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Residential Exposure to Carbamate, Organophosphate, and Pyrethroid Insecticides in House Dust and Risk of Childhood Acute Lymphoblastic Leukemia

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Abstract

Background—Self-reported residential use of pesticides has consistently been associated with increased risk of childhood leukemia. However, these studies were limited in their ability to identify specific insecticide active ingredients that were associated with risk.

Objective—We used household carpet dust measurements of 20 insecticides (two carbamate, 10 organophosphate, two organochlorine, and six pyrethroid) as indicators of exposure and evaluated associations with the risk of childhood acute lymphoblastic leukemia (ALL).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Human Subjects Research

The study protocol was approved by the institutional review boards at the University of California, Berkeley, the California Committee for Protection of Human Subjects, and the National Cancer Institute.

Methods—We conducted a population-based case-control study of 252 ALL cases diagnosed from 1999 to 2007 and 306 birth certificate controls from 35 counties in Central and Northern California. Carpet dust was collected at a second interview (2001–2007) for cases who had not moved since diagnosis (comparable reference date for controls) using a specialized vacuum cleaner in the room where the child spent most of their time or from the household vacuum. Insecticides were categorized as detected (yes/no), or as tertiles or quartiles of their distributions among controls. We calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression adjusting for demographic characteristics, interview year, and season of dust collection.

Results—Permethrin, chlorpyrifos, diazinon, and carbaryl were the most frequently detected insecticide active ingredients. When we compared the highest quartile to the lowest or to non-detections, there was no association with ALL for permethrin (OR Q4 vs. Q1=0.81; 95% CI 0.50–1.31), carbaryl (OR Q4 vs. non-detects=0.61, 95% CI 0.34–1.08) or chlorpyrifos (OR Q4 vs. Q1=0.60; 95% CI 0.36–1.00). The highest quartile of diazinon concentration was inversely associated with risk in the single pesticide model but without a monotonic exposure-response (p-trend=0.14). After adjusting for other common insecticides, the OR was not significant (OR Q4 vs. Q1=0.58; 95% CI 0.33–1.05). None of the other insecticides were associated with risk.

Conclusion—Our results should be interpreted within the limitations of the case-control study design including the use of a single post-diagnosis dust sample and restriction to residentially stable participants, which may have resulted in selection bias. Although difficult to implement, additional studies with assessment of exposure to insecticide active and non-active ingredients are necessary to elucidate the role of these common exposures in childhood leukemia risk.

Keywords

childhood leukemia; childhood acute lymphoblastic leukemia; dust; insecticides; organophosphate; carbamate; pyrethroid

1. Introduction

Globally, leukemia is the most frequently diagnosed childhood cancer (Roman et al. 2017; Steliarova-Foucher et al. 2017). Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed form of leukemia, accounting for 70% of all diagnoses (Lupo and Spector 2020). Worldwide estimates suggest leukemia accounts for approximately 40% of cancers in children and young adults under 20 years old (Force et al. 2019). In the United States, an estimated 4.8 per 100,000 children under 19 years old are diagnosed with leukemia each year (Howlader et al. 2019). Both genetic and environmental factors play a role in the development of leukemia (Buffler et al. 2005; Hunger and Mullighan 2015; Lupo and Spector 2020), however, the etiologic risk factors for childhood leukemia have not been well delineated. Children ages one to four years have the highest incidence rates of childhood leukemias (Howlader et al. 2019), indicating that early life environmental exposures are likely to be component causes of disease development among children.

Insecticides are used extensively in residential and agricultural settings, resulting in the potential for the general population to be exposed through dermal, inhalation, and ingestion

pathways. Children may be exposed through inhalation and dermal exposure to insecticides applied to nearby agricultural fields, in and around the home, on the lawn and garden, and by eating foods with insecticide residues. In indoor residential settings, these chemicals are protected from weather-degradation and to some extent from microbial-driven degradation and may persist in carpet dust, which is another source of exposure from non-dietary ingestion (Butte and Heinzow 2002; Roberts et al. 2009). Ingestion of house dust is an important route of exposure for young children who spend a large amount of time indoors and engage in crawling and hand to mouth behaviors (Butte and Heinzow 2002; Xue et al. 2010).

The active ingredients used in insecticides have changed over the last several decades. The most frequently applied and well-studied are the organochlorine insecticides, which are now banned from use in most countries. For example, in the United States dichlorodiphenyltrichloroethane (DDT) was banned in 1972 (United States Environmental Protection Agency, 2020), and chlordane in 1988 (Agency for Toxic Substances and Disease Registry (ATSDR) 2018). This led to new replacement formulations for insecticides that included active ingredients from carbamate, organophosphate, and pyrethroid chemical classes. By 2000, organophosphate insecticides accounted for approximately 72% of total insecticide uses in the United States. Carbaryl (a carbamate), diazinon (an organophosphate), and malathion (an organophosphate) were ranked in the top-ten most-commonly used home and garden insecticides in 2001 (Grube et al. 2011; Kiely et al. 2004). Population-based biomarker studies conducted in the early 2000s confirmed widespread exposure to these insecticides among children and adults (Barr et al. 2010; Barr et al. 2011). These pesticides are still in use; 2012 estimates of use indicate that chlorpyrifos (an organophosphate) is frequently used in agricultural settings, and carbaryl and permethrin (a pyrethroid) are among the most commonly used home and garden sector insecticides (Atwood and Paisley-Jones 2017).

Prior individual studies and meta-analyses of residential insecticide exposures have utilized exposure metrics based on self-reported home and garden insecticides that were applied by either household members or professional pest control services. Most of these studies have suggested that pesticide use is associated with an increased risk of childhood leukemia (Bailey et al. 2015; Ma et al. 2002; Turner et al. 2010; Van Maele-Fabry et al. 2019), although mixed and null findings have been reported as well (Meinert et al. 2000). To our knowledge, no prior epidemiologic studies have directly measured residential insecticide concentrations to evaluate their relationships with childhood leukemia risk. The objective of this analysis was to evaluate the association between carbamate, organophosphate, organochlorine, and pyrethroid insecticide active ingredients measured in household dust and the risk of ALL in a case-control study of children living in Northern and Central California.

2. Methods

2.1 Study Population

The California Childhood Leukemia Study (CCLS) is a population-based case-control study of childhood leukemia that enrolled 997 children with leukemia and 1226 healthy controls

from 18 counties in the Central Valley and 17 counties in the San Francisco Bay area of California during the period from 1995 to 2008. The study design has been described previously (Bartley et al. 2010; Chang et al. 2006; Ma et al. 2004; Ma et al. 2005; Metayer et al. 2013). Briefly, children with leukemia newly diagnosed at nine pediatric clinical centers were enrolled using rapid ascertainment if they were less than 15 years old, resided in one of the study counties, and had a parent who spoke English or Spanish. Controls were randomly selected from California statewide birth certificate files and were matched to cases on age, sex, Hispanic ethnicity, and maternal race. Diagnosis and reference dates ranged from December 1999 through January 2007. After enrollment, the caregiver for each child participated in a home interview (tier 1; March 2000 through August 2007) that included a residential and occupational history. A second interview (tier 2) was offered to cases and controls who were seven years of age or younger at the time of the diagnosis or reference date and living in the same home residence that they occupied at the diagnosis/reference date. The details of the tier 2 interview (October 2001-November 2007) have been described previously (Deziel et al. 2014; Metayer et al. 2013; Ward et al. 2014; Ward et al. 2009), and included the collection of a carpet dust sample and a detailed interview about residential characteristics, pesticides stored in the home, home and garden pesticide use, and whether or not anyone in the home worked in an agricultural or groundskeeping occupation in the prior 12 months. In total, 731 participants (324 cases and 407 controls) were eligible for the tier 2 interview; 296 cases (91%) and 333 controls (81%) participated. In this study, we restricted our analyses to the 269 ALL cases (91%) who participated in the tier 2 interview, excluding 27 leukemia cases with different histology. The study protocol was approved by the institutional review boards at the University of California, Berkeley, the California Committee for Protection of Human Subjects, and the National Cancer Institute.

2.2 Dust Sample Collection

We attempted to collect a residential dust sample from each tier 2 residence. The methods for residential dust sampling have been previously described (Colt et al. 2008). In short, parents were asked to identify the room in which the child spent most of their waking time in the year prior to the diagnosis or reference date. If the room had a carpet or area rug measuring at least 0.84 square meters (nine square feet) that was reported as being present before the reference date, a dust sample was collected. Initially, a carpet dust sample was collected using a high-volume small-surface sampler (HVS3; Cascade Stack Sampling System, Venice, FL), with interviewers also collecting any dust present in the household vacuum cleaner in most homes. After determining that the household vacuum cleaner was a reasonable alternative to the HVS3 for dust sample collection and analysis (Colt et al. 2008), dust samples were collected exclusively from the household vacuum cleaner bag (Ward et al. 2014). A total of 17 ALL cases and 27 controls were excluded from the analysis because they either didn’t have any eligible carpet or the amount of collected dust was insufficient for insecticide quantification, resulting in a final analytic sample of 252 ALL cases (94%) and 306 controls (92%) of which 161 samples (29%) were from the household vacuum and 397 (71%) were from the HSV3. Among cases, the time between enrollment and the dust sample collection ranged from 0.4 to 3.4 years, with a median of 0.9 years (interquartile range [IQR] 0.7–1.3). Due to the longer time it took to enroll controls, the time between

enrollment and the dust sample collection for control participants ranged from 0.6 to 4.8 years, with a median of 1.7 years (IQR 1.3–2.2).

2.3 Laboratory Analysis

Dust samples were shipped to the Battelle Memorial Institute (Columbus, OH) where they were stored in −20° Celsius freezers until being processed and analyzed. The laboratory quantification and quality control methods have been previously described (Colt et al. 2008). Dust samples were sieved to remove the coarse (> 150 μm) dust fraction. Extraction was performed using 0.5 g aliquot of fine dust and a hexane:acetone solution, except for piperonyl butoxide, which was extracted with dichloromethane. For the hexane:acetone method, the dust was spiked with 250 ng each of five ^{13}C-labeled surrogate recovery standards (SRS) and for the dichloromethane method the dust was spiked with one SRS. Extracts were analyzed using gas chromatography (GC)/mass spectrometry (MS) with quality control samples (instrument blanks, sample duplicates, and duplicate laboratory spikes) included in each batch. Mean sample recoveries from the dust spikes ranged from 73% to 122%. Among the 45 samples run in duplicate, the mean percent differences ranged from 0.5% for tetramethrin 1 to 38% for carbaryl. Table 1 shows the chemical class, method detection limit, and detection frequency for the 20 insecticides and piperonyl butoxide (a synergist) that we measured. Insecticides were measured using the hexane:acetone method for 557 participants (251 cases and 306 controls) and piperonyl butoxide (dichloromethane method) was measured for 556 participants (252 cases and 304 controls).

2.4 Statistical Analysis

We examined the detection frequency for each insecticide, overall and by case/control status. Six insecticides with less than a 5% detection frequency (acephate, dicofol, dimethoate, methidathion, methyl parathion, and phorate; Table 1) were excluded from further analysis. For our analysis, we summed concentrations of all insecticide isomers (allethrin, cyfluthrin, cypermethrin, tetramethrin, and permethrin). The insecticide concentrations were log normally distributed, so we calculated the median and interquartile range and geometric mean and standard deviation among cases and controls. To prevent possible bias from substituting imputed values for samples with non-detectable insecticide concentrations, summary values are presented for those with detectable concentrations for each insecticide. To evaluate correlations among each insecticide that had at least a 40% detection rate, we calculated Spearman rank correlations after applying a single imputation method (Lubin et al. 2004) to assign values for each sample where the insecticide was below the detection limit. This method selects a value from the modeled log-normal transformed distribution of the measured insecticide using the LIFEREG procedure in SAS (Version 9.4; SAS Institute Inc., Cary, NC). When applicable, we included isomers of each insecticide as covariates in the imputation model. We summarized the characteristics of the case and control participants using frequencies and percentages. Chi-square tests were used to examine bivariate differences in characteristics comparing cases to controls.

For risk analyses of six insecticides detected in 5% to ≤12% of samples, we categorized the exposure as detected vs. non-detected. Cyfluthrin and phosmet were detected in 25.6% and 26.9% of homes, respectively, and were modeled as no detections (reference), less than

or equal to the median, and greater than the median value among controls. For analysis of cypermethrin, detected in 48% of samples, the reference group was those with no detectable concentration of the active ingredient and we categorized the concentrations into tertiles based on the concentration distribution of controls. Carbaryl and propoxur were detected in 67.6% and 66.9% of homes, respectively. The reference group was those with no detectable concentration of the active ingredient and we categorized the concentrations into quartiles based on the concentration distribution of controls. For the four insecticides that were detected in greater than or equal to 75% of the samples, we categorized the distribution into quartiles based on detected concentrations and imputed values among controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression.

We used separate models to estimate the association of each insecticide with ALL. We evaluated linear trend by modeling medians of the tertile and quartile concentrations as continuous variables. Models were initially adjusted for the child's age (continuous, years), sex (male or female), and race/ethnicity (Hispanic, non-Hispanic White, or non-Hispanic other). We examined additional covariates as potential confounders, including household income, maternal age, maternal education, season and year of dust sampling, and characteristics of the residence such as year the home was built and type of structure. In our final models, we included confounding variables that caused a 10% change in the estimate or that had p-values ≤ 0.1 during a stepwise backward elimination process. Fully adjusted models included the child's age, sex, and race/ethnicity, as well as one or more of the following variables: household income (annual), breastfed the child (ever, yes/no), season of dust collection, and year of the interview. To explore the consistency of our findings and evaluate the potential effects of selection bias due to socioeconomic and demographic differences in the response rates of cases and controls, we evaluated interaction terms and stratified models by household income (<$60,000 compared to ≥$60,000) and Hispanic ethnicity (Hispanic compared to non-Hispanic white) for insecticides with at least 40% detection rates.

We also evaluated risk of ALL associated with self-reported home and garden insecticide use during three periods: 1) in the 12 months prior to dust collection; 2) in the three months prior to or during pregnancy; and 3) from birth through three years of age. Due to changes in the Tier 2 study questionnaire over time, only a subset of parents/caregivers were asked about usage in the earlier time periods. Questions about professional insect treatments in all three time periods were added in 2002. For the analyses of self-reported insecticide use, we excluded participants missing data on household uses (n=7) and professional applications (n=76) in the 12 months prior to dust collection, and participants missing data on household uses (n=84) and professional applications (n=153) in the other two time periods. We used individual logistic regression models to estimate ORs and 95% CIs for each self-reported use category using unconditional logistic regression adjusted for covariates.

3. Results

The percent detection ranged from 0.4% to 99.6% for the 29 insecticide active ingredients and isomers and one synergist we measured (Table 1). The organophosphate insecticides

diazinon (79.4%) and chlorpyrifos (89.2%) and the pyrethroid insecticide permethrin (99.6%) were detected most frequently. The insecticide synergist piperonyl butoxide also had a high detection frequency (96.8%). Geometric means and median concentrations of the various insecticides were similar in the dust samples from cases and controls (Table 2). Carbaryl and permethrin concentrations were lower in samples from homes of cases relative to controls. Among the insecticides that were detected in at least 40% of samples (cypermethrin, propoxur, carbaryl, diazinon, chlorpyrifos, piperonyl butoxide, and permethrin), most of the Spearman rank correlation coefficients (r_s) were less than 0.30 (Supplemental Table 1) with the exception of diazinon and chlorpyrifos (r_s=0.38), piperonyl butoxide and permethrin (r_s=0.37), and propoxur and chlorpyrifos (r_s=0.32).

Characteristics of ALL cases and controls (Table 3) did not differ by age or sex. The proportion of children of Hispanic ethnicity was higher among cases compared to controls (37.3 vs. 29.1%), and a larger proportion of controls were non-Hispanic white compared to cases (49.3 vs. 36.9%). There was little difference between cases and controls in relation to the urbanicity of the neighborhood (urban, suburban, or rural) and age of the residence. Annual household income and the season of dust collection differed among cases and controls. Relative to cases, a larger proportion of controls lived in households with annual incomes greater than $75,000 (37.7% vs. 52.0%). Only a small proportion of participants (<5%) had anyone living in the home that reported working in a job in which pesticides were used; proportions did not differ by case status. Fewer controls than cases had dust collected in the winter; whereas, more controls had dust collected in the spring and fall.

There were no associations with ALL among any of the insecticides that were modeled as dichotomous exposures (detectable vs. non-detectable) (Table 4). No association was observed for phosmet and cyfluthrin concentrations categorized as non-detects, ≤median, and > median or for cypermethrin categorized as tertiles. In fully adjusted multivariable models for the more commonly detected (≥60% of homes) active ingredients, the results were null. Compared with those with non-detectable levels of carbaryl, the highest quartile compared to the non-detects was not significant (carbaryl Q4 vs. non-detects OR=0.61, 95% CI 0.34–1.08, p for trend=0.06). Compared with those in the lowest quartile of chlorpyrifos, the highest quartile was inversely associated with risk (OR Q4 vs. OR Q1 =0.60; 95% CI 0.36–1.00) but the trend was nonsignificant (p for trend =0.16). A similar inverse association was observed for diazinon (OR Q4 vs. OR Q1 =0.50; 95% CI 0.29–0.87; p for trend =0.14) but estimates lacked a monotonic exposure-response. When the three insecticides were included in the same fully adjusted model, the p-value for trend was not significant for any of the insecticides and the ORs for the highest level compared to the lowest were not significant (carbaryl Q4 vs. non-detects OR=0.66, 95% CI 0.36–1.18, p for trend=0.11; chlorpyrifos Q4 vs. Q1 OR=0.73, 95% CI 0.42–1.24, p for trend=0.36; diazinon Q4 vs. Q1 OR=0.59, 95% CI 0.33–1.05, p for trend=0.28). Permethrin was the most frequently detected insecticide; it was not associated with ALL risk (OR Q4 vs. OR Q1 =0.81; 95% CI 0.50–1.31; p for trend =0.83). Concentrations of propoxur and piperonyl butoxide were not associated with ALL risk.

When we restricted our analyses to children who lived at their tier 2 home for at least two years or longer prior to their diagnosis or reference date (n=340) and evaluated fully

adjusted individual models for insecticides with ≥ 60% detection, only the OR for the highest level compared to the lowest and trend for diazinon was significant (OR Q4 vs. Q1= 0.44, 95% CI 0.22–0.92; p for trend=0.08). When we restricted our analyses to the 276 children who lived in their tier 2 home since birth, the ORs for chlorpyrifos were of similar magnitude and the ORs for the other insecticides were closer to one but none of the ORs or trends were significant (not shown).

There were no significant interactions with self-reported annual household income levels (<$60,000 compared to ≥$60,000) or race/ethnicity (Hispanic compared to non-Hispanic white) for cypermethrin, propoxur, chlorpyrifos, diazinon, or permethrin insecticides (not shown). For carbaryl, the interaction with income was of borderline significance (p-value=0.15). There was no association of carbaryl and ALL among the lower income group (Table 5); whereas, among those with household incomes ≥$60,000, the highest carbaryl quartile was inversely associated with risk (OR=0.43; 95% CI 0.19–0.97). There was no interaction for carbaryl and Hispanic ethnicity (p=0.30).

To compare with our analysis of insecticide active ingredients, we assessed associations with self-reported insecticide treatments within the 12 months prior to the tier 2 visit date. None of the insect treatments were associated with ALL risk (Supplemental Table 2). For the subset of participants who provided information on home and garden insecticide use in the three months prior to or during pregnancy, and birth through three years of age, we found results that were generally consistent with our results for insecticide active ingredients within the previous 12 months, i.e., the findings were null and non-significant (data not shown).

4. Discussion

In this study we measured multiple carbamate, organophosphate, and pyrethroid insecticides in household dust and examined the associations with risk of childhood ALL. Among the 14 insecticides and one insecticide synergist that were detected in at least 5% of homes, we did not observe any associations with risk of ALL. Although some estimates were in the inverse direction, neither the ORs nor the trends were statistically significant in adjusted models.

To the best of our knowledge, no prior epidemiologic study has measured carbamate, organophosphate, or pyrethroid insecticide active ingredients in household dust to evaluate the risk of childhood leukemia. However, multiple studies have evaluated self-reported pesticide use data and childhood leukemia risk. Pooled analyses, systematic reviews, and meta-analyses suggest pesticide use in and around the home during pregnancy and in early childhood increases the risk of childhood leukemia (Bailey et al. 2015; Turner et al. 2010; Van Maele-Fabry et al. 2019). In a pooled study from the Childhood Leukemia International Consortium (CLIC), increased odds of ALL were observed for any household pesticide use reported during the periods shortly before conception, during pregnancy and after birth. Increased risk during these time periods was associated with exposure to professional pest control treatments, household insecticides, pesticides used on pets, and insecticides used on plants or trees (Bailey et al. 2015). In Turner et al.'s meta-analysis of four studies, the summary odds ratio for residential insecticide use during pregnancy and ALL was

2.14 (95% CI 1.83–2.50); whereas insecticide use during childhood was not significantly associated with risk (OR=1.35, 95% CI 0.76–2.38) (Turner et al. 2010). In an updated meta-analysis of eight studies, six of which were published after 2010, the summary odds ratios for pesticide exposure during preconception and pregnancy were both increased (OR=1.30, 95% CI 1.12–1.51 and OR=1.39, 95% CI 1.21–1.60, respectively) and exposure during childhood was also positively associated with ALL risk (OR=1.24, 95% CI 0.90–1.70) (Van Maele-Fabry et al. 2019). When the authors evaluated insecticide use specifically, the summary odds ratio for ALL and prenatal use was 1.28 (95% CI 1.07–1.53), whereas use during childhood was not significant 1.19 (95% CI 0.90–1.57). Taken together, these studies indicate that self-reported residential pesticide use during pregnancy shows the strongest association with risk. Differences in associations during varying time periods of exposure may be related to the etiology of the disease and mechanisms of detoxification that could change from preconception through childhood. For example, organophosphate insecticide active ingredients can cross the placenta, exposing the fetus in utero (Barr et al. 2007; Whyatt et al. 2003). During this period of development, detoxifying enzymes that can deactivate organophosphates may not be present at levels for effective metabolism, thus increasing susceptibility during the pregnancy period. Decreased ability to detoxify compounds may persist in early infancy as the immune, nervous, and other systems continue to develop. One such example is paraoxonase (PON1), an important organophosphate-detoxifying enzyme synthesized in the liver (Costa et al. 2008). A developing infant does not have PON1 levels adequate for organophosphate metabolization until 6–15 months of age (Cole et al. 2003), indicating that very early childhood, but perhaps not late childhood could be another important period of susceptibility to organophosphate exposure.

It is not clear why we did not also observe increased risk of ALL associated with residential use of insecticides in our study of residentially-stable younger cases and controls in the CCLS who participated in the tier 2 interview. In an early report from the CCLS based on 162 pairs of cases and controls, self-reported personal and professional household insecticide use (excluding flea control products) during pregnancy was associated with the highest risk of ALL (OR=2.3, 95% CI 1.3–4.0) (Ma et al. 2002). This finding persisted in a recent analysis of the CCLS that included 840 cases and 1,226 controls, in which increased risk of ALL was observed among children whose caregivers reported personal and/or professional pesticide use in the home during pregnancy (OR=1.31, 95% CI 1.05–1.62 and OR=1.28, 95% CI 1.04–1.59, respectively) (Bailey et al. 2015). Another recent CCLS study found increased risk of ALL among children whose fathers were occupationally exposed to pesticides during the perinatal period (OR=1.7, 95% CI 1.2–2.5) (Gunier et al. 2017).

Prior work in the CCLS Tier 2 study population showed that the percent agreement between self-reported insect treatments during the 12 months before the birth and the 12 months before the dust sampling ranged from 61% for ants/cockroaches to 93% for carpenter ants/termites and was similar among cases and controls (Deziel et al. 2015). In that study of self-reported pest treatments and dust levels in the homes, concentrations of insecticide active ingredients were higher in homes that reported insect treatments and there were no case-control differences in the relationships of self-reported use and insecticide or herbicides concentrations in the dust. In the current study we used household carpet dust as an indicator

of past exposure to insecticides that were likely present in the home prior to diagnosis. Dust is a well-documented reservoir for many compounds, and inadvertent ingestion of house dust is a major route of exposure among children (Butte and Heinzow 2002). Although carbamate, organophosphate, and pyrethroid insecticides have relatively longer half-lives in household dust compared to outdoor areas, it is likely that one sample of house dust may not accurately represent average levels of household concentrations that were present in the home during the period prior to ALL diagnosis for these particular classes of insecticides. In a complementary exposure study that used the same sampling and laboratory methods and that was conducted during the same time period in one of our study counties, the intraclass correlation coefficients (ICC) calculated on repeat samples over a two-year period demonstrated that carbaryl and chlorpyrifos had the lowest ICCs of the seven insecticides evaluated (0.45 and 0.48, respectively) (Deziel et al. 2013). The low ICCs indicate that there was large variability in the concentrations of carbaryl and chlorpyrifos over the two-year period within homes, suggesting that dust concentrations of these insecticides are not likely to be stable over time. Therefore, measurement of these insecticides using only one dust sample is unlikely to be a satisfactory representation of exposure during the period prior to ALL diagnosis. In the exposure study, ICCs for diazinon, propoxur, cypermethrin, and permethrin were 0.75, 0.73, 0.83, and 0.87 respectively, suggesting that one dust sample is a good indicator of household concentrations over a two-year period (Deziel et al. 2013).

Little is known about the ability of insecticide active ingredients to act as leukemogens in children. The International Agency for Research on Cancer (IARC) classifies the organophosphate insecticides diazinon and malathion as probably carcinogenic to humans based on mechanistic studies, animal studies, and limited evidence from epidemiologic studies of non-Hodgkin lymphoma, leukemia, prostate, and lung cancer and occupational exposures in adults (Guyton et al. 2015; International Agency for Research on Cancer, 2017). IARC has additionally reviewed dicofol (organochlorine), deltamethrin (organochlorine), methyl parathion (organophosphate), carbaryl (carbamate), and permethrin (pyrethroid) insecticides and deemed these insecticides not classifiable as to their carcinogenicity in humans (International Agency for Research on Cancer 2020).

Few epidemiologic studies have examined associations of specific carbamate, organophosphate, and pyrethroid pesticide active ingredients with childhood cancer risk. These studies are difficult to conduct due to the cost and time needed to collect and measure active ingredients in environmental samples and the lack of a suitable biomarker of long-term exposure. A previous CCLS study used the California agricultural pesticide use reporting data for 213 ALL cases and 268 controls, and observed increased odds of ALL among those with moderate, but not high, exposure to agricultural insecticides used within a half-mile radius of the home compared to those with no use within this distance (Rull et al. 2009). Recently, Wheeler et al. (Wheeler et al. 2021) used grouped weighted quantile sum regression to estimate exposure mixture effects for six groups of chemicals that we measured in CCLS homes (polychlorinated biphenyls, insecticides, herbicides, metals, polycyclic aromatic hydrocarbons, and tobacco). They found an inverse association with all childhood leukemias and the insecticide group that was similar to the inverse associations we observed for several insecticides in individual models. One population-based case-control study in Denver, Colorado found increased odds of childhood leukemia among children of mothers

that used pest strips in the home during three time periods that included the last three months of pregnancy, birth through two years prior to diagnosis, and two years prior to diagnosis (Leiss and Savitz 1995). Given the time period of the study, the authors suggested that the active ingredient in the pest strips was likely to be dichlorvos, which is an organophosphate insecticide that was not feasible to measure in our study due to its high volatility. A study of childhood leukemia cases and hospital-based controls in Shanghai, China examined associations with five nonspecific pyrethroid insecticide metabolites and five nonspecific organophosphate metabolites measured in urine samples collected shortly after diagnosis (Ding et al. 2012). Concentrations of three pyrethroid metabolites that indicated exposure to cypermethrin and permethrin were associated with increased risk of ALL, but the associations between self-reported household pesticide use during the period from birth to diagnosis and ALL were null except for use of mosquito repellant (OR=1.63, 95% CI 1.04–2.55) (Ding et al. 2012). Additionally, self-reported household pesticide use from birth to diagnosis was not correlated with urinary pyrethroid metabolite levels (Ding et al. 2012). These findings may reflect the limits of urinary biomarkers for estimating past exposure to insecticides as post-diagnosis measures may not accurately represent exposure levels during the time period most relevant to childhood leukemia etiology. Similar findings were observed in another study where urinary organophosphate metabolites were positively associated with odds of childhood leukemia, but not highly correlated with household insecticide use (Zhang et al. 2015). No other studies exist for which we can make comparisons with our study results.

Although there have been changes in insecticide use and formulations since the completion of our study, many of the insecticides we measured are currently used in agriculture and on lawns and gardens. Chlorpyrifos and diazinon were restricted from household use in 2001 and 2004, and product registrations for household use of carbaryl and propoxur were voluntarily cancelled by manufacturers in 2008, including all indoor uses of carbaryl. Despite this, chlorpyrifos is registered for over 50 agricultural uses including on a broad spectrum of crops, such as apples, almonds, broccoli, corn, and grapes. In 2012, an estimated 6 million pounds of chlorpyrifos were used in US agricultural applications (Atwood and Paisley-Jones 2017). In that same year, an estimated 2–4 million pounds of carbaryl and 1–3 million pounds of permethrin and other pyrethroids were purchased for application in the home and garden market (Atwood and Paisley-Jones 2017). Continued use of these insecticides justifies investigation of these and other common pesticides as risk factors for the development of childhood leukemia.

Major strengths of our study include objective measurement of the active ingredients that were some of the most widely used agricultural, home, and garden insecticides available during the study period. We incorporated detailed environmental sampling methods to collect a dust sample from the room in the home where the child spent most of their time. We enrolled population-based controls selected from birth certificates and were able to enroll cases quickly following diagnosis (median=117 days from diagnosis to the tier 1 interview; 25^{th}–75^{th} percentile=81–168 days).

Our study has several limitations that should be considered when interpreting our findings. Although we recognize that diet is an important pesticide exposure pathway, we did not

ask any questions related to organic versus non-organic diet. The exposure assessment in our study is focused on sources that contribute to dust exposure in the home environment, such as home and garden use of insecticides or nearby agricultural uses. Although cases and controls were matched on race/ethnicity at enrollment, the tier 2 interview eligibility requirement that participants had not moved since diagnosis (similar reference date for controls) resulted in slight differences by race/ethnicity. Among this residentially-stable population, 29% of controls were Hispanic compared to 37% of ALL cases, whereas in the larger CCLS study population, 45% of controls and 46% of ALL cases were Hispanic (Bartley et al. 2010). However, when we stratified our analyses to evaluate potential interaction by ethnicity, we observed similar null associations among Hispanics and non-Hispanic whites. Among the full study population, household income was higher among controls compared with cases (Bartley et al. 2010). Similarly, in our tier 2 population, a smaller proportion of control households reported annual incomes less than $60,000 compared to cases (38% vs. 55%). The interaction term between carbaryl and income level was borderline significant; we observed an inverse association between carbaryl concentrations and ALL risk among the higher income group, whereas there was no association among lower income participants. These results suggest that the inverse association between carbaryl and ALL may be due to selection bias attributed to higher participation rates among wealthier controls than less wealthy controls at the tier 1 and tier 2 interviews (Bartley et al. 2010; Ma et al. 2002; Ward et al. 2009). Additionally, control homes had higher dust levels of some of the active ingredients, which is consistent with the larger number of control households that reported using insecticides in and around the home. These results are consistent with previous findings that showed CCLS tier 2 participants in higher income households stored more pesticide products in their homes relative to lower income households (Guha et al. 2013).

Dust samples were collected at a second interview that took place after the initial study enrollment interview. Due to regulatory changes and the resulting decreases in use, concentrations of chlorpyrifos, diazinon, and propoxur in carpet dust declined during the study period (Gunier et al. 2016). If there was substantial difference in the timing of dust collection between cases and controls, our results could be diluted by temporal trends in insecticide use. Indeed, the time between the reference date and dust collection was slightly less for cases compared to controls. However, cases and controls were interviewed over the entire period 2001–2007 and results were adjusted for interview year. Further, stratification by the median interview year revealed results that were similar to those for the entire time period. Although indoor dust samples have been used previously as surrogates for long-term exposures to other analytes (Colt et al. 2005; Deziel et al. 2014; Lewis et al. 1994; Metayer et al. 2013; Ward et al. 2014; Ward et al. 2009), the active ingredients we measured may be less stable over time (Deziel et al. 2013) indicating that one dust sample may not represent a chronic exposure level. Our measurements may be most reflective of recent exposures, and since the sample was taken after diagnosis it may not reflect the most etiologically relevant time period for childhood ALL, particularly if case households changed their insecticide use after diagnosis. This may explain, in part, why we did not observe increased odds of ALL with any insecticide concentrations. Given the limitations to our study, our results should be interpreted within the context of the study design.

5. Conclusion

In summary, we did not observe any risk of ALL associated with the carbamate, organophosphorus, or pyrethroid insecticide active ingredients that we measured in household dust. In light of the consistent positive associations observed with self-reported pesticide use and ALL risk in other studies, additional investigation of these and other common pesticide active ingredients during time periods critical to the development of childhood leukemia, such as preconception or during pregnancy, are warranted to further evaluate specific insecticides and other pesticides that may be etiologic risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary of 20 insecticide active ingredients and one synergist measured in house-dust from ALL cases (n=252) and controls (n=306) with detection limits and frequencies of detection.

Insecticide	Chemical class	Detection limit (ng/g dust)	Detected n (%)
trans-Permethrin	Pyrethroid	2	556 (99.6)
cis-Permethrin	Pyrethroid	2	549 (98.4)
Piperonyl butoxide	Synergist	4	540 (96.8)
Chlorpyrifos	Organophosphate	5	498 (89.2)
Diazinon	Organophosphate	2	443 (79.4)
Carbaryl	Carbamate	2	377 (67.6)
Propoxur	Carbamate	5	373 (66.9)
Cypermethrin 2	Pyrethroid	20	269 (48.2)
Cypermethrin 3	Pyrethroid	20	269 (48.2)
Cypermethrin 4	Pyrethroid	20	264 (47.3)
Cypermethrin 1	Pyrethroid	20	258 (46.2)
Phosmet	Organophosphate	25	150 (26.9)
Cyfluthrin 3	Pyrethroid	20	142 (25.5)
Cyfluthrin 4	Pyrethroid	20	140 (25.1)
Cyfluthrin 2	Pyrethroid	20	136 (24.4)
Cyfluthrin 1	Pyrethroid	20	115 (20.6)
Tetramethrin 2	Pyrethroid	2	69 (12.4)
Deltamethrin	Pyrethroid	50	68 (12.2)
Malathion	Organophosphate	10	48 (8.6)
Azinphos methyl	Organophosphate	100	42 (7.5)
Allethrin 1	Pyrethroid	20	40 (7.2)
Allethrin 2	Pyrethroid	20	40 (7.2)
Tetramethrin 1	Pyrethroid	2	40 (7.2)
Heptachlor	Organochlorine	10	27 (4.8)
Methyl parathion	Organophosphate	20	18 (3.2)
Dimethoate	Organophosphate	25	14 (2.5)
Phorate	Organophosphate	25	12 (2.2)
Dicofol	Organochlorine	50	8 (1.4)
Acephate	Organophosphate	100	3 (0.5)
Methidathion	Organophosphate	10	2 (0.4)

Table 2.

Summary of concentrations[a] (ng/g) of 14 insecticides and one synergist that were detected in ≥5% of house dust samples among 252 childhood ALL cases and 306 controls in the California Childhood Leukemia Study, 2001–2007

	ALL cases (n=252)			Controls (n=306)		
Insecticide	**Detection frequency n (%)**	**Median (25^{th}–75^{th} percentile)**	**Geometric Mean (SD)**	**Detection frequency n (%)**	**Median (25^{th}–75^{th} percentile)**	**Geometric Mean (SD)**
Heptachlor	13 (5.2)	27.8 (13.6–46.0)	26.6 (2.8)	14 (4.6)	29.3 (16.3–45.2)	28.9 (2.0)
Allethrin	17 (6.7)	269.4 (105.6–528.6)	208.6 (2.6)	23 (7.5)	251.0 (75.7–1724.0)	333.0 (6.3)
Malathion	19 (7.5)	98.7 (62.1–251.0)	111.0 (3.8)	29 (9.5)	88.8 (54.3–176.9)	109.3 (4.1)
Azinphos methyl	21 (8.3)	99.6 (54.2–138.6)	90.6 (3.1)	21 (6.9)	148.3 (93.7–232.7)	143.7 (2.4)
Tetramethrin	28 (11.1)	198.8 (62.0–752.4)	254.0 (6.6)	43 (14.1)	102.6 (27.6–293.1)	127.9 (7.3)
Deltamethrin	31 (12.3)	400.7 (176.2–911.1)	449.0 (3.2)	37 (12.1)	463.8 (198.6–964.6)	567.6 (4.2)
Cyfluthrin	63 (25.0)	453.3 (192.3–1507.6)	567.5 (4.3)	80 (26.1)	501.2 (240.2–927.1)	632.9 (4.1)
Phosmet	66 (26.2)	20.7 (9.5–70.1)	25.9 (3.4)	84 (27.5)	19.0 (10.4–40.1)	25.6 (3.9)
Cypermethrin	117 (46.4)	596.4 (240.2–1278.9)	674.3 (3.6)	152 (49.7)	548.6 (258.7–1489.8)	701.5 (4.3)
Carbaryl	163 (64.7)	22.4 (11.7–53.3)	28.8 (4.5)	214 (69.9)	34.9 (14.8–108.2)	45.4 (4.9)
Propoxur	167 (66.3)	20.9 (9.4–52.7)	24.9 (4.1)	206 (67.3)	21.9 (8.3–55.2)	22.3 (3.9)
Diazinon	193 (76.6)	17.0 (6.1–37.0)	18.3 (4.2)	250 (81.7)	14.1 (6.1–43.0)	18.8 (4.8)
Chlorpyrifos	219 (86.9)	32.7 (14.2–80.6)	38.9 (3.7)	279 (91.2)	32.8 (15.8–87.7)	38.7 (3.4)
Piperonyl butoxide	244 (96.8)	158.6 (54.3–680.1)	220.4 (6.6)	296 (96.7)	171.2 (57.1–705.5)	238.8 (7.0)
Permethrin	250 (99.2)	859.5 (341.7–4415.8)	1301.8 (6.4)	306 (100.0)	1182.1 (449.7–4207.8)	1671.8 (6.2)

[a]Distributions of concentrations for samples with detectable levels only (no imputed values for non-detects)

Table 3.

Demographic and residential characteristics of 252 childhood ALL cases and 306 controls in the California Childhood Leukemia Study[a], 2001–2007

Children's Characteristics	Cases n (%)	Controls n (%)	p-value[h]
Sex			
Male	146 (57.9)	181 (59.1)	0.77
Female	106 (42.1)	125 (40.9)	
Age, years (mean ±SD)	4.0 ±1.8	3.7 ±1.8	
< 1	5 (2.0)	12 (3.9)	0.32
1 to <2	32 (12.7)	41 (13.4)	
2 to 5	142 (56.3)	181 (59.2)	
> 5	73 (29.0)	72 (23.5)	
Race/ethnicity			
Hispanic	94 (37.3)	89 (29.1)	0.01
White, non-Hispanic	93 (36.9)	151 (49.3)	
Other, non-Hispanic	65 (25.8)	66 (21.6)	
Maternal age, years (mean ±SD) [b]	29.8±6.2	30.5±5.8	
<30	114 (45.2)	138 (45.1)	0.95
≥30	135 (53.6)	165 (53.9)	
Unknown	3 (1.2)	3 (1.0)	
Breastfeeding			
Yes	235 (93.2)	272 (88.9)	0.07
No[c]	17 (6.8)	34 (11.1)	
None to <3 months	84 (33.3)	90 (29.4)	
3 to <6 months	43 (17.1)	49 (16.0)	
6 to <12 months	64 (25.4)	78 (25.5)	
12 or more months	61 (24.2)	89 (29.1)	0.16
Annual household income			
<$15,000	24 (9.5)	16 (5.2)	0.006
$15,000 to $29,999	33 (13.1)	27 (8.8)	
$30,000 to $44,999	41 (16.3)	36 (11.8)	
$45,000 to $59,999	41 (16.3)	39 (12.7)	
$60,000 to $74,999	18 (7.1)	29 (9.5)	
>$75,000	95 (37.7)	159 (52.0)	
Neighborhood type			
Urban	181 (71.8)	225 (73.5)	0.13
Suburban	36 (14.3)	28 (9.1)	
Rural	29 (11.5)	44 (14.4)	
Unknown	6 (2.4)	9 (3.0)	

Children's Characteristics	Cases n (%)	Controls n (%)	p-value[h]
Residence build year			
1980 to present	96 (38.1)	123 (40.2)	0.96
1950 to 1979	88 (34.9)	109 (35.6)	
Before 1950	33 (13.1)	44 (14.4)	
Unknown	35 (13.9)	30 (9.8)	
Household member occupation [d]			
Farmer/farm or ranch worker	11 (4.4)	15 (4.9)	0.76
Gardener, groundskeeper, landscape, or nursery worker	11 (4.4)	14 (4.6)	0.90
Packer or agricultural worker	7 (2.8)	6 (2.0)	0.52
Pesticide handler or mixer	4 (1.6)	7 (2.3)	0.76
Season of dust collection			
Winter	62 (24.6)	42 (13.7)	0.001
Spring	54 (21.4)	91 (29.7)	
Summer	82 (32.6)	85 (27.8)	
Fall	54 (21.4)	88 (28.8)	
Year of interview			
2001–2002	63 (25.0)	62 (20.3)	0.10
2003–2004	92 (36.5)	94 (30.7)	
2005–2006	67 (26.6)	101 (33.0)	
2007	30 (11.9)	49 (16.0)	
Self-reported insecticide use			
Household [e]			
Ant/cockroach use	169 (67.1)	224 (73.2)	0.10
Carpenter ants/termites	10 (4.0)	22 (7.2)	0.10
Flying insects[f]	63 (25.0)	93 (30.4)	0.15
Fleas/ticks in home	23 (9.1)	35 (11.4)	0.37
Fleas/ticks on pets	56 (22.2)	90 (29.4)	0.05
Indoor insects	200 (79.4)	260 (85.0)	0.07
Lawn/garden insects	65 (25.8)	98 (32.0)	0.10
Professional [g]			
Professional indoor	24 (9.5)	41 (13.4)	0.20
Professional outdoor	57 (22.6)	76 (24.8)	0.71

[a] Participants are cases and controls from the CCLS that consented to the tier 2 visit, and had adequate dust samples for measurement of insecticide concentrations

[b] n=3 mothers of cases and n=3 mothers of controls missing age

[c] n=1 participant missing data on breastfeeding was categorized as "no"

[d] n=1 participant missing data on occupations was categorized as "no"

[e] n=7 (n=3 cases and n=4 controls) missing household insecticide use information

[f] Flying insects defined as any product to treat bees, wasps, hornets, flies, or mosquitos

[g] n=76 (n=39 cases and n=37 controls) missing professional insecticide use information

[h] Chi-Square tests were used to examine differences in characteristics comparing cases to controls; unknown values for maternal age, neighborhood type, year the residence was built, and insecticide uses were excluded for testing differences between cases and controls

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Table 4.

Multivariable adjusted odds ratios (ORs) and 95% CIs for childhood ALL associations with 14 insecticides[a] and one synergist[b] measured in house-dust from homes of 252 childhood ALL cases and 306 controls in the California Childhood Leukemia Study, 2001–2007

Insecticide Concentration (ng/g)	Number of cases	Number of controls	Model 1 (minimally adjusted) OR (95% CI)[c]	Model 2 (fully adjusted) OR (95% CI)
Insecticides with <40% detection				
Allethrin				
Non-detect	234	283	1.0 (ref)	1.0 (ref)
Detect	17	23	0.80 (0.41–1.56)	0.89 (0.44–1.79)[d]
Azinphos methyl				
Non-detect	230	285	1.0 (ref)	1.0 (ref)
Detect	21	21	1.26 (0.67–2.39)	1.25 (0.64–2.43)[e]
Deltamethrin				
Non-detect	220	269	1.0 (ref)	1.0 (ref)
Detect	31	37	1.03 (0.61–1.73)	0.96 (0.56–1.66)[e]
Heptachlor				
Non-detect	238	292	1.0 (ref)	1.0 (ref)
Detect	13	14	1.10 (0.50–2.42)	1.19 (0.53–2.69)[e]
Malathion				
Non-detect	232	277	1.0 (ref)	1.0 (ref)
Detect	19	29	0.83 (0.44–1.52)	0.73 (0.39–1.39)[e]
Tetramethrin				
Non-detect	223	263	1.0 (ref)	1.0 (ref)
Detect	28	43	0.73 (0.44–1.22)	0.70 (0.41–1.21)[e]
Cyfluthrin				
Non-detect	188	226	1.0 (ref)	1.0 (ref)
≤ 501.2 ng/g	37	40	1.20 (0.73–1.99)	1.13 (0.67–1.90)
> 501.2 ng/g	26	40	0.82 (0.48–1.41)	0.91 (0.52–1.60)[e]

Insecticide Concentration (ng/g)	Number of cases	Number of controls	Model 1 (minimally adjusted) OR (95% CI)[c]	Model 2 (fully adjusted) OR (95% CI)
Phosmet				
Non-detect	185	222	1.0 (ref)	1.0 (ref)
≤ 19.0 ng/g	30	42	0.88 (0.52–1.47)	1.10 (0.63–1.86)
> 19.0 ng/g	36	42	0.99 (0.60–1.62)	1.12 (0.67–1.89)[e]
Insecticides with 40% to <60% detection				
Cypermethrin				
Non-detect	134	154	1.0 (ref)	1.0 (ref)
T1 ≤ 323.5 ng/g	36	51	0.85 (0.52–1.39)	0.81 (0.49–1.35)
T2 323.6 ng/g to 897.2 ng/g	35	50	0.76 (0.46–1.26)	0.68 (0.40–1.16)
T3 > 897.2 ng/g	46	51	1.03 (0.64–1.64)	0.89 (0.54–1.44)[f]
p-value for trend			0.84	0.70
Insecticides with ≥60% detection				
Carbaryl				
Non-detect	88	92	1.0 (ref)	1.0 (ref)
Q1 ≤14.8 ng/g	61	54	1.16 (0.72–1.88)	1.14 (0.68–1.89)
Q2 > 14.8 ng/g to 34.9 ng/g	46	53	0.93 (0.57–1.54)	0.81 (0.47–1.39)
Q3 > 34.9 ng/g to 108.2 ng/g	27	54	0.57 (0.33–0.99)	0.49 (0.27–0.89)
Q4 >108.2 ng/g	29	53	0.57 (0.33–0.98)	0.61 (0.34–1.08)[e]
p-value for trend			0.02	0.06
Propoxur				
Non-detect	84	99	1.0 (ref)	1.0 (ref)
Q1 ≤8.3 ng/g	35	52	0.82 (0.48–1.38)	0.65 (0.37–1.14)
Q2 > 8.3 ng/g to 21.9 ng/g	51	51	1.20 (0.73–1.97)	0.96 (0.57–1.62)
Q3 > 21.9 ng/g to 55.1 ng/g	40	52	0.83 (0.49–1.39)	0.63 (0.36–1.10)
Q4 >55.1 ng/g	41	51	0.95 (0.57–1.59)	0.66 (0.37–1.17)[e]
p-value for trend			0.86	0.25
Chlorpyrifos				
Q1 (≤ 12.6 ng/g includes non-detects)	75	77	1.0 (ref)	1.0 (ref)

Insecticide Concentration (ng/g)	Number of cases	Number of controls	Model 1 (minimally adjusted) OR (95% CI)[c]	Model 2 (fully adjusted) OR (95% CI)
Q2 > 12.6 ng/g to 28.6 ng/g	56	76	0.75 (0.47–1.21)	0.68 (0.41–1.12)
Q3 > 28.6 ng/g to 72.4 ng/g	60	77	0.77 (0.48–1.23)	0.64 (0.39–1.07)
Q4 > 72.4 ng/g	60	76	0.76 (0.47–1.22)	0.60 (0.36–1.00)[e]
p-value for trend			0.48	0.16
Diazinon				
Q1 (≤ 3.2 ng/g includes non-detects)	75	77	1.0 (ref)	1.0 (ref)
Q2 > 3.2 ng/g to 9.3 ng/g	50	76	0.66 (0.41–1.08)	0.54 (0.32–0.89)
Q3 > 9.3 ng/g to 28.9 ng/g	66	77	0.81 (0.51–1.30)	0.58 (0.35–0.97)
Q4 > 28.9 ng/g	60	76	0.79 (0.50–1.27)	0.50 (0.29–0.87)[e]
p-value for trend			0.77	0.14
Permethrin				
Q1 (≤ 449.6 includes non-detects)	86	77	1.0 (ref)	1.0 (ref)
Q2 > 449.6 ng/g to 1182.1	57	76	0.70 (0.44–1.11)	0.70 (0.43–1.13)
Q3 > 1182.1 ng/g to 4207.8 ng/g	43	77	0.49 (0.30–0.81)	0.46 (0.28–0.77)
Q4 > 4207.8 ng/g	65	76	0.78 (0.50–1.24)	0.81 (0.50–1.31)[e]
p-value for trend			0.99	0.83
Piperonyl butoxide (synergist)				
Q1 (≤ 53.3 ng/g includes non-detects)	68	76	1.0 (ref)	1.0 (ref)
Q2 > 53.3 ng/g to 156.6 ng/g	61	76	0.89 (0.55–1.43)	0.80 (0.49–1.32)
Q3 > 156.6 ng/g to 656.5 ng/g	61	76	0.87 (0.54–1.40)	0.83 (0.50–1.38)
Q4 > 656.5 ng/g	62	76	0.89 (0.55–1.44)	0.78 (0.47–1.29)[e]
p-value for trend			0.84	0.55

[a] Insecticides were measured using the hexane:acetone method for 557 participants (251 cases and 306 controls)

[b] Piperonyl butoxide was measured using the dichloromethane method for 556 participants (252 cases and 304 controls

[c] Adjusted for age (continuous, years), sex (male or female), race/ethnicity (Hispanic, non-Hispanic White, or non-Hispanic Other) of the child

[d] Additionally adjusted for household income (annual), breastfeeding (ever, yes/no), season of dust collection, and year of the interview

[e] Additionally adjusted for household income (annual), season of dust collection, and year of the interview

[f] Additionally adjusted for household income (annual) and season of dust collection

Table 5.

Multivariable adjusted odds ratios (ORs) and 95% CIs for childhood ALL associations with carbaryl insecticide concentrations measured in house-dust by income group in the California Childhood Leukemia Study, 2001–2007

Insecticide Concentration (ng/g)	Income <60k			Income ≥60k		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
Carbaryl	**(n)**	**(n)**		**(n)**	**(n)**	
Non-detect	39	38	1.0 (ref)	49	54	0.98 (0.52, 1.83)
Q1	38	18	2.14 (1.01–4.53)	23	36	0.67 (0.33–1.38)
Q2	30	20	1.42 (0.67–3.04)	16	33	0.50 (0.23–1.22)
Q3	15	22	0.64 (0.28–1.49)	12	32	0.42 (0.18–0.98)
Q4	16	20	0.95 (0.42–2.18)	13	33	0.43 (0.19–0.97)

[a]Adjusted for age (continuous, years), sex (male or female), race/ethnicity (Hispanic, non-Hispanic White, or non-Hispanic Other) of the child, year and season of the interview