1.52 (0.70-3.24)	1.52 (0.70-3.24)	1.52 (0.70-3.24)	1.51 (0.70-3.24)
Distance to PL, m	Ca/Co	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
≥300	4714/4652	Ref	Ref	Ref	Ref
150-300	92/110	0.81 (0.62-1.08)	0.81 (0.61-1.07)	0.81 (0.61-1.08)	0.81 (0.61-1.08)
50-150	50/58	0.84 (0.60-1.18)	0.84 (0.60-1.18)	0.84 (0.60-1.18)	0.85 (0.60-1.18)
0-50	23/15	1.46 (0.88-2.42)	1.46 (0.88-2.42)	1.46 (0.88-2.42)	1.45 (0.88-2.41)

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values.
PL power line, m meters, Ca cases, Co controls, kV kilovolts, µT microTesla, OR odds ratio, CI confidence interval, Ref reference

Table 4.3: Childhood leukemia risk as a function of pesticide exposure, calculated fields, and distance to power lines 200+ kV, with exclusions and restrictions on subjects based on putative exposures, California Power Line Study

Subjects	Calculated Fields ≥0.4 µT (Ref: <0.1 µT)		Power line <50 m (Ref: >600 m)	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
No Exclusion	17/11	1.52 (0.70-3.24)	23/15	1.46 (0.88-2.42)
Exclude if exposed to Dimethoate	17/11	1.51 (0.71-3.25)	23/13	1.64 (0.94-2.86)
Exclude if exposed to Oryzalin	15/11	1.31 (0.70-2.46)	21/14	1.45 (0.86-2.45)
Exclude if exposed to Pendimethalin	17/11	1.51 (0.70-3.23)	23/15	1.45 (0.88-2.41)

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values.
m meters, kV kilovolts, µT microTesla, Ca cases, Co controls, OR odds ratio, CI confidence interval, Ref reference

Table 4.4: Sensitivity analysis for risk of childhood leukemia and nursery pesticide applications within 600 m of residences

	Ca	Co	OR (95% CI)	Ca	Co	OR	Ca	Co	OR (95% CI)	Ca	Co	OR (95% CI)
Pesticide	ALL subtype			Age of diagnosis <5 years			Age of diagnosis ≥5 years			Birth years ≥1990		
Glyphosate	39	39	1.03 (0.72-1.47)	31	28	1.08 (0.72-1.62)	20	17	1.27 (0.73-2.22)	47	44	1.09 (0.75-1.62)
Acephate	29	35	0.89 (0.61-1.30)	23	27	0.86 (0.56-1.33)	13	13	1.25 (0.66-2.33)	32	38	0.93 (0.63-1.45)
Abamectin	21	30	0.77 (0.50-1.18)	17	22	0.74 (0.45-1.20)	9	11	1.15 (0.55-2.43)	23	32	0.79 (0.52-1.23)
Chlorpyrifos	27	24	1.11 (0.73-1.67)	24	20	1.20 (0.76-1.88)	11	8	1.52 (0.75-3.10)	32	28	1.20 (0.77-1.71)
Diazinon	27	29	1.02 (0.69-1.52)	16	17	1.03 (0.62-1.71)	15	15	1.11 (0.62-2.00)	28	32	0.99 (0.66-1.48)
Iprodione	18	18	1.03 (0.63-1.68)	15	13	1.21 (0.70-2.09)	7	8	1.25 (0.55-2.83)	20	20	1.05 (0.67-1.72)
Metalaxyl	19	31	0.70 (0.45-1.06)	14	21	0.73 (0.44-1.21)	12	13	1.22 (0.65-2.31)	22	29	0.75 (0.51-1.09)
Thiophanate-Methyl	18	24	0.85 (0.54-1.35)	16	17	0.95 (0.57-1.58)	6	8	1.14 (0.49-2.66)	21	25	0.93 (0.57-1.41)
Tau-Fluvalinate	18	29	0.71 (0.46-1.09)	18	20	0.93 (0.58-1.51)	7	12	0.78 (0.38-1.61)	23	30	0.84 (0.51-1.20)
Malathion	22	21	1.02 (0.65-1.60)	21	14	1.35 (0.82-2.24)	7	8	1.01 (0.46-2.23)	26	21	1.24 (0.84-1.95)
Dienochlor	15	22	0.76 (0.47-1.22)	15	16	0.93 (0.55-1.58)	5	8	0.66 (0.29-1.54)	18	22	0.87 (0.54-1.31)
Mancozeb	14	12	1.14 (0.66-1.98)	10	8	1.13 (0.58-2.23)	9	5	1.65 (0.72-3.78)	17	13	1.27 (0.73-2.08)
Chemical Class												
Organophosphorus compounds	60	57	1.12 (0.80-1.57)	48	45	1.11 (0.76-1.63)	24	22	1.27 (0.74-2.17)	67	61	1.18 (0.82-1.62)
Carbamate	31	34	0.94 (0.65-1.38)	28	21	1.33 (0.86-2.07)	12	15	1.01 (0.55-1.87)	37	35	1.11 (0.74-1.53)
Pyrethroid	30	41	0.77 (0.53-1.12)	27	30	0.93 (0.62-1.40)	10	16	0.75 (0.40-1.41)	35	44	0.84 (0.56-1.16)

Organochlorine	25	34	0.77 (0.52-1.14)	23	27	0.88 (0.57-1.37)	10	11	0.98 (0.50-1.91)	31	36	0.92 (0.63-1.29)
Intended Use												
Insecticide	65	67	1.05 (0.73-1.51)	55	53	1.10 (0.71-1.69)	25	26	1.14 (0.66-1.96)	74	72	1.07 (0.77-1.53)
Herbicide	54	57	0.99 (0.71-1.39)	42	38	1.14 (0.78-1.67)	25	25	1.12 (0.65-1.94)	62	61	1.03 (0.75-1.42)
Fungicide	53	62	0.81 (0.58-1.15)	47	46	1.02 (0.69-1.50)	20	25	0.81 (0.47-1.40)	57	62	0.88 (0.62-1.20)
Acaracide	47	50	0.95 (0.68-1.33)	39	38	1.06 (0.72-1.55)	17	17	1.16 (0.66-2.06)	50	50	1.05 (0.72-1.38)
Plant growth regulator	13	13	1.15 (0.65-2.04)	9	9	1.02 (.53-1.98)	6	6	1.54 (0.61-3.90)	14	15	1.08 (0.62-1.83)
Molluscicide	24	21	1.13 (0.73-1.74)	22	14	1.50 (0.92-2.44)	8	11	0.77 (0.37-1.59)	27	24	1.17 (0.74-1.77)
Rodenticide	12	8	1.37 (0.72-2.61)	11	5	1.67 (0.78-3.60)			N/A	11	9	1.20 (0.64-2.25)
IARC												
Group 1/2A	54	50	1.29 (0.73-2.29)	44	37	1.57 (0.79-3.12)	24	20	1.42 (0.82-2.46)	64	55	1.35 (0.77-2.37)

All models were adjusted for age, sex, socioeconomic status, and race/ethnicity, using multiple imputation for missing values.
m meters, Ca cases, Co controls, ALL acute lymphocytic leukemia, OR odds ratio, CI confidence interval, N/A not applicable, IARC International Agency for Research on Cancer

4.5 Discussion

In our statewide, records-based case-control study of childhood leukemia and pesticide exposures, we observed elevated childhood leukemia risks for exposure to several individual pesticides used throughout California. Subjects residing within 600 m of pesticide applications of: permethrin, chlorpyrifos, dimethoate, mancozeb, oxyfluorfen, oryzalin, and pendimethalin had increased risks for childhood leukemia. Childhood leukemia associations with power line proximity and calculated MF exposure were not explained by pesticide exposure.

Permethrin is a commonly applied pyrethroid insecticide to which subjects may be exposed through various routes, including through skin contact, ingestion and inhalation; previous studies have found permethrin residue in food, dust, hand and hard floor surface wipes, as well as indoor air samples within households (Morgan, 2012). The widespread use in both consumer and industrial products increases the potential for exposure and concern, as there may be potential adverse health effects of permethrin exposure. Previous studies have studied permethrin exposure and reported leukemia-associated gene aberrations (Navarrete-Meneses et al., 2017, 2018). Exposure to permethrin produces breaks and fusions in genes involved in leukemia development, supporting its role in the etiology of leukemia (Navarrete-Meneses et al., 2017; Pui et al., 2008). A hospital-based case-control study conducted in 13 Brazilian states reported increased childhood leukemia risks among children born to mothers with maternal exposure to permethrin (Ferreira et al., 2013). Exposure to other pesticides, pendimethalin, oryzalin, as well as both herbicides and rodenticides, have also been observed to increase childhood leukemia risks (Bailey, Infante-Rivard, et al., 2015; Park et al., 2020).

Our epidemiologic observations are plausible given animal and human data on individual pesticides and findings from other epidemiologic studies. Animal studies have found that both male and female rats developed monocytic leukemia when given the insecticide, dimethoate; additionally, increased granulocytic leukemia incidence occurred with dermal applications of the pesticide (Reuber, 1984). Dimethoate exposure may inflict DNA damage and affect the cell cycle (Nazam et al., 2020). Mancozeb, a commonly used fungicide, produced genotoxic and oxidative damage in rat cells, which provides support for its role in cancer development. Animal studies on the herbicide, oxyfluorfen, demonstrated that exposure plays a role in developing other forms of cancer (Narayanan et al., 2015; Takahashi et al., 1994, 1997). Another study examined California farm workers and pesticide exposure and reported elevated risk (OR 2.35, 95% CI 1.12-2.48) of adult leukemia and mancozeb exposure (Mills et al., 2005). A study conducted on human primary bone marrow mesenchymal stem/stromal cells and exposure to a low dose mixture of pesticides, that included dimethoate and mancozeb, reported oxidative stress, DNA damage, a decrease in aldehyde dehydrogenase-2 activity, and an altered ability of primitive hematopoiesis, providing evidence that low dose exposures to pesticides may be conducive to the development of a pre-leukemic disease.

When we grouped pesticides by intended use, we observed possible elevated childhood leukemia risks for rodenticide exposure. A pooled analysis that utilized 12 case-control studies in the Childhood Leukemia International Consortium (CLIC) also observed increased risk for childhood leukemia with rodenticide exposure (Bailey, Infante-Rivard, et al., 2015). IARC exposures that were considered to be carcinogenic or probably carcinogenic to humans presented increased childhood leukemia risks.

Controlling for pesticide exposure did not result in material change in associations for childhood leukemia and distance to high voltage power lines or magnetic fields exposure. As a result, our findings do not support pesticide exposure (dimethoate, oryzalin, pendimethalin) as a significant confounder.

Strengths of our study include our large sample size, with 5,788 cases and an equal number of controls. Moreover, cases and controls were obtained from population-based registries with complete registration for the state of California ensuring high quality data as well as avoiding participation bias. Additionally, all assessments were conducted blinded to case and control status to avoid information bias. Pesticide applications were obtained from PUR; PUR is recognized for its data quality and as the most comprehensive pesticide reporting program in the world, thus ensuring high data quality for this study (California Department of Pesticide Regulation, 2021). We also verified pesticide applications used at nurseries by utilizing historic aerial satellite images to confirm nursery presence where pesticide applications occurred as well as to determine proximity to subjects.

Possible limitations for our study were PUR's spatial data resolution; PUR incorporates reporting based on the Public Land Survey System (PLSS), which reports the location of pesticide applications within approximately 1 mi^2. This possible limitation was addressed by confirming pesticide application areas by augmenting PUR data with historic aerial satellite images to visually confirm nursery pesticide application areas as well as determine subject proximity to the pesticide application area. Some plant nurseries have irregularly shaped footprints and as a result, using historic aerial satellite images was imperative to accurately capture subject exposures by increasing the native data resolution of the pesticide application location as well as accurately determine the proximity of nursery pesticide applications. By combining historic aerial satellite images with PUR data, we were able to more finely determine where pesticide applications occurred and as a result examine the relationship between childhood leukemia and pesticides on a more fine scale that would not be possible natively.

Numerous studies have reported on associations between childhood leukemia and MF exposure. Several potential risk factors for childhood leukemia may also act as confounders, including viral exposure, SES, residential mobility, housing type, and other environmental exposures (World Health Organization, 2007). Individual studies and pooled analyses examining these other potential risk factors have reported that childhood leukemia risk did not materially change after adjustment, suggesting that these other factors did not confound the relationship between MF and childhood leukemia (Amoon, Crespi, et al., 2018b). To better understand associations between childhood leukemia and MF exposure and to search for potential factors that may explain observed associations, we examined if pesticides materially changed these associations after adjustment. We did not find support that several specific pesticides confound the relationship between childhood leukemia and high voltage power line proximity or calculated fields.

In conclusion, our findings do not support pesticides as an explanation for observed childhood leukemia and MF associations. However, several pesticides may be independent risk factors for childhood leukemia, and further research should be done to better understand these observed elevated risks. The ubiquitous nature of pesticide use may result in widespread exposure for many people; therefore, it is imperative to understand the potential effects of exposure, as they may have deleterious effects on health.

4.6 Appendix

Supplemental Table 4.1: Classification of pesticide active ingredients

Pesticide	**Chemical Class**	**Intended Use**	**IARC 1/2A**
Glyphosate	Other	Herbicide	Yes
Permethrin	Pyrethroid	Insecticide	No
Acephate	Organophosphorus	Insecticide	No
Abamectin	Other	Insecticide	No
Chlorpyrifos	Organophosphorus	Insecticide	No
Diazinon	Organophosphorus	Insecticide	Yes
Iprodione	Other	Fungicide	No
Metalaxyl	Other	Fungicide	No
Thiophanate-Methyl	Other	Fungicide	No
Imidacloprid	Other	Insecticide	No
Dimethoate	Organophosphorus	Insecticide	No
Tau-Fluvalinate	Pyrethroid	Insecticide	No
Malathion	Organophosphorus	Insecticide	Yes
Fosetyl-Al	Other	Fungicide	No
Dienochlor	Organochlorine	Insecticide	No
Mancozeb	Other	Fungicide	No
Oxyfluorfen	Other	Herbicide	No
Oryzalin	Other	Herbicide	No
Pendimethalin	Other	Herbicide	No

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Chapter 5. Conclusion and Public Health Relevance

This dissertation examined the role pesticides and commercial plant nurseries may have in childhood leukemia risks, both independently as well as their potential role in explaining observed childhood leukemia risks with high magnetic fields exposure or high voltage power line proximity. We found that subjects living in close proximity (<75 m) to commercial plant nurseries had elevated childhood leukemia risks, with the acute lymphocytic leukemia subtype having the most elevated risk. Our study was the first to evaluate childhood leukemia risk and proximity to commercial plant nurseries. Commercial plant nurseries present a unique possible chronic exposure pathway for people, as many plant nurseries are in urban environments, which may result in chronic pesticide exposure for individuals, even if they do not live in an agricultural community or are involved in agricultural work. Furthermore, urban living environments may have higher population densities, which would result in a larger amount of people potentially exposed in a smaller area compared to less urban environments.

We further expanded on childhood leukemia and pesticide work by exploring if pesticides may play a role in explaining previously observed childhood leukemia associations with high magnetic fields exposure or high voltage power line proximity. Our findings found that childhood leukemia associations with magnetic fields or high voltage power line proximity did not materially change after controlling for plant nursery proximity; therefore, our findings do not support plant nursery proximity as a strong confounder. Childhood leukemia associations with close plant nursery proximity also did not materially change when controlling for magnetic fields exposure or high voltage power line proximity; ORs remained elevated and above 2 when excluding subjects with high magnetic fields exposure or close high voltage power line proximity, thus close proximity to commercial plant nurseries may act as an independent childhood leukemia risk factor.

We observed elevated childhood leukemia risks for several specific pesticide active ingredients as well as intended pesticide target exposures. Childhood leukemia risks remained similar for magnetic fields exposure or power line proximity after adjusting for or removing pesticide exposures. Our findings suggest that pesticide exposure may act as an independent risk factor and does not explain previously observed childhood leukemia risks with calculated fields exposure or high voltage power line proximity.

The etiology of childhood leukemia is largely unknown, with ionizing radiation and certain genetic syndromes as the only established risk factors. Our findings about residing in close proximity to plant nurseries as well as exposure to pesticides provide more backing that pesticides may be a risk factor for childhood leukemia. Additionally, our findings also provide evidence that high magnetic fields exposure and close proximity to high voltage power lines are not explained by pesticide exposure. Further research should be conducted on these possible risk factors. Moreover, it is imperative to conduct research for different environments, as our findings suggest that living in close proximity to plant nurseries is a childhood leukemia risk factor, even though the subjects may not live in agricultural communities. Our studies provide evidence that interventions, policies, and further research on the etiology of childhood leukemia are required, as our living environment may act as sources of chronic exposure to potential risk factors.

References

Ahlbom, A., Day, N., Feychting, M., Roman, E., Skinner, J., Dockerty, J., Linet, M., McBride, M., Michaelis, J., Olsen, J. H., Tynes, T., & Verkasalo, P. K. (2000). A pooled analysis of magnetic fields and childhood leukaemia. *British Journal of Cancer*, *83*(5), 692–698. https://doi.org/10.1054/bjoc.2000.1376

American Cancer Society. (2021a, January 12). *Key Statistics for Childhood Cancers*. https://www.cancer.org/cancer/cancer-in-children/key-statistics.html

American Cancer Society. (2021b, January 12). *Key Statistics for Childhood Leukemia*. https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html

Amoon, A. T., Arah, O. A., & Kheifets, L. (2019). The sensitivity of reported effects of EMF on childhood leukemia to uncontrolled confounding by residential mobility: A hybrid simulation study and an empirical analysis using CAPS data. *Cancer Causes & Control*, *30*(8), 901–908. https://doi.org/10.1007/s10552-019-01189-9

Amoon, A. T., Crespi, C. M., Ahlbom, A., Bhatnagar, M., Bray, I., Bunch, K. J., Clavel, J., Feychting, M., Hémon, D., Johansen, C., Kreis, C., Malagoli, C., Marquant, F., Pedersen, C., Raaschou-Nielsen, O., Röösli, M., Spycher, B. D., Sudan, M., Swanson, J., … Kheifets, L. (2018a). Proximity to overhead power lines and childhood leukaemia: An international pooled analysis. *British Journal of Cancer*, *119*(3), 364–373. https://doi.org/10.1038/s41416-018-0097-7

Amoon, A. T., Crespi, C. M., Ahlbom, A., Bhatnagar, M., Bray, I., Bunch, K. J., Clavel, J., Feychting, M., Hémon, D., Johansen, C., Kreis, C., Malagoli, C., Marquant, F., Pedersen, C., Raaschou-Nielsen, O., Röösli, M., Spycher, B. D., Sudan, M., Swanson, J., … Kheifets, L. (2018b). Proximity to overhead power lines and childhood leukaemia: An international pooled analysis. *British Journal of Cancer*, *119*(3), 364–373. https://doi.org/10.1038/s41416-018-0097-7

Amoon, A. T., Crespi, C. M., Nguyen, A., Zhao, X., Vergara, X., Arah, O. A., & Kheifets, L. (2020). The role of dwelling type when estimating the effect of magnetic fields on childhood leukemia in the California Power Line Study (CAPS). *Cancer Causes & Control*, *31*(6), 559–567. https://doi.org/10.1007/s10552-020-01299-9

Amoon, A. T., Oksuzyan, S., Crespi, C. M., Arah, O. A., Cockburn, M., Vergara, X., & Kheifets, L. (2018). Residential mobility and childhood leukemia. *Environmental Research*, *164*, 459–466. https://doi.org/10.1016/j.envres.2018.03.016

Amoon, A. T., Swanson, J., Magnani, C., Johansen, C., & Kheifets, L. (2022). Pooled analysis of recent studies of magnetic fields and childhood leukemia. *Environmental Research*, *204*, 111993. https://doi.org/10.1016/j.envres.2021.111993

Arellano-Galindo, J., Barrera, A. P., Jiménez-Hernández, E., Zavala-Vega, S., Campos-Valdéz, G., Xicohtencatl-Cortes, J., Ochoa, S. A., Cruz-Córdova, A., Crisóstomo-Vázquez, M. del P., Fernández-Macías, J. C., & Mejía-Aranguré, J. M. (2017). Infectious Agents in Childhood Leukemia. *Archives of Medical Research*, *48*(4), 305–313. https://doi.org/10.1016/j.arcmed.2017.09.001

Atwood, D., & Paisley-Jones, C. (2017). *Pesticides Industry Sales and Usage: 2008-2012 Market Estimates*. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf

Bailey, H. D., Infante-Rivard, C., Metayer, C., Clavel, J., Lightfoot, T., Kaatsch, P., Roman, E., Magnani, C., Spector, L. G., Petridou, E., Milne, E., Dockerty, J. D., Miligi, L., Armstrong, B. K., Rudant, J., Fritschi, L., Simpson, J., Zhang, L., Rondelli, R., … Schüz, J. (2015). Home pesticide exposures and risk of childhood leukemia: Findings from the Childhood Leukemia International Consortium. *International Journal of Cancer. Journal International Du Cancer*, *137*(11), 2644–2663. https://doi.org/10.1002/ijc.29631

Bailey, H. D., Infante-Rivard, C., Metayer, C., Clavel, J., Lightfoot, T., Kaatsch, P., Roman, E., Magnani, C., Spector, L. G., Petridou, E. T., Milne, E., Dockerty, J. D., Miligi, L., Armstrong, B. K., Rudant, J., Fritschi, L., Simpson, J., Zhang, L., Rondelli, R., … Schüz, J. (2015). Home pesticide exposures and risk of childhood leukemia: Findings from the childhood leukemia international consortium. *International Journal of Cancer*, *137*(11), 2644–2663. https://doi.org/10.1002/ijc.29631

Barnum, K. J., & O'Connell, M. J. (2014). Cell Cycle Regulation by Checkpoints. *Methods in Molecular Biology (Clifton, N.J.)*, *1170*, 29–40. https://doi.org/10.1007/978-1-4939-0888-2_2

Belson, M., Kingsley, B., & Holmes, A. (2007). Risk Factors for Acute Leukemia in Children: A Review. *Environmental Health Perspectives*, *115*(1), 138–145. https://doi.org/10.1289/ehp.9023

Buffler, P. A., Kwan, M. L., Reynolds, P., & Urayama, K. Y. (2005). Environmental and genetic risk factors for childhood leukemia: Appraising the evidence. *Cancer Investigation*, *23*(1), 60–75.

Bunch, K. J., Swanson, J., Vincent, T. J., & Murphy, M. F. G. (2016). Epidemiological study of power lines and childhood cancer in the UK: Further analyses. *Journal of Radiological Protection*, *36*(3), 437–455. https://doi.org/10.1088/0952-4746/36/3/437

California Cancer Registry. (2020). *Data Standards and Reporting*. https://www.ccrcal.org/submit-data/

California Department of Food and Agriculture. (2021). *CDFA - Plant Health—Nursery Services*. https://www.cdfa.ca.gov/plant/pe/nsc/nursery/

California Department of Pesticide Regulation. (2019a). *Summary of Pesticide Use Report Data 2017*. California Department of Pesticide Regulation. https://www.cdpr.ca.gov/docs/pur/pur17rep/17sum.htm

California Department of Pesticide Regulation. (2019b, June). *Summary of Pesticide Use Report Data 2017*. https://www.cdpr.ca.gov/docs/pur/pur17rep/17sum.htm

California Department of Pesticide Regulation. (2021). *Pesticide Use Reporting (PUR)*. https://www.cdpr.ca.gov/docs/pur/purmain.htm

Carroquino, M. J., Posada, M., & Landrigan, P. J. (2012). Environmental Toxicology: Children at Risk. *Environmental Toxicology*, 239–291. https://doi.org/10.1007/978-1-4614-5764-0_11

Chang, E. T., Adami, H.-O., Boffetta, P., Cole, P., Starr, T. B., & Mandel, J. S. (2014). A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and cancer risk in humans. *Critical Reviews in Toxicology*, *44*(sup1), 1–81. https://doi.org/10.3109/10408444.2014.905767

Chen, M., Chang, C.-H., Tao, L., & Lu, C. (2015a). Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis. *Pediatrics*, *136*(4), 719–729. https://doi.org/10.1542/peds.2015-0006

Chen, M., Chang, C.-H., Tao, L., & Lu, C. (2015b). Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis. *Pediatrics*, *136*(4), 719–729. https://doi.org/10.1542/peds.2015-0006

Chokkalingam, A. P., Metayer, C., Scelo, G. A., Chang, J. S., Urayama, K. Y., Aldrich, M. C., Guha, N., Hansen, H. M., Dahl, G. V., Barcellos, L. F., Wiencke, J. K., Wiemels, J. L., & Buffler, P. A. (2012). Variation in xenobiotic transport and metabolism genes, household chemical exposures, and risk of childhood acute lymphoblastic leukemia. *Cancer Causes & Control*, *23*(8), 1367–1375. https://doi.org/10.1007/s10552-012-9947-4

Colby-Graham, M. F., & Chordas, C. (2003). The childhood leukemias. *Journal of Pediatric Nursing*, *18*(2), 87–95. https://doi.org/10.1053/jpdn.2003.9

Costa, L. G., Aschner, M., Vitalone, A., Syversen, T., & Soldin, O. P. (2004). Developmental Neuropathology of Environmental Agents. *Annual Review of Pharmacology and Toxicology*, *44*, 87. https://doi.org/10.1146/annurev.pharmtox.44.101802.121424

Crespi, C. M., Swanson, J., Vergara, X. P., & Kheifets, L. (2019a). Childhood leukemia risk in the California Power Line Study: Magnetic fields versus distance from power lines. *Environmental Research*, *171*, 530–535. https://doi.org/10.1016/j.envres.2019.01.022

Crespi, C. M., Swanson, J., Vergara, X. P., & Kheifets, L. (2019b). Childhood leukemia risk in the California Power Line Study: Magnetic fields versus distance from power lines. *Environmental Research*, *171*, 530–535. https://doi.org/10.1016/j.envres.2019.01.022

Crespi, C. M., Vergara, X. P., Hooper, C., Oksuzyan, S., Wu, S., Cockburn, M., & Kheifets, L. (2016a). Childhood leukaemia and distance from power lines in California: A population-based case-control study. *British Journal of Cancer*, *115*(1), Article 1. https://doi.org/10.1038/bjc.2016.142

Crespi, C. M., Vergara, X. P., Hooper, C., Oksuzyan, S., Wu, S., Cockburn, M., & Kheifets, L. (2016b). Childhood leukaemia and distance from power lines in California: A population-based case-control study. *British Journal of Cancer*, *115*(1), Article 1. https://doi.org/10.1038/bjc.2016.142

da Silva, E. Z. M., Jamur, M. C., & Oliver, C. (2014). Mast Cell Function. *Journal of Histochemistry and Cytochemistry*, *62*(10), 698–738. https://doi.org/10.1369/0022155414545334

Daniels, J. L., Olshan, A. F., & Savitz, D. A. (1997). Pesticides and childhood cancers. *Environmental Health Perspectives*, *105*(10), 1068–1077.

Dawson, J. B., Galvin, K., Thorne, P. S., & Rohlman, D. S. (2018). Organophosphorus pesticide residue levels in homes located near orchards. *Journal of Occupational and Environmental Hygiene*, *15*(12), 847–856. https://doi.org/10.1080/15459624.2018.1515489

Dereumeaux, C., Fillol, C., Quenel, P., & Denys, S. (2020). Pesticide exposures for residents living close to agricultural lands: A review. *Environment International*, *134*, 105210. https://doi.org/10.1016/j.envint.2019.105210

Deziel, N. C., Freeman, L. E. B., Graubard, B. I., Jones, R. R., Hoppin, J. A., Thomas, K., Hines, C. J., Blair, A., Sandler, D. P., Chen, H., Lubin, J. H., Andreotti, G., Alavanja, M. C. R., & Friesen, M. C. (2017). Relative Contributions of Agricultural Drift, Para-Occupational, and Residential Use Exposure Pathways to House Dust Pesticide Concentrations: Meta-Regression of Published Data. *Environmental Health Perspectives*, *125*(3), 296–305. https://doi.org/10.1289/EHP426

Dores, G. M., Devesa, S. S., Curtis, R. E., Linet, M. S., & Morton, L. M. (2012). Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood*, *119*(1), 34–43. https://doi.org/10.1182/blood-2011-04-347872

Fenske, R. A., Black, K. G., Elkner, K. P., Lee, C. L., Methner, M. M., & Soto, R. (1990). Potential exposure and health risks of infants following indoor residential pesticide applications. *American Journal of Public Health*, *80*(6), 689–693. https://doi.org/10.2105/ajph.80.6.689

Fenske, R. A., Lu, C., Barr, D., & Needham, L. (2002). Children’s exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. *Environmental Health Perspectives*, *110*(5), 549–553.

Ferreira, J. D., Couto, A. C., Pombo-de-Oliveira, M. S., Koifman, S., & Brazilian Collaborative Study Group of Infant Acute Leukemia. (2013). In utero pesticide exposure and leukemia in Brazilian children < 2 years of age. *Environmental Health Perspectives*, *121*(2), 269–275. https://doi.org/10.1289/ehp.1103942

Feychting, M., & Alhbom, M. (1993). Magnetic Fields and Cancer in Children Residing Near Swedish High-voltage Power Lines. *American Journal of Epidemiology*, *138*(7), 467–481. https://doi.org/10.1093/oxfordjournals.aje.a116881

Filippini, T., E. Heck, J., Malagoli, C., Del Giovane, C., & Vinceti, M. (2015). A Review and Meta-Analysis of Outdoor Air Pollution and Risk of Childhood Leukemia. *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews*, *33*(1), 36–66. https://doi.org/10.1080/10590501.2015.1002999

Filippini, T., Hatch, E. E., Rothman, K. J., Heck, J. E., Park, A. S., Crippa, A., Orsini, N., & Vinceti, M. (2019). Association between Outdoor Air Pollution and Childhood Leukemia: A Systematic Review and Dose–Response Meta-Analysis. *Environmental Health Perspectives*, *127*(4). https://doi.org/10.1289/EHP4381

Finegan, P. (1989). FIFRA Lite: A Regulatory Solution or Part of the Pesticide Problem? *Pace Environmental Law Review*, *6*(2), 615.

Freeman, N. C. G., Hore, P., Black, K., Jimenez, M., Sheldon, L., Tulve, N., & Lioy, P. J. (2005). Contributions of children’s activities to pesticide hand loadings following residential pesticide application. *Journal of Exposure Science & Environmental Epidemiology*, *15*(1), Article 1. https://doi.org/10.1038/sj.jea.7500348

Friedman, D. R., Hatch, E. E., Tarone, R., Kaune, W. T., Kleinerman, R. A., Wacholder, S., Boice, J. D. J., & Linet, M. S. (1996). Childhood Exposure to Magnetic Fields: Residential Area Measurements Compared to Personal Dosimetry. *Epidemiology*, *7*(2), 151.

Green, L. M., Miller, A. B., Agnew, D. A., Greenberg, M. L., Li, J., Villeneuve, P. J., & Tibshirani, R. (1999). Childhood leukemia and personal monitoring of residential exposures to electric and magnetic fields in Ontario, Canada. *Cancer Causes & Control: CCC*, *10*(3), 233–243. https://doi.org/10.1023/a:1008919408855

Greenland, S., Sheppard, A. R., Kaune, W. T., Poole, C., & Kelsh, M. A. (2000). A Pooled Analysis of Magnetic Fields, Wire Codes, and Childhood Leukemia: *Epidemiology*, *11*(6), 624–634. https://doi.org/10.1097/00001648-200011000-00003

Gunier, R. B., Ward, M. H., Airola, M., Bell, E. M., Colt, J., Nishioka, M., Buffler, P. A., Reynolds, P., Rull, R. P., Hertz, A., Metayer, C., & Nuckols, J. R. (2011). Determinants of Agricultural Pesticide Concentrations in Carpet Dust. *Environmental Health Perspectives*, *119*(7), 970–976. https://doi.org/10.1289/ehp.1002532

He, J.-R., Ramakrishnan, R., Hirst, J. E., Bonaventure, A., Francis, S. S., Paltiel, O., Håberg, S. E., Lemeshow, S., Olsen, S., Tikellis, G., Magnus, P., Murphy, M. F. G., Wiemels, J. L., Linet, M. S., & Dwyer, T. (2020). Maternal Infection in Pregnancy and Childhood Leukemia: A Systematic Review and Meta-analysis. *The Journal of Pediatrics*, *217*, 98-109.e8. https://doi.org/10.1016/j.jpeds.2019.10.046

Hernández, A. F., & Menéndez, P. (2016). Linking Pesticide Exposure with Pediatric Leukemia: Potential Underlying Mechanisms. *International Journal of Molecular Sciences*, *17*(4). https://doi.org/10.3390/ijms17040461

Howlader, N., Noone, A. M., Krapcho, M., Miller, D., Brest, A., Yu, M., Tatalovich, Z., Mariotto, A., Lewis, D., Chen, H., Feuer, E., & Cronin, K. (2020). *SEER Cancer Statistics Review, 1975-2017*. National Cancer Institute. https://seer.cancer.gov/csr/1975_2017/

Hwee, J., Tait, C., Sung, L., Kwong, J. C., Sutradhar, R., & Pole, J. D. (2018). A systematic review and meta-analysis of the association between childhood infections and the risk of childhood acute lymphoblastic leukaemia. *British Journal of Cancer*, *118*(1), 127–137. https://doi.org/10.1038/bjc.2017.360

IARC. (2007). *Non-ionizing Radiation, Part 1: Static and Extremely Low-frequency (ELF) Electric and Magnetic Fields* (Vol. 80). https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Non-ionizing-Radiation-Part-1-Static-And-Extremely-Low-frequency-ELF-Electric-And-Magnetic-Fields-2002

IARC. (2012). *Radiation: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* (Vol. 100D). https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Radiation-2012

IARC. (2022). *Agents Classified by the IARC Monographs, Volumes 1–132 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans*. https://monographs.iarc.who.int/agents-classified-by-the-iarc/

Juutilainen, J., Kumlin, T., & Naarala, J. (2006). Do extremely low frequency magnetic fields enhance the effects of environmental carcinogens? A meta-analysis of experimental studies. *International Journal of Radiation Biology*, *82*(1), 1–12. https://doi.org/10.1080/09553000600577839

Kabuto, M., Nitta, H., Yamamoto, S., Yamaguchi, N., Akiba, S., Honda, Y., Hagihara, J., Isaka, K., Saito, T., Ojima, T., Nakamura, Y., Mizoue, T., Ito, S., Eboshida, A., Yamazaki, S., Sokejima, S., Kurokawa, Y., & Kubo, O. (2006). Childhood leukemia and magnetic fields in Japan: A case-control study of childhood leukemia and residential power-frequency magnetic fields in Japan. *International Journal of Cancer*, *119*(3), 643–650. https://doi.org/10.1002/ijc.21374

Karalexi, M. A., Tagkas, C. F., Markozannes, G., Tseretopoulou, X., Hernández, A. F., Schüz, J., Halldorsson, T. I., Psaltopoulou, T., Petridou, E. T., Tzoulaki, I., & Ntzani, E. E. (2021). Exposure to pesticides and childhood leukemia risk: A systematic review and meta-analysis. *Environmental Pollution*, *285*, 117376. https://doi.org/10.1016/j.envpol.2021.117376

Kaune, W. T., & Zaffanella, L. E. (1992). Analysis of magnetic fields produced far from electric power lines. *IEEE Transactions on Power Delivery*, *7*(4), 2082–2091. https://doi.org/10.1109/61.157011

Kheifets, L., Ahlbom, A., Crespi, C. M., Feychting, M., Johansen, C., Monroe, J., Murphy, M. F. G., Oksuzyan, S., Preston-Martin, S., Roman, E., Saito, T., Savitz, D., Schuz, J., Simpson, J., Swanson, J., Tynes, T., Verkasalo, P., & Mezei, G. (2010). A Pooled Analysis of Extremely Low-Frequency Magnetic Fields and Childhood Brain Tumors. *American Journal of Epidemiology*, *172*(7), 752–761. https://doi.org/10.1093/aje/kwq181

Kheifets, L., Crespi, C. M., Hooper, C., Cockburn, M., Amoon, A. T., & Vergara, X. P. (2017). Residential magnetic fields exposure and childhood leukemia: A population-based case-control study in California. *Cancer Causes & Control : CCC*, *28*(10), 1117–1123. https://doi.org/10.1007/s10552-017-0951-6

Kheifets, L., Crespi, C. M., Hooper, C., Oksuzyan, S., Cockburn, M., Ly, T., & Mezei, G. (2015). Epidemiologic study of residential proximity to transmission lines and childhood cancer in California: Description of design, epidemiologic methods and study population. *Journal of Exposure Science & Environmental Epidemiology*, *25*(1), 45–52. https://doi.org/10.1038/jes.2013.48

Kheifets, L., Park, A. S., Swanson, J., & Vergara, X. (2018). Epidemiologic Studies of Extremely Low Frequency Electromagnetic Field. In *Biological and Medical Aspects of Electromagnetic Fields* (4th ed.). CRC Press.

Kheifets, L., Repacholi, M., Saunders, R., & van Deventer, E. (2005). The Sensitivity of Children to Electromagnetic Fields. *Pediatrics*, *116*(2), e303–e313. https://doi.org/10.1542/peds.2004-2541

Kheifets, L., Swanson, J., Yuan, Y., Kusters, C., & Vergara, X. (2017). Comparative analyses of studies of childhood leukemia and magnetic fields, radon and gamma radiation. *Journal of Radiological Protection*, *37*(2), 459–491. https://doi.org/10.1088/1361-6498/aa5fc7

Khong, P.-L., Ringertz, H., Donoghue, V., Frush, D., Rehani, M., Appelgate, K., & Sanchez, R. (2013). ICRP Publication 121: Radiological Protection in Paediatric Diagnostic and Interventional Radiology. *Annals of the ICRP*, *42*(2), 1–63. https://doi.org/10.1016/j.icrp.2012.10.001

Kim, K.-H., Kabir, E., & Jahan, S. A. (2017). Exposure to pesticides and the associated human health effects. *Science of The Total Environment*, *575*, 525–535. https://doi.org/10.1016/j.scitotenv.2016.09.009

Kostoff, R. N., & Lau, C. G. Y. (2017). Modified Health Effects of Non-ionizing Electromagnetic Radiation Combined with Other Agents Reported in the Biomedical Literature. In C. D. Geddes (Ed.), *Microwave Effects on DNA and Proteins* (pp. 97–157). Springer International Publishing. https://doi.org/10.1007/978-3-319-50289-2_4

Kroll, M. E., Swanson, J., Vincent, T. J., & Draper, G. J. (2010). Childhood cancer and magnetic fields from high-voltage power lines in England and Wales: A case–control study. *British Journal of Cancer*, *103*(7), 1122–1127. https://doi.org/10.1038/sj.bjc.6605795

Kumar, R., & De Jesus, O. (2021). Radiation Effects On The Fetus. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK564358/

Linet, M. S., Hatch, E. E., Kleinerman, R. A., Robison, L. L., Kaune, W. T., Friedman, D. R., Severson, R. K., Haines, C. M., Hartsock, C. T., Niwa, S., Wacholder, S., & Tarone, R. E. (2009, August 20). *Residential Exposure to Magnetic Fields and Acute Lymphoblastic Leukemia in Children* (world) [Research-article]. Http://Dx.Doi.Org/10.1056/NEJM199707033370101; Massachusetts Medical Society. https://doi.org/10.1056/NEJM199707033370101

London, S. J., Thomas, D. C., Bowman, J. D., Sobel, E., Cheng, T.-C., & Peters, J. M. (1991). Exposure to Residential Electric and Magnetic Fields and Risk of Childhood Leukemia. *American Journal of Epidemiology*, *134*(9), 923–937. https://doi.org/10.1093/oxfordjournals.aje.a116176

Lu, C., Fenske, R. A., Simcox, N. J., & Kalman, D. (2000a). Pesticide exposure of children in an agricultural community: Evidence of household proximity to farmland and take home exposure pathways. *Environmental Research*, *84*(3), 290–302. https://doi.org/10.1006/enrs.2000.4076

Lu, C., Fenske, R. A., Simcox, N. J., & Kalman, D. (2000b). Pesticide exposure of children in an agricultural community: Evidence of household proximity to farmland and take home exposure pathways. *Environmental Research*, *84*(3), 290–302. https://doi.org/10.1006/enrs.2000.4076

Lupi, D., Palamara Mesiano, M., Adani, A., Benocci, R., Giacchini, R., Parenti, P., Zambon, G., Lavazza, A., Boniotti, M. B., Bassi, S., Colombo, M., & Tremolada, P. (2021). Combined Effects of Pesticides and Electromagnetic-Fields on Honeybees: Multi-Stress Exposure. *Insects*, *12*(8), Article 8. https://doi.org/10.3390/insects12080716

Lushchak, V. I., Matviishyn, T. M., Husak, V. V., Storey, J. M., & Storey, K. B. (2018). Pesticide toxicity: A mechanistic approach. *EXCLI Journal*, *17*, 1101–1136. https://doi.org/10.17179/excli2018-1710

Lyengar, V., & Shimanovsky, A. (2021). Leukemia. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK560490/

Ma, X., Buffler, P. A., Gunier, R. B., Dahl, G., Smith, M. T., Reinier, K., & Reynolds, P. (2002). Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environmental Health Perspectives*, *110*(9), 955–960.

Maia, R. da R. P., & Wünsch, V. (2013). Infection and childhood leukemia: Review of evidence. *Revista de Saúde Pública*, *47*(6), 1172–1185. https://doi.org/10.1590/S0034-8910.2013047004753

Mason, A. F. (1928). Spraying, Dusting and Fumigating of Plants. A Popular Handbook on Crop Protection. *Spraying, Dusting and Fumigating of Plants. A Popular Handbook on Crop Protection.* https://www.cabdirect.org/cabdirect/abstract/19280500986

McBride, M. L., Gallagher, R. P., Thériault, G., Armstrong, B. G., Tamaro, S., Spinelli, J. J., Deadman, J. E., Fincham, S., Robson, D., & Choi, W. (1999). Power-Frequency Electric and Magnetic Fields and Risk of Childhood Leukemia in Canada. *American Journal of Epidemiology*, *149*(9), 831–842. https://doi.org/10.1093/oxfordjournals.aje.a009899

Metayer, C., Petridou, E., Aranguré, J. M. M., Roman, E., Schüz, J., Magnani, C., Mora, A. M., Mueller, B. A., de Oliveira, M. S. P., Dockerty, J. D., McCauley, K., Lightfoot, T., Hatzipantelis, E., Rudant, J., Flores-Lujano, J., Kaatsch, P., Miligi, L., Wesseling, C., Doody, D. R., … Clavel, J. (2016). Parental Tobacco Smoking and Acute Myeloid Leukemia. *American Journal of Epidemiology*, *184*(4), 261–273. https://doi.org/10.1093/aje/kww018

Mills, P. K., Yang, R., & Riordan, D. (2005). Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. *Cancer Causes & Control: CCC*, *16*(7), 823–830. https://doi.org/10.1007/s10552-005-2703-2

Morgan, M. K. (2012). Children's Exposures to Pyrethroid Insecticides at Home: A Review of Data Collected in Published Exposure Measurement Studies Conducted in the United States. *International Journal of Environmental Research and Public Health*, *9*(8), 2964–2985. https://doi.org/10.3390/ijerph9082964

Moya, J., Bearer, C. F., & Etzel, R. A. (2004). Children's behavior and physiology and how it affects exposure to environmental contaminants. *Pediatrics*, *113*(4 Suppl), 996–1006.

Narayanan, K. B., Ali, M., Barclay, B. J., Cheng, Q. (Shawn), D'Abronzo, L., Dornetshuber-Fleiss, R., Ghosh, P. M., Gonzalez Guzman, M. J., Lee, T.-J., Leung, P. S., Li, L., Luanpitpong, S., Ratovitski, E., Rojanasakul, Y., Romano, M. F., Romano, S., Sinha, R. K., Yedjou, C., Al-Mulla, F., … Park, H. H. (2015). Disruptive environmental chemicals and cellular mechanisms that confer resistance to cell death. *Carcinogenesis*, *36*(Suppl 1), S89–S110. https://doi.org/10.1093/carcin/bgv032

National Cancer Institute. (2019, January 3). *Electromagnetic Fields and Cancer* (nciglobal,ncienterprise) [CgvArticle]. https://www.cancer.gov/about-cancer/causes-prevention/risk/radiation/electromagnetic-fields-fact-sheet

National Cancer Institute. (2020). *SEER Cancer Statistics Review (CSR), 1975-2017*. https://seer.cancer.gov/csr/1975_2017/sections.html

National Institute of Environmental Health Sciences. (2021, February 10). *Pesticides*. https://www.niehs.nih.gov/health/topics/agents/pesticides/index.cfm

Navarrete-Meneses, M. P., Pedraza-Meléndez, A. I., Salas-Labadía, C., Moreno-Lorenzana, D., & Pérez-Vera, P. (2018). Low concentrations of permethrin and malathion induce numerical and structural abnormalities in KMT2A and IGH genes in vitro. *Journal of Applied Toxicology*, *38*(9), 1262–1270. https://doi.org/10.1002/jat.3638

Navarrete-Meneses, M. P., Salas-Labadía, C., Sanabrais-Jiménez, M., Santana-Hernández, J., Serrano-Cuevas, A., Juárez-Velázquez, R., Olaya-Vargas, A., & Pérez-Vera, P. (2017). "Exposure to the insecticides permethrin and malathion induces leukemia and lymphoma-associated gene aberrations in vitro." *Toxicology in Vitro*, *44*, 17–26. https://doi.org/10.1016/j.tiv.2017.06.013

Nazam, N., Lone, M. I., Hamid, A., Qadah, T., Banjar, A., Alam, Q., Saeed, M., & Ahmad, W. (2020). Dimethoate Induces DNA Damage and Mitochondrial Dysfunction Triggering Apoptosis in Rat Bone-Marrow and Peripheral Blood Cells. *Toxics*, *8*(4), E80. https://doi.org/10.3390/toxics8040080

Negrini, S., Gorgoulis, V. G., & Halazonetis, T. D. (2010). Genomic instability—An evolving hallmark of cancer. *Nature Reviews Molecular Cell Biology*, *11*(3), Article 3. https://doi.org/10.1038/nrm2858

Nguyen, A., Crespi, C. M., Vergara, X., Chun, N., & Kheifets, L. (2021). Residential proximity to plant nurseries and risk of childhood leukemia. *Environmental Research*, *200*, 111388. https://doi.org/10.1016/j.envres.2021.111388

Nguyen, A., Crespi, C. M., Vergara, X., & Kheifets, L. (2022). Commercial outdoor plant nurseries as a confounder for electromagnetic fields and childhood leukemia risk. *Environmental Research*, *212*(Pt C), 113446. https://doi.org/10.1016/j.envres.2022.113446

Nybo Andersen, A.-M., & Urhoj, S. K. (2017). Is advanced paternal age a health risk for the offspring? *Fertility and Sterility*, *107*(2), 312–318. https://doi.org/10.1016/j.fertnstert.2016.12.019

Oksuzyan, S., Crespi, C., Cockburn, M., Mezei, G., & Kheifets, L. (2012). Birth weight and other perinatal characteristics and childhood leukemia in California. *Cancer Epidemiology*, *36*(6), e359–e365. https://doi.org/10.1016/j.canep.2012.08.002

Oksuzyan, S., Crespi, C., Cockburn, M., Mezei, G., Vergara, X., & Kheifets, L. (2015a). Race/ethnicity and the risk of childhood leukaemia: A case-control study in California. *Journal of Epidemiology and Community Health*, *69*(8), 795–802. https://doi.org/10.1136/jech-2014-204975

Oksuzyan, S., Crespi, C., Cockburn, M., Mezei, G., Vergara, X., & Kheifets, L. (2015b). Socio-Economic Status and Childhood Leukemia in California. *Journal of Cancer Prevention & Current Research*, *Volume 3*(Issue 4). https://doi.org/10.15406/jcpcr.2015.03.00087

Park, A. S., Ritz, B., Yu, F., Cockburn, M., & Heck, J. E. (2020). Prenatal pesticide exposure and childhood leukemia – A California statewide case-control study. *International Journal of Hygiene and Environmental Health*, *226*, 113486. https://doi.org/10.1016/j.ijheh.2020.113486

Pesticide Action Network. (2022). *Pesticide Info | Search by a chemical or product*. PesticideInfo. https://www.pesticideinfo.org/

Pui, C.-H., Robison, L. L., & Look, A. T. (2008). Acute lymphoblastic leukaemia. *The Lancet*, *371*(9617), 1030–1043. https://doi.org/10.1016/S0140-6736(08)60457-2

Quandt, S. A., Arcury, T. A., Rao, P., Snively, B. M., Camann, D. E., Doran, A. M., Yau, A. Y., Hoppin, J. A., & Jackson, D. S. (2004). Agricultural and residential pesticides in wipe samples from farmworker family residences in North Carolina and Virginia. *Environmental Health Perspectives*, *112*(3), 382–387.

Rajkovic, V., Matavulj, M., & Johansson, O. (2010). Combined exposure of peripubertal male rats to the endocrine-disrupting compound atrazine and power-frequency electromagnetic fields causes degranulation of cutaneous mast cells: A new toxic environmental hazard? *Archives of Environmental Contamination and Toxicology*, *59*(2), 334–341. https://doi.org/10.1007/s00244-010-9477-6

Rao, K. N., & Brown, M. A. (2008). Mast cells: Multifaceted immune cells with diverse roles in health and disease. *Annals of the New York Academy of Sciences*, *1143*, 83–104. https://doi.org/10.1196/annals.1443.023

Reisz, J. A., Bansal, N., Qian, J., Zhao, W., & Furdui, C. M. (2014). Effects of Ionizing Radiation on Biological Molecules—Mechanisms of Damage and Emerging Methods of Detection. *Antioxidants & Redox Signaling*, *21*(2), 260–292. https://doi.org/10.1089/ars.2013.5489

Reuber, M. D. (1984). Carcinogenicity of dimethoate. *Environmental Research*, *34*(2), 193–211. https://doi.org/10.1016/0013-9351(84)90089-6

Richardson, D., Sugiyama, H., Nishi, N., Sakata, R., Shimizu, Y., Grant, E. J., Soda, M., Hsu, W.-L., Suyama, A., Kodama, K., & Kasagi, F. (2009). Ionizing Radiation and Leukemia Mortality among Japanese Atomic Bomb Survivors, 1950–2000. *Radiation Research*, *172*(3), 368–382. https://doi.org/10.1667/RR1801.1

Roberts, J. R., & Karr, C. J. (2012). Pesticide Exposure in Children. *Pediatrics*, *130*(6), e1765–e1788. https://doi.org/10.1542/peds.2012-2758

Rudant, J., Lightfoot, T., Urayama, K. Y., Petridou, E., Dockerty, J. D., Magnani, C., Milne, E., Spector, L. G., Ashton, L. J., Dessypris, N., Kang, A. Y., Miller, M., Rondelli, R., Simpson, J., Stiakaki, E., Orsi, L., Roman, E., Metayer, C., Infante-Rivard, C., & Clavel, J. (2015). Childhood Acute Lymphoblastic Leukemia and Indicators of Early Immune Stimulation: A Childhood Leukemia International Consortium Study. *American Journal of Epidemiology*, *181*(8), 549–562. https://doi.org/10.1093/aje/kwu298

Rull, R. P., Gunier, R., Von Behren, J., Hertz, A., Crouse, V., Buffler, P. A., & Reynolds, P. (2009). Residential proximity to agricultural pesticide applications and childhood acute lymphoblastic leukemia. *Environmental Research*, *109*(7), 891–899. https://doi.org/10.1016/j.envres.2009.07.014

Russell, E. (1999). The Strange Career of DDT: Experts, Federal Capacity, and Environmentalism in World War II. *Technology and Culture*, *40*(4), 770–796. https://doi.org/10.1353/tech.1999.0192

Sabarwal, A., Kumar, K., & Singh, R. P. (2018). Hazardous effects of chemical pesticides on human health–Cancer and other associated disorders. *Environmental Toxicology and Pharmacology*, *63*, 103–114. https://doi.org/10.1016/j.etap.2018.08.018

Savitz, D. A., Wachtel, H., Barnes, F. A., John, E. M., & Tvrdik, J. G. (1988). Case-control study of childhood cancer and exposure to 60-Hz magnetic fields. *American Journal of Epidemiology*, *128*(1), 21–38. https://doi.org/10.1093/oxfordjournals.aje.a114943

Schüz, J., & Erdmann, F. (2016a). Environmental Exposure and Risk of Childhood Leukemia: An Overview. *Archives of Medical Research*, *47*(8), 607–614. https://doi.org/10.1016/j.arcmed.2016.11.017

Schüz, J., & Erdmann, F. (2016b). Environmental Exposure and Risk of Childhood Leukemia: An Overview. *Archives of Medical Research*, *47*(8), 607–614. https://doi.org/10.1016/j.arcmed.2016.11.017

Sergentanis, T. N., Thomopoulos, T. P., Gialamas, S. P., Karalexi, M. A., Biniaris-Georgallis, S.-I., Kontogeorgi, E., Papathoma, P., Tsilimidos, G., Skalkidou, A., Iliadou, A. N., & Petridou, E. T. (2015). Risk for childhood leukemia associated with maternal and paternal age. *European Journal of Epidemiology*, *30*(12), 1229–1261. https://doi.org/10.1007/s10654-015-0089-3

Sermage-Faure, C., Demoury, C., Rudant, J., Goujon-Bellec, S., Guyot-Goubin, A., Deschamps, F., Hemon, D., & Clavel, J. (2013). Childhood leukaemia close to high-voltage power lines – the Geocap study, 2002–2007. *British Journal of Cancer*, *108*(9), 1899–1906. https://doi.org/10.1038/bjc.2013.128

Siegel, D. A., King, J., Tai, E., Buchanan, N., Ajani, U. A., & Li, J. (2014). Cancer Incidence Rates and Trends Among Children and Adolescents in the United States, 2001–2009. *Pediatrics*, *134*(4), e945–e955. https://doi.org/10.1542/peds.2013-3926

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2021). Cancer Statistics, 2021. *CA: A Cancer Journal for Clinicians*, *71*(1), 7–33. https://doi.org/10.3322/caac.21654

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2022). Cancer statistics, 2022. *CA: A Cancer Journal for Clinicians*, *72*(1), 7–33. https://doi.org/10.3322/caac.21708

Simcox, N. J., Fenske, R. A., Wolz, S. A., Lee, I.-C., & Kalman, D. A. (1995). Pesticides in household dust and soil: Exposure pathways for children of agricultural families. *Environmental Health Perspectives*, *103*(12), 9.

Simon, A. K., Hollander, G. A., & McMichael, A. (2015). Evolution of the immune system in humans from infancy to old age. *Proceedings of the Royal Society B: Biological Sciences*, *282*(1821). https://doi.org/10.1098/rspb.2014.3085

Stieglitz, E., & Loh, M. L. (2013). Genetic predispositions to childhood leukemia. *Therapeutic Advances in Hematology*, *4*(4), 270–290. https://doi.org/10.1177/2040620713498161

Swanson, J., Kheifets, L., & Vergara, X. (2019). Changes over time in the reported risk for childhood leukaemia and magnetic fields. *Journal of Radiological Protection: Official Journal of the Society for Radiological Protection*, *39*(2), 470–488. https://doi.org/10.1088/1361-6498/ab0586

Takahashi, O., Oishi, S., Fujitani, T., Tanaka, T., & Yoneyama, M. (1994). Chronic Toxicity Studies of Piperonyl Butoxide in F344 Rats: Induction of Hepatocellular Carcinoma. *Fundamental and Applied Toxicology*, *22*(2), 293–303. https://doi.org/10.1006/faat.1994.1033

Takahashi, O., Oishi, S., Fujitani, T., Tanaka, T., & Yoneyama, M. (1997). Chronic toxicity studies of piperonyl butoxide in CD-1 mice: Induction of hepatocellular carcinoma1This study was conducted equally by the five authors named, so that the order used here is of no consequence.1. *Toxicology*, *124*(2), 95–103. https://doi.org/10.1016/S0300-483X(97)00136-4

Talibov, M., Olsson, A., Bailey, H., Erdmann, F., Metayer, C., Magnani, C., Petridou, E., Auvinen, A., Spector, L., Clavel, J., Roman, E., Dockerty, J., Nikkilä, A., Lohi, O., Kang, A., Psaltopoulou, T., Miligi, L., Vila, J., Cardis, E., & Schüz, J. (2019). Parental occupational exposure to low-frequency magnetic fields and risk of leukaemia in the offspring: Findings from the Childhood Leukaemia International Consortium (CLIC). *Occupational and Environmental Medicine*, *76*(10), 746–753. https://doi.org/10.1136/oemed-2019-105706

Turner, M. C., Wigle, D. T., & Krewski, D. (2010a). Residential Pesticides and Childhood Leukemia: A Systematic Review and Meta-Analysis. *Environmental Health Perspectives*, *118*(1), 33–41. https://doi.org/10.1289/ehp.0900966

Turner, M. C., Wigle, D. T., & Krewski, D. (2010b). Residential pesticides and childhood leukemia: A systematic review and meta-analysis. *Environmental Health Perspectives*, *118*(1), 33–41. https://doi.org/10.1289/ehp.0900966

Turner, M. C., Wigle, D. T., & Krewski, D. (2011). Residential pesticides and childhood leukemia: A systematic review and meta-analysis. *Ciência & Saúde Coletiva*, *16*(3), 1915–1931. https://doi.org/10.1590/S1413-81232011000300026

U.S. Department of the Interior Bureau of Land Management. (n.d.). *RIGHTS-OF-WAY*. Retrieved March 10, 2021, from https://www.blm.gov/programs/lands-and-realty/rights-of-way

US EPA. (2013, October 30). *Types of Pesticide Ingredients* [Overviews and Factsheets]. US EPA. https://www.epa.gov/ingredients-used-pesticide-products/types-pesticide-ingredients

Van Maele-Fabry, G., Gamet-Payrastre, L., & Lison, D. (2019). Household exposure to pesticides and risk of leukemia in children and adolescents: Updated systematic review and meta-analysis. *International Journal of Hygiene and Environmental Health*, *222*(1), 49–67. https://doi.org/10.1016/j.ijheh.2018.08.004

Vergara, X. P., Kavet, R., Crespi, C. M., Hooper, C., Silva, J. M., & Kheifets, L. (2015). Estimating magnetic fields of homes near transmission lines in the California Power Line Study. *Environmental Research*, *140*, 514–523. https://doi.org/10.1016/j.envres.2015.04.020

Vinson, F., Merhi, M., Baldi, I., Raynal, H., & Gamet-Payrastre, L. (2011). Exposure to pesticides and risk of childhood cancer: A meta-analysis of recent epidemiological studies. *Occupational and Environmental Medicine*, *68*(9), 694–702. https://doi.org/10.1136/oemed-2011-100082

Ward, E., DeSantis, C., Robbins, A., Kohler, B., & Jemal, A. (2014). Childhood and adolescent cancer statistics, 2014. *CA: A Cancer Journal for Clinicians*, *64*(2), 83–103. https://doi.org/10.3322/caac.21219

Weaver, V. M., Buckley, T. J., & Groopman, J. D. (1998). Approaches to environmental exposure assessment in children. *Environmental Health Perspectives*, *106 Suppl 3*, 827–832. https://doi.org/10.1289/ehp.98106827

Weiss, B., Amler, S., & Amler, R. W. (2004). Pesticides. *Pediatrics*, *113*(Supplement_3), 1030–1036. https://doi.org/10.1542/peds.113.S3.1030

Weppner, S., Elgethun, K., Lu, C., Hebert, V., Yost, M. G., & Fenske, R. A. (2006). The Washington aerial spray drift study: Children's exposure to methamidophos in an agricultural community following fixed-wing aircraft applications. *Journal of Exposure Science & Environmental Epidemiology*, *16*(5), Article 5. https://doi.org/10.1038/sj.jea.7500461

Wertheimer, N., & Leeper, E. (1979). ELECTRICAL WIRING CONFIGURATIONS AND CHILDHOOD CANCER. *American Journal of Epidemiology*, *109*(3), 273–284. https://doi.org/10.1093/oxfordjournals.aje.a112681

Whitehead, T. P., Metayer, C., Wiemels, J. L., Singer, A. W., & Miller, M. D. (2016). Childhood Leukemia and Primary Prevention. *Current Problems in Pediatric and Adolescent Health Care*, *46*(10), 317–352. https://doi.org/10.1016/j.cppeds.2016.08.004

Wiemels, J. (2012). Perspectives on the Causes of Childhood Leukemia. *Chemico-Biological Interactions*, *196*(3). https://doi.org/10.1016/j.cbi.2012.01.007

Wigle, D. T., Turner, M. C., & Krewski, D. (2009a). A Systematic Review and Meta-analysis of Childhood Leukemia and Parental Occupational Pesticide Exposure. *Environmental Health Perspectives*, *117*(10), 1505–1513. https://doi.org/10.1289/ehp.0900582

Wigle, D. T., Turner, M. C., & Krewski, D. (2009b). A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. *Environmental Health Perspectives*, *117*(10), 1505–1513. https://doi.org/10.1289/ehp.0900582

World Health Organization. (2007). *Extremely Low Frequency Fields Environmental Health Criteria Monograph* (No. 238). World Health Organization. http://www.who.int/peh-emf/publications/elf_ehc/en/

World Health Organization. (2008). *Children are not little adults*. World Health Organization. https://www.who.int/ceh/capacity/Children_are_not_little_adults.pdf

World Health Organization. (2016). *Ionizing radiation, health effects and protective measures*. https://www.who.int/news-room/fact-sheets/detail/ionizing-radiation-health-effects-and-protective-measures

World Health Organization. (2021a). *Cancer today*. http://gco.iarc.fr/today/home

World Health Organization. (2021b). *WHO | Radiation, Non-ionizing*. WHO; World Health Organization. https://www.who.int/topics/radiation_non_ionizing/en/

Zhou, J., Mainelis, G., & Weisel, C. P. (2019). Pyrethroid levels in toddlers' breathing zone following a simulated indoor pesticide spray. *Journal of Exposure Science & Environmental Epidemiology*, *29*(3), 389. https://doi.org/10.1038/s41370-018-0065-6

Ziegelberger, G., Dehos, A., Grosche, B., Hornhardt, S., Jung, T., & Weiss, W. (2011). Childhood leukemia – Risk factors and the need for an interdisciplinary research agenda. *Progress in Biophysics and Molecular Biology*, *107*(3), 312–314. https://doi.org/10.1016/j.pbiomolbio.2011.09.010