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Authors

Park, Andrew S
Ritz, Beate
Yu, Fei
et al.

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

Andrew S Park[a], Beate Ritz[a], Fei Yu[b], Myles Cockburn[c], Julia E. Heck[a, d]

[a] Department of Epidemiology, Fielding School of Public Health, University of California, 650 Charles E. Young Dr. S, Box 951772, Los Angeles, CA 90095-1772 USA
[b] Department of Biostatistics, Fielding School of Public Health, University of California, 650 Charles E. Young Dr. S, Box 951772, Los Angeles, CA 90095-1772 USA
[c] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 2001 N. Soto Street, Suite 318-A, Los Angeles, CA, USA
[d] Jonsson Comprehensive Cancer Center, University of California, Box 951781 Los Angeles, CA 90095-1781, USA

Corresponding Author: Dr. Julia E. Heck
Address: 650 Charles E. Young Dr. S, 73-257 CHS, Los Angeles, CA 90095-1772
Email: jeheck@ucla.edu

Abstract

Background

A number of epidemiologic studies with a variety of exposure assessment approaches have implicated pesticides as risk factors for childhood cancers. Here we explore the association of pesticide exposure in pregnancy and early childhood with childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) utilizing land use and pesticide use data in a sophisticated GIS tool.

Methods

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

Results

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

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

Conclusion

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

Keywords: Childhood leukemia; pesticide; agriculture; ambient exposure; pregnancy

Introduction

Leukemia, which makes up 40% of all childhood cancers, is the most frequent childhood malignancy. The most common subtype, acute lymphocytic leukemia (ALL) alone accounts for 25% of all childhood malignancies in children younger than 15 years of age (Howlader, 2013b), and 78% of all childhood leukemia cases. Nevertheless, it is a rare disease with an incidence of 39 cases per million, with diagnoses peaking between ages 2-5 and the highest rates estimated for Hispanics (CDC, 2009). Acute myeloid leukemia accounts for most of the remaining cases of childhood leukemia (16%). Few risk factors for childhood leukemia are considered established apart from ionizing radiation and specific genetic abnormalities.

In 2010, 173 million pounds of pesticide active ingredients were used in California (CDPR, 2011). Higher concentrations of pesticides have been measured in communities abutting agricultural fields, as measured by urine and hand wipe samples as well as in house dust (Loewenherz et al., 1997; Lu et al., 2000; Simcox et al., 1995; Ward et al., 2006). Previous studies have shown that pesticides and their metabolites (organophosphates, pyrethroids) persist in media such as house dust and clothing in families of farmworkers living near agricultural fields (Arcury et al., 2007; Bradman et al., 2005; Bradman et al., 2007).These families show a higher body burden of pesticides compared to those living further away from fields (Curwin et al., 2007; Fenske et al., 2005). This is of great concern as pesticide residues may build up in residences located in agricultural communities and expose pregnant women and infants (Arcury et al., 2007).

A number of previous studies suggested that pesticide exposures are risk factors for childhood ALL (Bailey et al., 2015; Infante-Rivard and Weichenthal, 2007; Jurewicz and Hanke, 2006; Nasterlack, 2007; Vinson et al., 2011). A meta-analysis (Vinson et al., 2011) concluded that exposure during pregnancy to any pesticide exposure increases the risk of leukemias (48%) and lymphomas (53%) in offspring. However, the contributing studies mainly relied on parental interviews to assess in-home pesticide use or professional applications of residences, and the retrospective assessment of exposures made these studies vulnerable to recall bias since parents of children with cancer may recall exposures in more detail and may want to explain their child's disease. In addition, interviews fail to assess levels of ambient exposure. In 2007, a study (Infante-Rivard and Weichenthal, 2007) critiqued the literature as lacking clarity on the most important time period of exposure, the type of leukemia most impacted by pesticide exposures, and which parent's exposure may be more important. This study aims to shed light on the subtypes of leukemia and to determine any differences in risks whether children were exposed during pregnancy or early childhood (<1 year).

Importantly, most prior studies did not report on risk related to individual pesticides, instead they assessed pesticides by type (insecticides, fungicides, herbicides, fumigants, etc.), chemical class (organophosphates, organochlorines, triazines, azoles, etc.), classifications according to level of carcinogenicity (Group A, B, probable carcinogen, etc.) (Alderton et al., 2006; Infante-Rivard and Sinnett, 1999; Lowengart et al., 1987), or they targeted specific pesticides but investigated all childhood leukemias together instead of separating ALL and AML (Reynolds et al., 2005). Our study expands upon earlier publications by identifying specific pesticide exposures and by assessing risk of ALL and AML separately. Since agricultural pesticide use changes frequently

due to improvements in formulations and to address pest adaptation and evolution (Tomasetto et al., 2017), updates with more recent exposure data are needed. We are focusing on children born in more recent years (1998-2011) and we are employing a very sophisticated GIS tool we developed that combines land use and pesticide use records for those years; we applied this tool to all rural areas in California that use pesticides agriculturally because urban communities apply pesticides for non-agricultural purposes such as home and building fumigations or right-of way and other public pesticide applications, which are not reported to the PUR on a fine spatial level (reported only at the county-level). While agricultural pesticide use is generally rarer in urban areas, urban dwellers nevertheless experience other types of ambient pesticide exposures that may impact risk (Heck et al., 2013; Park et al., 2017). Hence we decided to focus on agricultural applications and rural populations with spatially well captured pesticide exposures. This exposure assessment method does not rely on recall and does not suffer the same limitations as many prior studies.

Methods

Study Population

Cases were collected from records of incident ALL [International Classification of Childhood Cancer, Third Edition (ICCC) code 011] and AML (ICCC code 012) diagnosed in 1986-2012 (born 1983-2011) in the California Cancer Registry, younger than age 6, and born in California. Using a probabilistic linkage program (LinkPlus, CDC), we linked cases to birth certificates using first and last names, date of birth, and social security number when available. With this method, 89% of cases were matched to a California birth certificate. The remaining 11% were likely born out of state and moved to California prior to diagnosis (Urayama et al., 2009).

Controls were selected at random from California birth records for the same time period, frequency-matched by year of birth to all childhood cancers in the study. Controls had no record of a cancer diagnosis in California before age 6. Results from cases and controls were restricted to birth years 1998-2011 in this study. As this was a record-based study, we did not seek informed consent from individual subjects. The study received approvals from the human subject protection boards of the University of California, Los Angeles, the University of Southern California, and the California Committee for the Protection of Human Subjects.

Exposure Assessment

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

and annual application rates (total pounds applied per acre in a PLSS section, within a given time period) for each pesticide as detailed elsewhere (Cockburn et al., 2011; Goldberg et al., 2008).

Previously, we successfully characterized chronic organophosphate (OP) pesticide exposure via differential DNA methylation (Paul et al., 2018). We used our geographic information system-based pesticide exposure assessment tools to generate long-term OP pesticide exposure measures in healthy control individuals and identified epigenetic profiles related to chronic OP exposures. Using systems analysis and marker set enrichment, we found that the OP-associated CpGs were enriched for nicotinic and muscarinic acetylcholine esterase receptors as a response to OP exposure.

Case data were obtained from California Cancer Registry records. Parental demographics such as age, education, race/ethnicity, socioeconomic status, as well as child's information including gestational age, and child's sex were obtained from birth certificates and additionally from the year 2000 census. Neighborhood socioeconomic status was measured with a multi-factorial index that used principal components analysis to develop a single, 5-level measure from seven census-level indicators (education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value) (Yost et al., 2001). Based on the date of last reported menses we excluded children with implausibly long (>45 weeks, n=2729) gestations, likely non-viable births (gestational age <20 weeks or birth weight <500g, n=32), and those with missing data for gestation length (n=12,786). In addition, those with a residential address outside of California (n=632), and controls who had died before age 6 (n=1,202) were excluded from the dataset

resulting in 5,112 cases of leukemia and 270,776 controls prior to restriction. We used an urban/rural designation based on rural-urban commuting area codes (RUCA) created by a collaboration of government organizations based on Census Tract information (Morrill, 2013) to restrict our sample to rural residents only (RUCA levels 4-10). Our rural study population contained 132 cases of ALL, 30 cases of AML, and 9,805 controls.

Residential addresses as listed on the birth certificate were mapped using Geographic Information System (GIS) tools based on street address (54%), street intersection (38%), city centroid, or ZIP code centroid (7%). We examined several buffer sizes (500m, 2000m, 4000m) around the home . Using the residential address, for each buffer size, the buffer radius is drawn around the residence to determine pesticide use within the respective buffer. Due to the distances that pesticides can reach from where they are initially applied (pesticide drift) (Wofford et al., 2014), and to improve sample size, we present results at the 4000m distance. We also examined smaller buffers (500m, 2000m) in sensitivity analyses.

We pre-selected 133 pesticides considered possible, likely, or probable carcinogens by the EPA (Vinson et al., 2011), (See Supplement 1 for more detail on EPA carcinogen classifications) (EPA, 2017). We further categorized pesticides according to physiochemical type and class, based on information from the Pesticide Action Network (PAN) Pesticide Database (Kegley, 2014) and we also considered 6 additional pesticides (methyl bromide, diazinon, paraquat, chlorpyrifos, glyphosate, and simazine (Metayer et al., 2013)) because these chemicals are widely used in California and little is known about potential adverse effects from co-exposures.

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

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

Statistical Analyses

Unconditional logistic regression was utilized to derive ORs and 95% CIs adjusting for the matching factor (birth year) in single and multiple-pesticides models for the 65 selected pesticides. We examined 'ever' exposure during pregnancy for each pesticide as well as for chemical class for ALL and AML outcomes. The single-pesticide models adjusted for any exposure to another carcinogenic pesticide as a binary variable. Multiple-pesticide models, co-adjusted for ever/never exposure to all other pesticides selected via semi-Bayesian hierarchical logistic regression, i.e. assuming that the estimated effects are either 1) drawn from the same distribution for all carcinogenic pesticides or 2) are specific to a pesticide class (2,6-dinitroanilines, azoles, chloroacetanilides, dithiocarbamates, n-methyl carbamates, organochlorines, organophosphates, pyrethroids, substituted benzenes, and triazines). Both assumptions yielded similar results, thus here we present the hierarchical logistic regression model results using the first assumption (same distribution of effects for all carcinogenic pesticides) only. Due to the highly correlated nature of agricultural pesticide use and exposure, we employed hierarchical logistic modelling (HLM) in an attempt to identify the pesticides with the most consistently estimated effects after adjusting for other carcinogenic pesticide exposures.

This, however, assumes that all carcinogenic pesticides have a similar (or mean) effect on childhood leukemia for exposure in pregnancy or early childhood. This assumption is likely not valid. We also conducted sensitivity analyses examining the entire state among those born 1998-2011 and restricted to those exposed to at least one pesticide in the PUR database.

Selection of variables for adjustment was based upon literature review as well as the 10% change in estimate criterion (Chow et al., 2010; Howlader, 2013a; Johnson et al., 2009; Oksuzyan et al., 2015). We adjusted for birth year (matching factor), mother's race (White non-Hispanic, Black, and Other race/refused to report), neighborhood socioeconomic index, and the binary indicator for any other carcinogenic pesticide exposure as possible confounders. We considered for inclusion in models neighborhood and individual level socioeconomic indicators: maternal education (years), paternal education (years), and the source of payment for prenatal care, which was defined as private insurance (including Health Maintenance Organizations, Blue Cross-Blue Shield, or any other private insurance) versus other payment methods (including self-pay and government aid programs, such as Medicare, Medi-Cal, worker’s compensation, Title V, and CHAMPUS/TRICARE), which we have previously observed to be a reasonable proxy for family income (Ritz et al., 2007). However, these socioeconomic factors were not included in final models due to not fulfilling the 10% change in estimate criterion.

Results

In terms of demographic characteristics (Table 1) fathers of ALL cases were more likely to be White non-Hispanics and Hispanics than any other race. Mothers of ALL cases were older and

more likely to be Hispanic. Families of ALL cases were more likely to have had their prenatal care paid by private insurance. ALL cases were more often male children.

Exposure to any of the 59 carcinogenic pesticides during pregnancy resulted in elevated odds for ALL (OR: 2.83, 95% CI: 1.67-4.82) and AML (OR: 3.75, 95% CI: 0.97-11.57). Table 2 and 3 provide the exposure distributions of cases and controls based on specific pesticide exposures during pregnancy, presented by pesticide class. We estimated elevated odds for ALL with exposures to the following classes in our single-pesticide models: 2,6-dinitroanilines (OR: 2.50, 95% CI: 1.56-3.99), anilides (OR: 2.16, 95% CI: 1.38-3.36), and ureas (OR: 2.18, 95% CI: 1.42-3.34). Point estimates for AML were elevated for organophosphates (OR: 1.82, 95% CI: 0.70-4.74) and ureas (OR: 3.38, 95% CI 1.22-9.38) but small sample sizes resulted in wide confidence intervals.

In Table 4 we present ORs for individual pesticides. We estimated elevated odds ratios for ALL with exposure to diuron (OR: 2.38, 95% CI: 1.57-3.60), phosmet (OR: 2.10, 95% CI: 1.46-3.02), kresoxim-methyl (OR: 1.77, 95% CI: 1.14-2.75), and propanil (OR: 2.58, 95% CI: 1.44-4.63) in the single-pesticide model. We also observed unexpectedly increased odds ratios for glyphosate (OR: 2.20, 95% CI: 1.33, 3.63) and paraquat dichloride (OR: 1.74, 95% CI: 1.16, 2.62). Using hierarchical regression models instead these effects estimates attenuated slightly except for phosmet (OR: 2.10, 95% CI: 1.3-3.39). The addition of all other pesticides in the hierarchical logistic models attenuated the effects of most pesticides, likely due in part to co-adjustment for the other pesticides in the list, along with drawing each pesticide to the overall mean of the carcinogenic pesticides.

In relation to AML (Table 5), we saw elevated odds for metam-sodium (OR: 2.56, 95% CI: 1.19, 5.49) and paraquat dichloride (OR: 3.38, 95% CI: 1.23, 9.27) in single-pesticide models.

Effect estimates were similar across trimesters and comparable in size to the estimates for entire pregnancy exposures (Supplemental table 1). Exposure correlations between the first and second trimesters, and second and third trimesters were around 0.40-0.55 while the first and third trimesters were not correlated (r^2 = -0.01-0.30). In the sensitivity analysis in which we relied on 2000m buffers to assess exposure, associations with the four pesticides mentioned above were slightly weaker for ALL but remained elevated with CIs including the null (ORs: 1.41-2.28) except for diuron, which was higher (OR: 2.28, 95% CI: 1.56-3.33). With regards to AML, paraquat dichloride remained elevated (OR: 2.59, 95% CI: 1.08-6.20), and metam-sodium had only 7 exposed cases at 2000m but remained elevated (OR: 2.17, 95% CI: 0.91-5.21). Results of sensitivity analyses statewide and among those exposed to at least one pesticide were similar among the pesticides with elevated effect estimates, although the magnitude of effect was generally closer to the null.

Discussion

In this rural population-based study of ALL and AML which was not subject to recall or participation biases, we observed an over two-fold increased odds for ALL and an over four-fold increased odds for AML with exposure to any carcinogenic pesticide. This risk estimate is higher than the estimates from meta-analyses for ALL (meta-OR: 1.74, 95% CI:1.37-2.21) (Van Maele-Fabry et al., 2011) and for AML, from a meta-analysis (meta-OR: 1.4) (Turner et al., 2010). The analyses for AML, however, were generally under-powered due to the small number of cases in less densely populated rural areas, which prevented us from estimating risks for one-third of the potentially carcinogenic pesticides. Many pesticides exhibited effect estimates above the null in single pollutant models. When comparing our results from the single-pesticide models to the multiple-pesticide adjusted model (with HLM), several specific pesticide associations remained elevated: diuron, phosmet, kresoxim-methyl, and propanil. The effects estimated for the classes of anilides and ureas can be explained by the presence of propanil and diuron in these classes, and these classes only contain two pesticides each for ALL. Additionally, propyzamide had no effect in the single-pesticide model, but showed an association in the hierarchical regression model.

While pesticides have previously been associated with increased risk of ALL, those results were almost exclusively based on studies that utilized ecological or case-control designs fraught with a potential for biased parental recall of pesticide exposure. Other studies that avoided retrospective self-reporting of exposures assessed exposures according to census block groups or acreage devoted to farming, exposure assessment methods that are relatively crude (Carozza et al., 2008; Reynolds et al., 2005; Reynolds et al., 2002; Ward et al., 2006). Our study is unique in that it

utilizes specific address information and time of pregnancy to assess exposures of subjects in the state of California.

A similar case-control study in California assessing residential proximity to agricultural fields and childhood cancers in 1990-1997 found elevated risks in children of mothers exposed to metam-sodium ($\geq 50^{th}$ percentile) and dicofol ($\geq 50^{th}$ percentile) for all leukemias grouped together (Reynolds et al., 2005). Our results suggest the elevated risk these authors observed with metam-sodium may have been driven by the association we also observed for AML. We were not able to confirm this study's finding of an increased risk of AML for dicofol as our point estimate was OR: 0.79, however, the ALL estimate was slightly elevated (OR: 1.41). Also, paraquat was found to increase risk of AML. However, while paraquat is currently not considered a carcinogen, the increased risk of AML might be linked to paraquat being an agent that causes oxidative stress and mitochondrial DNA damage (Sanders, 2017). These mechanisms may explain the increase in risk for AML seen here.

Of the pesticides we identified as being associated with ALL, diuron, a substituted phenylurea, is classified as a "known/likely" carcinogen according to the EPA. It is currently approved for use as an herbicide on terrestrial crops, for terrestrial non-crops (highways, pipelines, storage areas, etc.), and aquatic non-crops (irrigation, drainage ditches). Diuron has previously been linked to reproductive toxicity in rats (Fernandes et al., 2007), and shown to harm placental choriocarcinoma cells (Huovinen et al., 2015). Studies of human cell lines (breast adenocarcinoma and placental choriocarcinoma cells) showed that diuron is cytotoxic and potentially genotoxic; generation of reactive oxygen species (ROS) is a likely mechanism for its

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

The second pesticide with strong and consistent associations to ALL, phosmet is an organophosphate (OP) insecticide, which have been shown to be able to cross the placental barrier and OP metabolites have been discovered in meconium and cord blood samples (Ostrea et al., 2009; Whyatt et al., 2003). A study testing phosmet exposures on a human choriocarcinoma cell line reported decreased cell viability, reduced DNA synthesis, and induction of inflammatory cytokines (Guinazu et al., 2012).

Propanil is an anilide classified as a suggestive carcinogen by EPA based upon studies in rats that found an increase in testicular interstitial cell adenomas after exposure (EPA, 2017). However, there is relatively little previous research in humans. Lastly, the strobilurin class fungicide kresoxim-methyl has been classified as a likely carcinogen by the EPA based on findings that it is highly toxic to several aquatic species such as *daphnia magna* and grass carp (Cui et al., 2017; Liu et al., 2013). It has also been seen as having neurotoxic effects in a study of cultured cortical neurons (Regueiro et al., 2015). This is the first human study to find a link between kresoxim-methyl and ALL.

Although we observed increases in risk of ALL and AML for those exposed to glyphosate and paraquat dichloride and these chemicals were chosen because they are widely used in California they were not included in the hierarchical models because they had not been classified in the 2011 document we originally used to select carcinogenic pesticides. However, more recently

glyphosate has been classified as a type 2A carcinogen by IARC (IARC Monographs Program., 2017) and been implicated in an increased risk of AML in farmers who apply pesticides (Andreotti et al., 2018).

Pesticides become airborne during and after applications with 'drift' determined by factors such as application method (aircraft dispersion vs. hydraulic spraying vs. controlled droplet application), wind direction, wind speed and pesticide volatility (Richards et al., 2001; Richter et al., 1986; Weppner et al., 2006). Validation studies of PUR data, which utilized biomarkers or employed air monitoring to compare pesticide use reported in the PUR system with chemical concentrations, have reported that pesticides have been measured at up to 8,000m from the location where they are applied (Curwin et al., 2005; Harnly et al., 2005; Rull and Ritz, 2003; Wofford et al., 2014). One validation study comparing air samples collected by the California EPA Toxic Air Contaminant program and California Department of Pesticide Regulation records showed strong correlations between reported agricultural applications within a 3-mile radius and pesticide air concentrations measured up to 4 days later (Harnly et al., 2005). In addition to these validations of our exposure assessment, another strength of our study was that we were able to examine individual-level exposures at the residential address at birth.

Our study attempts to identify true confounders and adjust for them accordingly. However, with correlated exposures, it is difficult to identify and adjust for true confounders while avoiding over-adjustment (Momoli et al., 2010). In order to address this, we presented single-pesticide models which only adjust for likely confounders while excluding other pesticide exposures, while the semi-Bayesian approach accounts for co-exposures among carcinogens. Our results

show most pesticides having effects greater than the null in the single-pesticide models while only a few survive the HLM. While HLM allowed us to adjust for other pesticide exposures, the HLM makes the unrealistic assumption that all pesticides examined are truly affecting leukemia risk in the same manner. At the current state of knowledge, it is however impossible to know which pesticide exposures are truly confounders and risk factors for the outcome or simply indicators of exposure to carcinogenic pesticides we should not be adjusting for. Thus, we prefer to present and interpret the ordinal logistic regression results as our main outcomes.

This study has some limitations common to studies of pregnancy exposures. Since fetuses would have had to survive to birth and into early childhood, it is possible that those exposed who would have later developed cancers may at the same time have been less likely to survive if high exposures to a pesticide results in miscarriage or spontaneous abortion, which would generate a live birth bias. That is, selection of healthier fetuses with less exposure would result in an attenuation of effects. Another limitation is that residential information was only available at birth and not throughout pregnancy or early childhood. Previous studies have estimated that between 11%-32% of pregnant women move at least once during pregnancy with median move distances ranging from 4.2 to 10 km (Lupo et al., 2010; Pennington et al., 2016; Pereira et al., 2016). With an expected low percentage of women moving, and those who do moving relatively small distances on average, our 4km exposure radius might have captured most residential ambient pesticide exposures from agricultural applications quite well. However, information on maternal occupational addresses and jobs that may also contribute to pesticide exposures and increased leukemia risk in these rural communities were not available (Bailey et al., 2014). Importantly, we did not have information whether parents were employed in agriculture and

incurred occupational exposures possibly leading to a severe underestimation of total exposures. In addition, exposure to in-home or active occupational pesticide use was not accounted for and may result in an underestimation of total pesticide exposure. Nevertheless, living on a farm not only generates ambient exposures, which we captured with our GIS tool, but is also associated with occupational exposures, thus our residential exposure estimates for these rural communities may reflect an appropriate exposure ranking for the most heavily exposed subjects.

Although this study focuses on a highly exposed population, these cases represent only a fraction of childhood leukemia cases in California. Nevertheless, we hope to shed light on the possible link between ambient carcinogenic pesticide exposures and the risk of childhood leukemia.

Conclusion

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

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Dr. Ritz currently is an expert witness and consultant for law suits against Monsanto that pertain to glyphosate and NHL and also has been retained as a consultant for a law suits against Syngenta on paraquat exposure and Parkinson's disease. Dr. Heck was retained to conduct a literature review on behalf of a lawsuit against the Monsanto Company.

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Table 1. Demographic characteristics of children in California born in 1998-2011 living in rural areas.

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

Table 2. Associations between ALL and exposure to agricultural pesticide applications within 4000m of the residential address, by pesticide class

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

[a]Adjusted for matching variable, birth year

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

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

Table 3. Associations between AML and exposure to agricultural pesticide applications within 4000m of the residential address, by pesticide class

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

[a]Adjusted for matching variable, birth year

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

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

Table 4. Associations between ALL and exposure to agricultural pesticide applications within 4000m of the residential address, by individual pesticide

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

	Dimethoate	82	4,982	1.56	1.44 (0.98, 2.12)	1.02 (0.61, 1.71)
	Malathion	78	4,515	1.67	1.54 (1.06, 2.22)	1.16 (0.73, 1.85)
	Diazinon†	76	4,731	1.38	1.27 (0.87, 1.83)	N/A
	Phosmet	76	3,757	2.09	2.10 (1.46, 3.02)	2.10 (1.30, 3.39)
	Acephate	48	3,146	1.18	1.06 (0.73, 1.54)	0.82 (0.50, 1.33)
	Methidathion	29	2,053	0.97	0.91 (0.58, 1.41)	0.62 (0.36, 1.07)
	S,S,S-Tributyl Phosphoro-trithioate	27	1,282	1.57	1.47 (0.94, 2.30)	1.59 (0.81, 3.12)
Pyrethroid						
	Permethrin	73	4,765	1.31	1.18 (0.81, 1.72)	0.65 (0.37, 1.14)
	Bifenthrin	56	3,760	1.27	1.18 (0.82, 1.70)	0.82 (0.51, 1.34)
	(S)-Cyper-methrin	40	2,768	1.25	1.13 (0.76, 1.69)	1.05 (0.64, 1.74)
Substituted Benzene						
	Chlorothalonil	67	4,262	1.34	1.19 (0.83, 1.72)	0.99 (0.59, 1.66)
	Dicloran	26	1,632	1.17	1.05 (0.67, 1.63)	0.96 (0.54, 1.68)
Triazine						
	Simazine†	72	4,340	1.50	1.49 (1.04, 2.14)	N/A
	Pymetrozine	14	980	1.17	1.08 (0.61, 1.91)	1.00 (0.52, 1.89)
Urea						
	Diuron	98	5,364	2.38	2.38 (1.57, 3.60)	1.79 (1.02, 3.15)
	Linuron	22	1,209	1.42	1.25 (0.78, 2.00)	1.63 (0.85, 3.12)
Other classes						
	Glyphosate‡	113	7,125	2.28	2.20 (1.33, 3.63)	N/A
	Oxyfluorfen	104	6,247	2.15	2.10 (1.35, 3.27)	1.43 (0.72, 2.81)
	Paraquat Dichloride†	95	5,711	1.83	1.74 (1.16, 2.62)	N/A
	Propargite	68	4,219	1.39	1.32 (0.91, 1.90)	0.76 (0.41, 1.42)
	Norflurazon	58	3,466	1.35	1.27 (0.88, 1.84)	0.84 (0.51, 1.38)
	Thiophanate-Methyl	56	3,127	1.61	1.52 (1.06, 2.17)	1.34 (0.87, 2.05)
	Captan	55	2,893	1.61	1.58 (1.10, 2.28)	1.52 (0.91, 2.56)
	Clofentezine	38	2,173	1.40	1.33 (0.90, 1.96)	1.09 (0.65, 1.83)
	Buprofezin	32	2,181	1.30	1.20 (0.78, 1.85)	1.01 (0.61, 1.67)
	Kresoxim-Methyl	31	1,673	1.86	1.77 (1.14, 2.75)	1.47 (0.83, 2.60)
	Hexythiazox	30	2,219	1.17	1.09 (0.71, 1.69)	0.74 (0.44, 1.26)
	Pyrithiobac-Sodium	24	1,666	1.01	0.94 (0.59, 1.50)	0.61 (0.31, 1.18)
	Metaldehyde	17	984	1.30	1.22 (0.73, 2.05)	1.39 (0.75, 2.56)
	Pyraflufen-Ethyl	16	1,310	1.18	1.11 (0.62, 1.99)	0.97 (0.50, 1.87)
	Chlorthal-Dimethyl	15	1,351	0.80	0.67 (0.39, 1.16)	0.41 (0.18, 0.93)
	Pyrimethanil	15	1,290	1.18	1.11 (0.60, 2.06)	0.85 (0.43, 1.68)
	Piperonyl Butoxide	15	911	1.15	1.08 (0.62, 1.87)	0.94 (0.51, 1.72)

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

†Added based on previous literature or high usage in California

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

[a]Adjusted for matching variable, birth year

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

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

Table 5. Associations between AML and exposure to agricultural pesticide applications within 4000m of the residential address, by individual pesticide

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

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

†Added based on previous literature or high usage in California

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

[a]Adjusted for matching variable, birth year

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

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

Appendix

Supplement 1

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

Supplemental Table 1. Associations between ALL and exposure to agricultural pesticide applications within 4000m of the residential address, by trimesters

	Trimester 1			Trimester 2			Trimester 3		
Chemical	**Exposed Cases** N=132	**Crude OR[a]**	**Single-pesticide model[b]**	**Exposed Cases** N=132	**Crude OR[a]**	**Single-pesticide model[b]**	**Exposed Cases** N=132	**Crude OR[a]**	**Single-pesticide model[b]**
Diuron	61	2.00	1.96 (1.37, 2.8)	67	1.94	1.87 (1.31, 2.68)	62	1.72	1.65 (1.15, 2.36)
Phosmet	34	1.85	1.80 (1.20, 2.70)	47	1.87	1.82 (1.24, 2.67)	37	1.55	1.48 (1.00, 2.20)
Propanil	2	1.34	1.31 (0.32, 5.39)	5	2.83	2.84 (1.14, 7.09)	5	2.59	2.55 (1.02, 6.34)
Kresoxim-methyl	8	1.50	1.42 (0.68, 2.98)	12	1.63	1.53 (0.83, 2.84)	15	2.09	1.94 (1.10, 3.42)

[a]Adjusted for matching variable, birth year

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