HHS Public Access

Author manuscript

J Expo Sci Environ Epidemiol. Author manuscript; available in PMC 2019 March 29.

Published in final edited form as:

J Expo Sci Environ Epidemiol. 2013 July ; 23(4): 363–370. doi:10.1038/jes.2012.115.

Exposure to Herbicides in House Dust and Risk of Childhood Acute Lymphocytic Leukemia

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Abstract

We examine the association between exposure to herbicides and childhood acute lymphoblastic leukemia (ALL). Dust samples were collected from homes of 269 ALL cases and 333 healthy controls (<8 years of age at diagnosis/reference date and residing in same home since diagnosis/reference date) in California, using a high-volume surface sampler or household vacuum bags. Amounts of agricultural or professional herbicides (alachlor, metolachlor, bromoxynil, bromoxynil octanoate, pebulate, butylate, prometryn, simazine, ethafluralin, and pendimethalin) and residential herbicides (cyanazine, trifluralin, MCPA, mecoprop, 2,4-D, chlorthal, and dicamba) were measured. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by logistic regression. Models included the herbicide of interest, age, sex, race/ethnicity, household income, year and season of dust sampling, neighborhood type, and residence type. The risk of childhood ALL was associated with dust levels of chlorthal; compared to homes with no detections, ORs for the first, second, and third tertiles were 1.49 (95% CI:0.82–2.72), 1.49 (95% CI:0.83–2.67), and OR =1.57 (95% CI:0.90–2.73), respectively (p-value for linear trend=0.05). The magnitude of this association appeared to be higher in the presence of alachlor. No other herbicides were identified

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Authorship: P.A.B designed the study; C.M., P.A.B., and M.H.W. co-directed its implementation; M.H.W. and JC supervised laboratory work; C.M. supervised the statistical analyses; C.M., H.D.R., and S.S. performed statistical analyses; C.M., and H.D.R. prepared the manuscript; all authors interpreted the data and provided critical review of the article.

Competing Interests Declaration

The authors declare they have no actual or potential competing financial interest.

as risk factors of childhood ALL. The data suggest that home dust levels of chlorthal, and possibly alachlor, are associated with increased risks of childhood ALL.

Keywords

childhood leukemia; herbicides; pesticides; dust

Introduction

Leukemia is the most common childhood cancer, accounting for about a third of all cancers in children ages 0–14. The overall annual incidence rate of childhood leukemia in the United States is 5.1 per 100,000.[1] Acute lymphoblastic leukemia (ALL) represents approximately 75% childhood leukemia cases, followed by acute myeloid leukemia (20%). A peak in the incidence of childhood ALL at 2–5 years of age suggests that environmental exposures early in life may play a role.

Herbicides are defined as pesticides used to control weeds and other unwanted vegetation in gardening, lawn-care, urban settings, forestry, and agriculture.[2] The potential carcinogenicity of most herbicides is unknown.[3–6] An association between self-reported use of residential herbicides during pregnancy and childhood leukemia has been identified in several case-control studies.[7–10] It is unclear, however, whether such an association exists for exposure to herbicides during childhood. A meta-analysis shows an increased risk of childhood leukemia associated with self-reported maternal occupational exposures to herbicides during pregnancy, based on two studies; associations reported for paternal occupational exposure are weak and inconsistent.[11]

Previous epidemiologic studies of childhood leukemia have relied on self-reports to assess herbicide exposure, which limits the ability to identify specific chemical agents and the amount of exposure. Additionally, classification bias may arise from inaccurate recall of herbicide use in caregivers of leukemia cases and caregivers of controls. Although these observations have been consistently noted in reviews on this topic during the last decade, [7, 9, 12] little attempt has been made to better characterize a child's exposure to pesticides, including herbicides.

Young children spend the majority of their time indoors, often on the floor, and frequently place their hands in their mouths. It is estimated that young children ingest approximately 100 mg of dust each day.[13] Dust from carpets and rugs is a reservoir for a variety of chemicals known to be persistent (e.g. organochlorine compounds, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, and nicotine) and a child's ingestion of house dust due to hand-to-mouth behavior is potentially an important route of chemical exposure.[14–20] Here, dust samples collected in a subset of households participating in the Northern California Childhood Leukemia Study (NCCLS) [8] are used to assess the association between dust concentration of 17 herbicides and the risk of childhood ALL.

Methods

Study population

The NCCLS is a population-based, matched case-control study in 17 counties in the San Francisco Bay area and 18 counties in the California Central Valley, a region with high agricultural pesticide use. Children eligible for inclusion in the study were under 15 years of age at the time of enrollment, had no prior cancer diagnosis, were resident in one of 35 counties at the time of diagnosis, and had an available English or Spanish speaking parent or guardian. Cases diagnosed with leukemia under the age of 15 were enrolled through rapid ascertainment from nine pediatric clinical centers. Ascertained cases represented 76% of all diagnosed cases within the 35 study counties. Consent to participate in the NCCLS was obtained from 86% of those determined to be eligible. Controls were randomly selected using birth certificates obtained through the California Office of Vital Records, and individually matched to cases for date of birth, sex, Hispanic ethnicity (either one or both parents being Hispanic, as reported on the birth certificate), and mother's race. Among the eligible controls contacted, 86% consented to participate. The control selection process is presented in more detail elsewhere.[21] Once consent was obtained, an extensive home interview was administered to the child's primary caregiver; 97% of the time, this was the child's biological mother. A total of 997 children with leukemia and 1226 healthy controls (including 882 case-control matched sets) were enrolled in the NCCLS from 1995 to 2008.

From 2001 to 2007, NCCLS families with children less than 8 years of age and living in the same home occupied at the time of diagnosis for cases or reference date for controls were eligible to participate in a follow-up home visit to collect a dust sample and conduct a second interview. The case-control matched sets could not be maintained due to the residential eligibility criteria and individuals' willingness to participate. Of the 731 eligible families (324 cases and 407 controls), 296 households with children with leukemia (91%) including 269 ALL, and 333 controls (82%) participated.

Sample collection

Dust was primarily collected using a high volume small surface sampler (HVS3). Parents were asked to identify the room (excluding the kitchen or the child's bedroom) where the child spent the most time while awake in the year prior to diagnosis (cases) or the reference date (controls). Most often, this room was the living room or family room. Dust was sampled from the room if it contained a carpet or area rug measuring 9 ft^2 or more. The interviewer marked a 4-ft by 6-ft space on the carpet or rug using tape and vacuumed the area in 3-inch strips, going back and forth 4 times on each strip until 10 mL of dust had been collected. Dust samples from household vacuum cleaners were also collected, to provide additional dust in the event a HVS3 sample was not available or sufficient. Starting in July 2006, only households vacuum cleaner bags were collected, after establishing that the two methods of dust collection in the CCLS (HVS3 sampler vs. household vacuum bag) were comparable in terms of detecting and quantifying dust concentrations of a number of herbicides (Pearson correlation coefficients ranging from 0.60 to 0.95 for 2,4-D, MCPA, mecoprop, trifluralin, bromoxynil, chlorthal, and simazine) and other chemical compounds.[22] In the current analyses, about two-thirds of herbicide measurements were performed using

HVS3 dust samples and one-third using vacuum bag samples. Families were asked not to vacuum or empty their vacuum cleaner the week before the interview. During the interview, we asked when the vacuum bag was last changed. The interview was scheduled at the convenience of the participating families. Samples were collected in all seasons, winter (19%), spring (26%), summer (30%), and fall (25%).

A standardized questionnaire was administered to collect information on characteristics of the residence and dust sampling and socio-demographic background (Table 1). Residence location was categorized as urban, suburban, or rural based on global positioning system measurements and the 2000 U.S. census block characteristics (U.S. Census Bureau, 2002). All research was conducted in accordance with the requirements of the institutional review boards at the University of California, Berkeley, the National Cancer Institute, and other participating institutions.

Herbicide selection and laboratory methods

Seventeen herbicides (named according to the International Organization for Standardization, ISO) [23, 24] were selected for analysis based on frequency of use in California and feasibility of laboratory analysis (Table 2). Specifically, the following agricultural or professional-use herbicides[25] commonly used according to the California Pesticide Reporting system were selected: alachlor, metolachlor, bromoxynil, bromoxynil octanoate, pebulate, butylate, prometryn, cyanazine, simazine, ethalfluralin, and pendimethalin.. The selected residential-use herbicides[25] included trifluralin, MCPA, mecoprop (also known as MCPP), 2,4-D, chlorthal (also known as dachtal or DCPA), and dicamba. With the exception of cyanazine, all herbicides studied are currently registered by United States Environmental Protection Agency (USEPA). The chemical analyses have been previously described.[22] In brief, dust samples were sieved with a 100 mesh stainless steel sieve and the fine fraction, particles <150 μm, was retained for analysis. Half gram of sieved dust was used to conduct current analyses. Chemicals were extracted from the fine fraction using either a hexane/acetone, acid herbicide, or dichloromethane extraction method, depending on the chemical nature of the analyte (Table 2). The dust measurement of glyphosate (commercial name Round-up), a common organophosphorus herbicide, requires a different extraction method, which was beyond the scope of the funded study. Detection and quantification of analytes were conducted using gas chromatography/mass spectrometry. The limits of detection for the herbicides (ng/g of dust) are presented in Table 2. Laboratory staff was blinded as to case-control status. Due to insufficient dust or interferences in the chemical analyses, herbicide concentrations could not be quantified in a number of dust samples. A total of 17 ALL cases and 27 controls with missing values for all herbicide concentrations were lost to analyses. A final sample size of 252 children with ALL and 306 controls was available for analysis.

Statistical Analyses

Chi-square tests were used to examine differences in demographic characteristics, residential characteristics, and time of dust collection between cases and controls. Pairwise Pearson correlation coefficients between herbicide concentrations in house dust were estimated. Fisher’s exact tests were used to evaluate differences in the percent detection of herbicides

between cases and controls. Herbicides detected in 12 or fewer households (< 5% detection) were excluded from the analyses. Odds ratios (ORs) and approximate 95% confidence intervals (CIs) were calculated from logistic regression analyses using either (i) binary detection variables for herbicides detected in 5% to 35% of homes, (ii) tertile concentration (above the detection limit) of herbicides detected in 35% to 75% of homes, based on the herbicide concentration distribution among controls, using non-detect as referent group, or (iii) logarithmic-transformed concentrations of herbicide detected in more than 75% homes, imputing one-half the limit of detection for any non-detects. In addition, an imputation method using Tobit regression analyses among controls was conducted to identify the determinants of dust levels. The "Tobit-based" values of herbicide dust level were then calculated for cases and controls with non-detects, using single imputation method. Results of the logistic regression analyses using "Tobit-based" values were similar to those using one-half of the limit of detection. Therefore analyses using one-half of the limit of detection are presented. All herbicides were analyzed individually in separate logistic models. Each model was applied to data by Hispanic status to evaluate difference by ethnic group. Wald chi-square test was use to test for interaction between herbicides.

All statistical analyses were conducted using the combined HVS3 and vacuum bag samples, after assessing that risk estimates for herbicide levels did not vary by dust collection method. Chemical loading was calculated for HVS3 samples. The chemical loading is an estimation of the amount of analyte per square meter of carpet calculated by multiplying the concentration of the analyte by the dust loading (mass of fine dust collected divided by the area sampled). The log-transformed herbicide loadings with one-half the limit of detection imputed for "non-detects" were regressed individually in separate logistic models for herbicides detected in at least 75% of households (simazine, mecoprop, and 2,4-D).

All models included child's sex, age at diagnosis for cases (or reference date for controls), Hispanic status (except for stratified analyses), and maternal race. Other potential confounders, including household income, season of dust sampling, year of dust sampling, neighborhood type (urban, suburban, rural), and residence type (single family home, duplex/townhouse, apartment/condominium, mobile home), were included in regression models when they resulted in changes to an herbicide regression coefficient by 10% or more. The variable for age was continuous; household income was an ordered categorical variable; and the remaining variables were binary. The goodness of fit of the models was assessed by using the Hosmer-Lemeshow test (p-value >0.05 indicates that the model fits the data well).

Results

Compared with case families, controls were more likely to be non-Hispanic White (49% vs. 37%), to have annual household incomes equal to or greater than $75,000 (52% vs. 38%), and to reside in single-family homes (88% vs. 80%) (Table 1). About 25% of case households were sampled in the winter compared to 14% controls. Cases and controls did not differ significantly by neighborhood type (urban, suburban, and rural), the year their residence was built, and the year of dust collection. Usually removing shoes upon entering the home and vacuuming more than once a week were reported by about 30% and 50% of participating families, respectively. These household habits were similar in case and control

families and were not associated with herbicides dust levels. By design, cases were enrolled in the NCCLS before controls, so that the interval between diagnosis (or reference) and dust sampling was shorter in cases (mean: 1.1 years; median: 0.9 year; range: <1 to 3.4 years) compared to controls (mean:1.8 years; median:1.7 years; range from <1 to 4.8 years; p-value for t-test <0.01). The mean interval from the time the child moved into the home where dust was sampled to her/his diagnosis (or reference) date was 2.7 years for cases (median:2.4; range: <1 yr to 8 years), similar to that observed among controls (mean= 2.8 years; median: 2.5 years; range: <1 yr to 8 years).

Table 2 provides a summary of herbicide detection and concentration in cases and controls. Of the 17 herbicides analyzed, seven were detected in less than 5% of households sampled: metolachlor, bromoxynil octanoate, pebulate, butylate, cyanazine, prometryn, and ethafluralin. These infrequently detected herbicides were primarily agricultural herbicides. Herbicides with the highest percent detection in cases and controls combined were 2,4-D (95%), simazine (90%), mecoprop (83%), followed by trifluralin (60%), and chlorthal (35%). Chlorthal was detected more frequently in households of leukemia cases (40%) compared to controls (30%; $p < 0.05$), while 2,4-D was detected more frequently in controls (97%) than cases (94%, $p < 0.05$). Table 3 shows the product-moment (Pearson) correlation coefficients between house dust concentrations of the 10 herbicides with the highest percent detection. Concentration of mecoprop was correlated to that of 2,4-D and dicamba (Pearson correlation coefficients equal to 0.64 and 0.46, respectively, $p < 0.001$). In general, the levels of the other herbicides had a moderate to low degree of correlation.

Logistic regression models using log-transformed concentrations of the most prevalent herbicides in our study (i.e., simazine, mecoprop, and 2,4-D) did not provide evidence of an association with childhood ALL (Table 4). The lack of associations was also observed when using log-transformed loadings for these herbicides (data not shown). An elevated risk of childhood ALL was associated with the presence of chlorthal in the dust (detected vs. not detected: OR=1.52, 95% CI:1.03, 2.23),, and the risk was highest for the third tertile of concentration (p-value for linear trend =0.05; p-value for goodness of fit test=0.46) (Table 4). The exposure-response relationship was limited to non-Hispanic families (p-value for linear trend =0.05 vs. 0.40 in Hispanics), households with median income of $60,000/year or more (pvalue for linear trend <0.01 vs. 0.40 for households with less than $60,000/year), and to children less than 3 years old at diagnosis or corresponding reference date for controls (p-value for linear trend =0.01 vs. 0.56 in older children), although these findings were based on small numbers of subjects within subgroups (Table 1). There was no evidence of associations with detections of trifluralin, alachlor, bromoxynil, pendimethalin, MCPA, or dicamba, overall (Table 4) or by ethnic or age groups (data not shown).

We examined the effect of chlorthal in the presence of other herbicides, using binary detection variables. Children residing in households where both chlorthal and alachlor (14 cases and 8 controls) were detected experienced a higher risk of ALL (OR=2.56; 95% CI 0.99, 6.63) compared to those exposed to chorthal only (OR=1.33; 95% CI 0.89, 2.01), using children not exposed to either herbicide as a comparison group (p-value for interaction=0.06) (Table 5). The elevated risk in homes with detections of both herbicides was not due to higher concentrations of chlorthal as the mean dust levels of chlorthal was

lower in homes where alachlor was detected versus those with no detects (1.05 ng/g and 4.48 ng/g, respectively; p-value for t-test <0.01). There was no suggestion of an interaction between chlorthal and herbicides other than alachlor.

For all herbicides, the risk estimates associated with dust levels were comparable for children living a short time in the house where dust was sampled (i.e., less than 2.5 years before diagnosis/reference date ~median value among controls), and those children residing 2.5 years of more (data not shown).

Discussion

This is the first study to assess the risk of childhood ALL in relation to agricultural and residential herbicides measured in household dust. We found an elevated risk of childhood ALL with detection of chlorthal in the house dust, and the risk appears greater when both chlorthal and alachlor are detected. Chlorthal is a weed killer used for agricultural and domestic purposes that has been registered for over 30 years. In California, it is used primarily on broccoli, which is grown throughout most of the year. Chlorthal degrades in the environment into monomethyl tetrachloroterephthalate (MTP) and tetrachloroterephthalic acid (TPA). Chlorthal may persist in the soil for up to three months,[26, 27] and both chlorthal and TPA have been detected in ground water.[28] Chlorthal is classified as Group C (Possible Human Carcinogen) by the US EPA.[28] There is no or limited information on the carcinogenicity of MTP and TPA, respectively. Chlorthal also contains 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) and hexachlorobenzene as impurities from the manufacturing process. These impurities have chronic toxicological properties (including oncogenic, teratogenic, fetotoxic, mutagenic and adverse effects on immune response in mammals. The International Agency for Research on Cancer (IARC) has classified TCDD as human carcinogen (Group1)[29] and hexachlorobenzene as a possible human carcinogen (Group 2B).[30] The leukemogenic effect of chlorthal, via its active parent compound, degradates, and/or impurities, remains unknown. Levels of chlorthal were moderately associated with those of polychlorinated biphenyls, which were previously reported to be associated with an increased risk of childhood ALL in the same subgroup of the study population,[14] and statistical models adjusting for these compounds did not modify the risk estimates for chlorthal. Also, there was no or low correlation between dust levels of chlorthal and those of pesticides other than herbicides (data not shown).

Alachlor is a restricted herbicide in the United States, which may be purchased and used only by certified applicators. It is classified as a Probable Human Carcinogen (Group B2) according to the US Environmental Protection Agency.[31] Studies of the Agricultural Health Study (AHS) cohort, which relied upon interviews from pesticide applicators, have reported an increased risk of adult cancers following exposures to alachlor, as well as to other herbicides (e.g., metolachlor, pendimethalin, and trifluralin).[4, 32–35] Specifically, alachlor was found to be associated with lymphohematopoietic cancers.[35] A follow-up study of 17,357 children of farm workers in Iowa and North Carolina showed an increased risk of childhood cancers overall (50 incident cases), but results by cancer site and by specific pesticide were inconclusive, likely due to the small number of affected children.[36] Little is known about the effect of herbicide mixtures on cancer risks. Alachlor is often a component

of mixed formulations with atrazine, glyphosate, trifluralin and imazaquin. None of the latter herbicides, however, have been classified as human carcinogens by regulatory agencies. Our data do not support associations between home dust level of phenoxyacetic acids herbicides (i.e., 2,4-D, MCPA, mecoprop) and childhood ALL. The carcinogenic potential of phenoxyacetic acids has been mostly studied in adults, revealing elevated risks of non-Hodgkin lymphomas,[37–39] leukemia,[37] and solid tumors,[40] while no evidence of risk was reported in other studies.[41] Similar to our data, one population-based study investigating the risk of adult non-Hodgkin lymphomas in relation to residential dust levels of phenoxyacetic acid herbicides (i.e., dicamba, 2,4-D, MCPA, and 2,4,5-T) in four states in the United States reported null findings; dust levels of chlorthal or alachlor were not measured.[41]

Previous case-control studies of childhood leukemia have solely relied on questionnaire-based exposure assessment and reported either positive or negative associations with home use of herbicides.[42–50] Two recent meta-analyses indicate that *in utero* exposure to herbicides, but not during the early years of life, is associated with increased risks of childhood, with pooled ORs equal to 1.6 and 2.8, respectively.[9, 10] While a questionnaire does allow assessment of exposure to herbicides at critical times of the child's development, it lacks specificity of information regarding the chemical class or parent compound of the herbicides. Also, even if herbicides were not used in or around the index child's home, herbicides present in neighboring treated areas or used by previous occupants may still be present in the dust of the child's residence, as shown in the NCCLS[51] and other studies.[52–54] Additionally, there is a potential for differential bias if respondents for cases recall more accurately such events than respondents for controls.

A major strength of this study was the innovative use of dust samples to quantify past exposure to a wide array of agricultural, professional, and residential herbicides. Other strengths of the study include ultra-rapid case ascertainment allowing second home visits on average within 1–2 years after diagnosis, selection of controls from the California birth registry, and a high participation rate for the dust sampling study. The study presents several limitations that warrant caution in interpreting the findings. While the lack of associations between several common herbicides measured in home dust in our study area and risk of childhood ALL may exist, true associations may be missed due to several methodological reasons. First, with the exception of simazine, all herbicides for agricultural and professional use had no or low detects in our study. This observation was expected since not all participating homes were located in agricultural areas. Indeed within the NCCLS, a linkage study using the California Pesticide Use Report databases and crop maps showed that agricultural pesticide use near residences predicted the concentrations of pesticides in carpet dust for most pesticides evaluated [51]. An observational study in California showed that chlorthal was not detected in all dust samples collected in homes located in the urban area of Oakland. In contrast, chlorthal was detected in almost all homes of farmers in the agricultural region of Salina valley, [55] which was consistent with an earlier report. [56] In our study, chlorthal was not detected in about 64% of homes in rural areas, 47% in suburban areas, and 68% in urban areas. Second, current dust measurements of chemicals with limited persistence in the environment are less likely to be representative of true past exposures prior to cancer onset, leading to non-differential misclassification and bias toward reduced associations. Degradation of herbicides applied outdoors depends on the soil characteristics

(pH, microorganisms), climatic conditions (sunlight, moisture), and the chemical characteristics of the herbicide and its formulation. For example, the soil persistence of the herbicides we measured varies from one month (e.g., phenoxyaceticacids), one to three months (e.g., mecoprop, alachlor, chlorthal), and three to twelve months (e.g., simazine, trifluralin),[26] which contrasts with the long-term persistence of older organochlorine pesticides and polychlorinated biphenyls (PCBs), that last for years or decades.[57] Herbicides used indoors or tracked indoors, however, are to some extent protected from these degradation processes. [58, 59] Studies implemented in an agricultural area of California similar to our study area, showed that indoor dust concentrations of chlorthal from repeated samples were relatively stable over 5 to 8 days (spearman correlation coefficient = 0.78) [60] and over 3 to 15 months (intraclass correlation coefficient=0.65; personal communication). Third, case-control studies have reported increased risks of childhood ALL following self-reported exposure to residential herbicides during pregnancy, but not during childhood. It is likely that our ability to accurately quantify potential for residential herbicide exposure during pregnancy is hampered as time elapses between *in utero* exposure and dust sampling. Finally, external concentration of herbicides as measured in dust samples may be a poor surrogate of internal dose. Although measuring herbicide metabolites from the child's blood or urine samples may more accurately assesses the biological dose, invasive collection of biological samples is difficult to obtain from young children, particularly controls. Also, biomarkers suffer from short half-lives, limiting their use for analysis of retrospective case-control data. To our knowledge, no data are available to quantify the correlation between dust levels of chlorthal and alachlor and corresponding biological measures.

Socio-demographic factors are related to both case-control status and to exposure to herbicides (e.g., Hispanic children were more likely to have parents with agricultural occupations compared to non-Hispanic whites (16% vs. 9%, respectively) while non-Hispanic households were more likely to report using pesticides to treat lawn/garden and indoor plants). While the statistical modeling may have accounted for household ethnicity, income and parental education, there may be residual confounding bias of the risk estimates from socio-demographic factors. Eligibility was limited to young children who are likely to spend more time at home than older children. However, in the event that levels of herbicides in the dust were significantly different in non-residentially stable households, our results could not be generalized to the general population. For herbicides detected in at least 75% of homes, the half-detection limit was used to estimate concentration levels, potentially leading to exposure misclassification. An imputation method that incorporates knowledge about the form of the data distribution [61] was also used to estimate "non-detects", leading to similar findings. For other less common herbicides, categorization of a continuous variable resulted in a loss of power and limitation in evaluating exposure-response relationships. Dust samples collected from vacuum bags are likely to represent dust aggregated from several rooms in the home. In contrast, dust sampled using HVS3 method was limited to the room in which child spent the majority of his/her time, as reported by the caregiver. Misclassification bias may have been introduced if the child spent a significant amount of time in a room where herbicide concentrations in the dust were different from the one sampled. However, concentration levels from HVS3 and vacuum bag dust samples were comparable for most herbicides,[22] reducing the potential for bias. Household habits such as removing shoes in the

home and frequency of vacuuming were similar between cases and controls and were not associated with herbicides dust levels. However, we do not have information on whether personal habits have changed over time, especially after a child was diagnosed with leukemia.

Our results suggesting that the magnitude of the association between chlorthal and childhood leukemia varies by socio-demographic characteristics need to be replicated. This observation may be due to differences in lifestyle, routes of exposure, or ability to transport or metabolize chemicals. In the context of multiple comparisons, our finding regarding an interaction of chlorthal and alachlor may be due to chance. Lastly, we did not collect dust from other sources (school, day care, the homes of other relatives or caregivers, etc.) that may have been important sources of exposure for certain children, nor were we able to assess the effect of glyphosate, a common herbicide found to be associated with adult non-Hodgkin lymphoma in some studies.[38, 62]

Conclusions

There were no apparent associations between the current dust levels of most herbicides analyzed, except chlorthal and possibly alachlor. Although these compounds or added impurities have carcinogenic properties, these findings need to be replicated in an independent series.

Acknowledgements

This research could not have been conducted without the important support from our clinical collaborators and participating hospitals which include: University of California Davis Medical Center (Dr. Jonathan Ducore), University of California San Francisco (Dr. Mignon Loh and Dr Katherine Matthay), Children's Hospital of Central California (Dr. Vonda Crouse), Lucile Packard Children's Hospital (Dr. Gary Dahl), Children's Hospital Oakland (Dr. James Feusner), Kaiser Permanente Sacramento (Dr. Vincent Kiley), Kaiser Permanente Santa Clara (Dr. Carolyn Russo and Dr. Alan Wong), Kaiser Permanente San Francisco (Dr. Kenneth Leung), and Kaiser Permanente Oakland (Dr. Stacy Month), and the families of the study participants. We also wish to acknowledge the effort and dedication our all our collaborators at the Northern California Childhood Leukemia Study who helped make this study possible, and the staff at the Battelle Memorial Institute, Columbus, Ohio who performed laboratory analyses.

Financial support: National Institute of Environmental Health Sciences, grants R01 ES09137 and P42-ES04705; the Intramural Research Program of the National Cancer Institute, [subcontracts 7590-S-04, 7590-S-01]; and the National Cancer Institute [contract N02-CP-11015], from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Environmental Health Sciences or the National Cancer Institute.

List of Abbreviations:

AHS	Agricultural Health Study
ALL	Acute Lymphoblastic Leukemia
CI	Confidence Interval
DCPA	Dimethyl tetrachloroterephthalate
IARC	International Agency for Research on Cancer
MCPA	2-methyl-4-chlorophenoxyacetic acid

MCPP	methylchlorophenoxypropionic acid
NCCLS	Northern California Childhood Leukemia Study
USEPA	United States Environmental Protection Agency
OR	Odds Ratio
PCB	polychlorinated biphenyls
2,4-D	2,4-dichlorophenoxyacetic acid
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin

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Table 1.

Socio-demographic, dust sampling, and residence characteristics of 252 ALL cases and 306 controls, the Northern California Childhood Leukemia Study, 2001–2007

Characteristics	Cases no. (%)	Controls no. (%)
Sex		
Male	146 (58)	181 (59)
Female	106 (4)	125 (41)
Age (years)		
0 – 1	5 (2.)	12 (4)
>1 – 2	32 (13)	41 (13)
>2 – 5	142 (56)	181 (59)
>5 – 7	73 (29)	72 (24)
Age (mean ± SD)	4.0 ± 1.8	3.7 ± 1.8
Race/Ethnicity		
Hispanic	94 (37)	89 (29)
Non-Hispanic White	93 (37)	151 (49)
Non-Hispanic others	65 (26)	66 (22)
Annual household income (US $)		
<15,000	24 (10)	16 (5)
15,000 – 29,999	33 (13)	27 (9)
30,000 – 44,999	41 (16)	36 (12)
45,000 – 59,999	41 (16)	39 (13)
60,000 – 74,999	18 (7)	29 (10)
≥75,000	95 (38)	159 (52)
Mother's education		
No schooling/elementary	22 (9)	19 (6)
High school/GED	64 (25)	69 (23)
Some college	68 (27)	100 (33)
Bachelor's degree	48 (19)	78 (26)
Post-Baccalaureate degree	40 (16)	29 (10)
Technical/trade school/other	10 (4)	11 (4)
Father's education		
No schooling/elementary	33 (13)	24 (8)
High school	66 (26)	71 (23)
Some college	53 (21)	93 (30)
Bachelor's degree	38 (15)	55 (18)
Post-Baccalaureate degree	50 (20)	42 (14)
Technical/trade school/other	7 (3)	15 (5)
Unknown	5 (2.)	6 (2)
Neighborhood type		
Urban	181 (72)	225 (74)
Suburban	36 (14)	28 (9)

Characteristics	Cases no. (%)	Controls no. (%)
Rural	29 (12)	44 (14)
Unknown	6 (2)	9 (3)
Residence type		
Single family	201 (80)	268 (88)
Duplex/townhouse	22 (9)	13 (4)
Apartment/condominium	22 (9)	20 (7)
Mobile home	7 (3)	4 (1)
Unknown	0 (0)	1 (<1)
Year residence built		
≤1939	14 (6)	19 (6)
1940–1949	19 (8)	25 (8)
1950–1959	29 (12)	37 (12)
1960–1969	24 (10)	33 (11)
1970–1979	35 (14)	39 (13)
1980–1984	10 (4)	19 (6)
1985–1989	14 (6)	22 (7)
≥1990	72 (29)	82 (27)
Unknown	35 (14)	30 (10)
Year of dust collection		
2001–2002	63 (25)	62 (20)
2003–2004	92 (37)	94 (31)
2005–2006	67 (27)	101 (33)
2007	30 (12)	49 (16)
Season of dust collection		
Winter	62 (25)	42 (14)
Spring	54 (21)	91 (30)
Summer	82 (33)	85 (28)
Fall	54 (21)	88 (29)

Abbreviations: ALL, acute lymphocytic leukemia; SD, standard deviation; %, percentage (do not add up to 100 due to rounding)

Table 2.

Summary of house-dust herbicide detection and concentrations for cases and controls, the Northern California Childhood Leukemia Study, 2001–2007

		Childhood ALL Cases (n=252)				Controls (n=306)				
Analyte[a]	Detection Limit[b]	Detected (%)	Not detected (%)	Missing[c] (%)	Arithmetic Mean[b] (SD)	Detected (%)	Not detected (%)	Missing[c] (%)	Arithmetic Mean[b] (SD)	p-value[d]
Alachlor[e, f]	4.7	25 (10)	226 (90)	1 (<1)	2.9 (12.5)	34 (11)	272 (89)	0 (0)	4.1 (19.4)	0.66
Metolachlor[e, f]	67.6	0 (0)	251 (100)	1 (<1)	n/a	2 (<1)	304 (99)	0 (0)	0.5 (5.6)	0.2
Bromoxynil[e, g]	0.8	15 (6)	232 (92)	5 (2)	0.2 (0.9)	25 (8)	275 (90)	6 (2)	0.6 (4.0)	0.31
Bromoxynil octanoate[e, h]	250.4	1 (<1)	250 (99)	1 (<1)	1.0 (15.8)	1 (<1)	302 (99)	3 (1)	1.0 (17.3)	0.89
Pebulate[e, f]	19.7	1 (<1)	250(99)	1 (<1)	0.1 (1.2)	2 (<1)	304(99)	0 (0)	0.2 (2.5)	0.68
Butylate[d, f]	81.2	0 (0)	251(99)	1 (<1)	n/a	1 (<1)	305(100)	0 (0)	0.3 (4.6)	0.37
Cyanazine[e, f]	65.1	8 (3)	243 (97)	1 (<1)	11.8 (93.9)	4 (1)	302 (99)	0 (0)	13.0 (153.5)	0.13
Prometryn[e, f]	7.2	2 (<1)	249 (99)	1 (<1)	0.1 (1.1)	2 (<1)	301 (98)	3 (1)	0.4 (5.6)	0.85
Simazine[e, f]	0.8	222 (88)	29 (12)	1 (<1)	28.7 (39.3)	282 (92)	24 (8)	0 (0)	56.8 (247.5)	0.14
Ethalfluralin[e, f]	54.5	0 (0)	251 (100)	1 (<1)	n/a	1 (<1)	305 (100)	0 (0)	0.2 (3.1)	0.37
Pendimethalin[e, f]	15.4	15 (6)	221 (88)	16 (6)	22.1 (224.7)	20 (7)	269 (88)	17 (6)	28.9 (199.4)	0.8
Trifluralin[f]	0.2	156 (62)	95 (38)	1 (<1)	2.3 (5.4)	180 (59)	126 (41)	0 (0)	3.4 (12.2)	0.42
MCPA[g]	1.4	35 (14)	212 (84)	5 (2)	4.6 (27.3)	53 (17)	277 (81)	6 (2)	5.5 (15.9)	0.27
Mecoprop[f, g, i]	2.2	215 (85)	32 (13)	5 (2)	149.2 (466.7)	246 (80)	54 (18)	6 (2)	165.7 (472.9)	0.11
2,4-D[g]	3.8	236 (94)	11 (4)	5 (2)	383.3 (804.0)	296 (97)	3 (1.0)	7(2)	831.4 (6041.7)	0.01
Chlorthal[g, j]	0.2	101 (40)	150 (60)	1 (<1)	2.2 (7.0)	94 (31)	212 (69)	0 (0)	5.7 (57.6)	0.02
Dicamba[g]	1.05	60 (24)	187 (74)	5 (2)	4.0 (11.7)	92 (30)	208 (68)	6(2)	5.6 (17.3)	0.1

Abbreviations: ALL, acute lymphocytic leukemia; SD, standard deviation; %, percentage (do not always add up to 100% due to rounding)

[a]Names according to the International Organization for Standardization (ISO)

[b] Analyte concentration in ng/g of dust

[c] Missing due to insufficient dust or interferences in the chemical analyses

[d] P-value derived from Fisher's exact test comparing % detected between cases and controls

[e] Primarily agricultural or professional-use herbicide

[f] Hexane-acetone extraction method

[g] Acid extraction method

[h] Acid extraction method

[i] Also known as MCPP

[j] Also known as DCPA or dacthal

Table 3.

Pearson correlation coefficients between herbicides[a] most frequently detected in house-dust, the Northern California Childhood Leukemia Study, 2001–2007

	Alachlor	Bromoxynil	Chlorthal[b]	Dicamba	MCPA	Mecoprop[c]	Pendimethalin	Simazine	Trifluralin	2,4-D
Alachlor	1	−0.02	−0.01	<0.01	<0.01	0.02	0.08	0.05	<0.01	<0.01
Bromoxynil		1	0.09[d]	−0.01	0.01	−0.02	−0.01	0.30[e]	0.03	−0.01
Chlorthal[b]			1	−0.01	0.15[e]	−0.01	−0.01	0.01	0.35[e]	−0.01
Dicamba				1	0.13[e]	0.46[e]	0.15[e]	−0.01	−0.01	0.44[e]
MCPA					1	0.01	<0.01	0.05	0.06	0.02
Mecoprop[c]						1	0.05	−0.02	−0.01	0.64[e]
Pendimethalin							1	−0.01	−0.01	0.01
Simazine								1	0.01	−0.01
Trifluralin									1	<0.01
2,4-D										1

[a] Names according to the International Organization for Standardization (ISO)

[b] Also known as DCPA or dacthal

[c] Also known as MCPP

[d] p-value < 0.05

[e] p-value < 0.001

Table 4.

Univariable ORs and 95% CIs for ALL associated with dust levels of herbicides[a], the Northern California Childhood Leukemia Study, 2001–2007

	No. of Cases	No. of Controls	OR (95% CI)[b]
Herbicides with 75% or more detects (log-transformed concentration[c])			
Simazine	--	--	0.93 (0.80, 1.08)
Mecoprop[d]	--	--	1.04 (0.93, 1.16)
2,4-D	--	--	0.96 (0.85, 1.08)
Herbicides with 35% to less than 75% detects (tertile concentrations above non-detects, in ng/g[e])			
Chlorthal[f]			
Non-detect	150	212	Reference
1.00 – 1.67	30	30	1.49 (0.82, 2.72)
1.68 – 3.30	30	31	1.49 (0.83, 2.67)
>3.30	41	33	1.57 (0.90, 2.73)
Trifluralin			
Non-detect	95	126	Reference
0.22 – 1.27	57	58	1.30 (0.80, 2.13)
1.28 – 2.72	46	58	1.05 (0.63, 1.76)
>2.72	53	64	1.02 (0.62, 1.68)
Herbicides with less than 35% detects (binary variables)			
Alachlor			
non-detect	226	272	Reference
detect	25	34	0.94 (0.52, 1.71)
Bromoxynil			
non-detect	215	266	Reference
detect	15	24	0.57 (0.28, 1.17)
Pendimethalin			
non-detect	221	269	Reference
detect	15	20	0.97 (0.45, 2.10)
MCPA			
non-detect	195	237	Reference
detect	35	53	0.87 (0.52, 1.45)
Dicamba			
non-detect	172	198	Reference
detect	58	92	0.75 (0.50, 1.14)

Abbreviations: ALL, acute lymphocytic leukemia; OR, odds ratio; CI, confidence interval.

[a]Names according to the International Organization for Standardization (ISO)

[b] Adjusted for child's sex, age, Hispanic status, maternal race, household income, season of dust sampling, year of dust sampling, neighborhood type, and residence type

[c] OR computed for each log of 1ng/g increment

[d] Also known as MCPP

[e] Quartile categories among control households with analyte detected

[f] Also known as DCPA or dacthal; p-value for linear trend=0.05

Table 5.

ORs and 95% CIs for ALL associated with detection of alachlor and chlorthal, the Northern California Childhood Leukemia Study, 2001–2007

Alachlor[a]	Chlorthal[a,b]	No. of cases	No. of controls	OR (95% CI)[c]
No	No	139	186	Reference
Yes	No	11	26	0.56 (0.25, 1.25)
No	Yes	87	86	1.33 (0.89, 2.01)
Yes	Yes	14	8	2.56 (0.99, 6.63)
				p-value for interaction=0.06

Abbreviations: ALL, acute lymphocytic leukemia; OR, odds ratio; CI, confidence interval.

[a]Names according to the International Organization for Standardization (ISO)

[b]Also known as DCPA or dacthal

[c]Adjusted for child's sex, age, Hispanic status, maternal race, household income, season of dust sampling, year of dust sampling, neighborhood type, and residence type