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Polycyclic Aromatic Hydrocarbons in Residential Dust and Risk of Childhood Acute Lymphoblastic Leukemia

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Abstract

Several polycyclic aromatic hydrocarbons (PAHs) are known or probable human carcinogens. We evaluated the relationship between PAH exposure and risk of childhood acute lymphoblastic leukemia (ALL) using concentrations in residential dust as an exposure indicator. We conducted a population-based case-control study (251 ALL cases, 306 birth-certificate controls) in Northern and Central California from 2001–2007. We collected residential dust using a high volume small surface sampler (HVS3) (n=185 cases, 212 controls) or by sampling from participants' household vacuum cleaners (n=66 cases, 94 controls). We evaluated log-transformed concentrations of 9 individual PAHs, the summed PAHs, and the summed PAHs weighted by their carcinogenic potency (the toxic equivalence). We calculated odds ratios (ORs) and 95% confidence intervals (CI) using logistic regression adjusting for demographic characteristics and duration between diagnosis/reference date and dust collection. Among participants with HVS3 dust, risk of ALL was not associated with increasing concentration of any PAHs (based on OR per ln(ng/g). Among participants with vacuum dust, we observed positive associations between ALL risk and increasing concentrations of benzo[*a*]pyrene (OR per ln[ng/g]=1.42, 95% CI=0.95, 2.12), dibenzo[*a,h*]anthracene (OR=1.98, 95% CI=1.11, 3.55), benzo[*k*]fluoranthene (OR=1.71, 95% CI= 0.91, 3.22), indeno[1,2,3-*cd*]pyrene (OR=1.81, 95% CI=1.04, 3.16), and the toxic equivalence

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(OR=2.35, 95% CI=1.18, 4.69). The increased ALL risk among participants with vacuum dust suggests that PAH exposure may increase the risk of childhood ALL; however, reasons for the different results based on HVS3 dust samples deserve further study.

Keywords

polycyclic aromatic hydrocarbons; childhood leukemia; dust; environmental exposures; environmental epidemiology

1. INTRODUCTION

Leukemia is the most common childhood cancer, accounting for approximately one third of incident cases in U.S. children under age 15 years. Acute lymphoblastic leukemia (ALL) constitutes approximately 80% of childhood leukemia cases in most Western countries (Ross and Spector, 2006). The incidence rates in industrialized countries are approximately four times higher than non-industrialized countries (Parkin et al., 1998), suggesting that the etiology of this disease is related to lifestyle factors or environmental exposures, though few specific risk factors have been identified (Buffler et al., 2005; Chang, 2009). The early peak in age of diagnosis (ages 2 to 5 years) suggests that the preconception, prenatal, and early childhood time periods may be etiologically relevant exposure windows.

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous byproducts of incomplete combustion. Sources of PAHs in air include domestic wood-burning, motor vehicles, industrial facilities such as power plants, forest fires, tobacco smoke, gas-burning appliances, and cooking smoke (ATSDR, 1995; Bostrom et al., 2002; IARC, 2010). PAHs can also be found in foods grown in areas with polluted air or soil and those that are charred or cooked over an open flame (Phillips, 1999). Several PAHs are classified as known or probable human carcinogens or mutagens based on epidemiologic studies of occupational groups and animal carcinogenicity studies (IARC, 2010). To our knowledge, no previous epidemiologic study of leukemia has measured levels of PAHs in environmental media. However, some studies have suggested that exposure to certain sources of PAHs are associated with the risk of childhood leukemia, including parental occupational exposure to vehicle exhaust (Castro-Jimenez and Orozco-Vargas, 2011; Colt and Blair, 1998; McKinney et al., 2003), paternal smoking (Chang, 2009; Milne et al., 2012), and proximity to traffic (Pearson et al., 2000; Visser et al., 2004), though results have been inconsistent, particularly for parental occupational exposures and residential proximity to traffic.

Children may be exposed to PAHs via inhalation of indoor and outdoor air, dietary ingestion, non-dietary ingestion of dust or soil, dermal absorption (Chuang et al., 1999), breastfeeding (Kim et al., 2008) and placental transfer (Perera et al., 2004). Non-dietary ingestion of residential dust represents an important PAH exposure pathway in children due to their high proportion of time spent on the floor and propensity to engage in hand-to-mouth activity. Non-dietary ingestion of residential dust and soil has been estimated to constitute approximately 24% of total PAH exposure for low-income children aged 2 to 4 years (Chuang et al., 1999). PAH concentrations in residential dust were associated with outdoor PAH concentrations, gas heating, older residence age, and household smoking

practices within the current study population (Whitehead et al., 2011; Whitehead et al., 2013). Because PAHs accumulate in carpets, measured levels in residential dust may also be indicative of children's early life exposures (Butte and Heinzow, 2002; Roberts et al., 2009; Whitehead et al., 2013). In a reproducibility study of a subset of the current study population (Whitehead et al., 2013), concentrations of PAH were moderately correlated between two dust sampling rounds separated by 3–8 years (range of $r_{Spearman}$: 0.44–0.54). Because the rank order of PAH dust levels remained relatively consistent across this study population for a period of five years, a single measurement made shortly after diagnosis could be a useful representation of PAH exposures that occurred during the etiologically relevant time period for ALL (Whitehead et al., 2013).

The Northern California Childhood Leukemia Study is a population-based case-control study of childhood leukemia in Northern and Central California. In the current analysis, we evaluated whether exposure to PAHs, as determined by concentrations in residential dust, is associated with risk of ALL in children in the Northern California Childhood Leukemia Study.

2. METHODS

2.1 Study population

As previously described (Bartley et al., 2010; Metayer et al., 2013), we rapidly ascertained leukemia cases (usually within 72 hours of diagnosis) from nine of the ten major pediatric clinical centers in 35 counties in the San Francisco Bay Area and the Central Valley (University of California Davis Medical Center, University of California San Francisco, Children's Hospital of Central California, Lucile Packard Children's Hospital, Children's Hospital Oakland, Kaiser Permanente Roseville, Kaiser Permanente Santa Clara, Kaiser Permanente San Francisco, and Kaiser Permanente Oakland). Only one hospital (Sutter Hospital) declined to participate. Children eligible for inclusion in the study were <15 years of age at the time of enrollment, had no prior cancer diagnosis, were resident in one of the 35 counties at the time of diagnosis, and had an available English- or Spanish-speaking parent. All pathological reports available in the medical chart were reviewed by an independent pediatric oncologist to confirm diagnosis. Comparison of case ascertainment in the 35-county study area with the California Cancer Registry (1997–2003) showed that approximately 95% of children diagnosed with leukemia in the participating study hospitals were included in the study, which corresponded to 76% of all cases diagnosed in any (participating and non-participating) hospital within the 35 study counties. We selected controls randomly from California birth certificate files maintained by the Center for Health Statistics in the California Department of Public Health and individually matched them to cases on child's sex, age, and Hispanic ethnicity and mother's race. A total of 997 children with leukemia and 1226 cancer-free controls were enrolled.

At an initial interview, we collected demographic and exposure information, including residential and parental occupational histories, from the child's caregiver (98% the mother) using a self-administered questionnaire and an in-person interview. Subsequently, children who were < 8 years of age at diagnosis (or at reference date for controls) and were still living at the home they occupied at diagnosis/reference were eligible for a second interview

(2001–2007) in the home. During the second interview, we collected a residential dust sample and obtained detailed information about the characteristics of the home (e.g., type, year the home was built), smoking habits of household members, and pesticide use in and around the home. We limited the eligibility for the second interview to younger cases and controls and to those who had not moved since diagnosis/reference so the residential dust sample would reflect exposures over a substantial portion of the child's early life. Because eligibility for the second interview was based strictly on residential eligibility criteria, matched case–control sets were not maintained in the study recruitment and in the statistical analysis. The participation rate in the first interview was 86% for both cases and controls. Among the 324 cases and 407 controls eligible for the second interview, 296 leukemia cases (91%), including 269 ALL cases, and 333 controls (82%) participated. The study protocols were reviewed and approved by the internal review boards at University of California Berkeley, the National Cancer Institute, the California Department of Health, and all participating hospitals. Informed consent was obtained from parents of participating children.

2.2 Dust sample collection

As described in detail previously (Colt et al., 2008; Ward et al., 2009), from October 2001 to June 2006, we collected carpet dust samples using a high volume small surface sampler (HVS3) (Cascade Stack Sampling Systems, Bend, OR). We sampled the room where the child had spent the most time while awake (other than the kitchen or the child's bedroom) in the year before the diagnosis/reference date if there was at least 9 ft^2 of carpets or rugs available. Most samples were collected from the living room or family room. We sampled a 6- by 4-foot area; if needed, additional carpeted areas of the room were sampled to collect approximately 10 mL of dust. Because this method was labor-intensive, we conducted a methodologic study to evaluate collection of the dust from the home vacuum cleaner. In 45 homes, including 33 from the current study, we collected dust samples using both methods and compared the concentrations of several chemicals in the pairs of samples from each home (Colt et al., 2008). We found that the correlations in chemical concentrations from the two methods were generally strong ($r_{Spearman} > 0.7$). Therefore, between July 2006 and November 2007, we collected the dust samples by removing the used bag from the home vacuum (~65% of participants), or emptying loose dust from bagless vacuums (~35% or participants) into a polyethylene bag. However, Spearman correlation coefficients showed only moderate correlations ($r_{Spearman} < 0.7$) between the two sampling methods for concentrations of some PAH compounds ($r_{Spearman}$: benzo[a]pyrene: 0.55, dibenzo[*a,h*]anthracene: 0.67, benzo[*a*]anthracene: 0.69, benzo[*b*]fluoranthene: 0.68, benzo[*k*]fluoranthene 0.55, chrysene: 0.78, indeno[1,2,3-*c,d*]pyrene: 0.77, coronene: 0.81, dibenzo[*a,e*]pyrene: 0.70) (Colt et al., 2008). Therefore, we decided *a priori* to conduct the statistical analyses separately by sample type and combine if results were similar.

2.3 Laboratory analysis

A total of 251 ALL cases and 306 controls had sufficient dust samples for analysis. We analyzed HVS3 dust for 185 ALL cases and 212 controls and vacuum dust was for 66 ALL cases and 94 controls. We used a multi-residue analysis method which covered 65 different analytes from polar and non-polar compound classes, including nine PAHs: benzo[*a*]pyrene,

dibenzo[*a,h*]anthracene, benzo[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, indeno[1,2,3-*c,d*]pyrene, coronene, and dibenzo[*a,e*]pyrene. Details of the dust sample shipping, processing, and chemical analyses have been described previously (Colt et al., 2008; Whitehead et al., 2011). Briefly, 0.5-g portions of dust were spiked with 250 ng of each of two surrogate recovery standards, $^{13}C_6$-benzo[*k*]fluoranthene and $^{13}C_6$-dibenzo[*a,e*]pyrene. Dust samples were extracted by ultrasonification in 1:1 hexane:acetone, solvent exchanged into hexane, purified by solid-phase extraction, and concentrated to 1 ml. Concentrated extracts were spiked with the internal standard d_{12}-benzo[*e*]pyrene and analyzed using gas chromatography-mass spectrometry in the multiple ion detection mode. Quality control samples in each batch included a duplicate of one sample in that batch, an additional aliquot of the duplicate sample spiked with 250 ng of each analyte, and a solvent method blank. All samples were spiked with the $^{13}C_6$ surrogate recovery standards to track method performance on a sample-by-sample basis. Batches contained 12 participant samples, including at least four case and four control samples; laboratory personnel were blind to case or control status. The mean ± standard deviation sample recovery for the two surrogate recovery standards in the dust samples were 83 ± 23% for $^{13}C_6$-benzo[*k*]fluoranthene and 99 ± 78% for $^{13}C_6$-dibenzo[*a,e*]pyrene, and the mean relative difference between analytes in duplicate samples was 27%. In the HVS3 case and control samples, the percentage of samples below the limit of detection ranged from 0 to 9.9%, and the percentages missing due to interference from co-eluting compounds during analysis ranged from 0 to 5.7%, depending on the PAH (Table 1). In the vacuum case and control samples, the percentage of samples below the limit of detection ranged from 0 to 7.6% and the percentage of samples missing due to interferences ranged from 0 to 3.2% (Table 2).

2.4 Statistical analysis

The Spearman correlation coefficients among the nine individual PAHs ranged from 0.19 to 0.90 in the HVS3 samples and 0.11 to 0.93 in the vacuum samples. We used a multiple imputation process to replace missing values (values below the detection limit or not quantifiable due to a chemical interference) with a randomly drawn value from a probability distribution that was conditional upon the values for the non-missing PAHs. The draw was repeated five times, resulting in five separate datasets (Whitehead et al., 2011).

We used the first imputed dataset in our descriptive analyses. We evaluated the concentrations of the 9 individual PAHs, the summed concentrations of the 9 PAHs, and the toxic equivalence (TEQ), which is sum of the PAH concentrations weighted by their toxic equivalency factors. Each toxic equivalency factor represents the carcinogenic potency for an individual PAH relative to that of benzo[*a*]pyrene, based on *in vivo* and *in vitro* studies (Table 1 and Table 2) (Nisbet and LaGoy, 1992). The 2 of 9 PAHs without toxic equivalency factors (*i.e.*, not classified with respect to carcinogenicity) were not included in this metric. We used the natural-log transformed PAH concentration in our statistical models, because it yielded improved fit (approximately linearly related to outcome on the logit scale) compared with untransformed or quadratic transformations. We also calculated the PAH loadings (i.e., mass of PAH per unit area sampled) for the HVS3 dust samples. Loadings could not be calculated for the vacuum samples because the sampling area was unknown. The PAH loadings and concentrations were significantly correlated and yielded

very similar risk estimates; therefore we only present the results for concentrations. We also categorized the PAH concentrations into tertiles based on distributions among controls, separately by dust type (HVS3 and vacuum).

We used logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the continuous and categorical dust concentrations of PAHs and risk of ALL, separately by dust type (HVS3 and vacuum). Because of the additional selection criteria for the second interview (i.e., <8 years old and no move), we conducted unmatched analyses. All regression models were adjusted for the matching variables: age, sex, and race/ethnicity (non-Hispanic white, Hispanic, non-Hispanic other race). For each sample type, we assessed whether the following potential confounders resulted in changes to the ORs of   10% for at least one PAH: household income (<$30,000, $30,000–$59,999, $60,000+), duration between the diagnosis/reference date and sample collection (in years), age of the home (grouped based on the sample sizes into built before 1980, 1980 or later, unknown), residence type (single family home or other), household smoking (none versus   1 cigarettes/day), season of dust collection (winter [December, January, February], spring [March, April, May], summer [June, July, August], and fall [September, October, November]), year of interview/dust collection, and the concentrations of previously noted ALL risk factors, total polychlorinated biphenyls (PCBs) and the herbicide dacthal (Metayer et al., 2013; Ward et al., 2009). Duration between diagnosis/reference and sampling date met our criterion for confounding in both the HVS3 and vacuum subsets and was therefore included in all regression models. We fit each PAH's model five times, once for each of the five imputed datasets, and combined the results using the PROC MIANALYZE procedure in SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) (Lubin et al., 2004; Rubin and Schenker, 1991). Because of differences between sample collection methods and to evaluate consistency of findings, we conducted stratified analyses to evaluate any differences in associations by sex, year of sample collection, duration between diagnosis/reference and sampling, and income. We were limited in our ability to do stratified analyses within the vacuum subset due to small numbers.

3. RESULTS

The carcinogenicity classifications and distributions of individual PAHs, the summed PAHs, and the PAH TEQ are shown by case-control status in Tables 1 and 2, for the HVS3 and vacuum dust samples, respectively. The distributions of each PAH in HVS3 and vacuum dust overlapped considerably among both cases and controls. However, in the HVS3 subset, the median concentrations were higher in cases compared to controls for 6 of the 11 PAH variables (Table 1). In the vacuum subset, the median concentrations were higher in cases for 9 of the 11 PAH variables (Table 2).

The distributions of socio-demographic characteristics for cases and controls by dust sample type are shown in Table 3. Within each sample type, cases and controls did not differ with respect to age, sex, the number of cigarettes smoked in the home, and age of the home. The duration between diagnosis or reference date and dust collection was less for cases than for controls with respect to both dust sample types due to the longer time period involved in identifying, enrolling, and interviewing controls. Controls were more likely than cases to be

non-Hispanic Whites. Among participants with HVS3 samples, controls had higher annual incomes than cases, were more likely to live in single-family homes, and were more likely to have samples collected in the spring and less likely in the winter.

We observed some differences in these demographic and housing factors between dust sample types (Table 3). A greater percentage of controls with vacuum samples were male than controls with HVS3 samples (68% and 55%, respectively). Due to the protocol change, a greater percentage of vacuum samples were collected in the summer and fall and during 2005–2007, compared to the HVS3 samples. The duration between reference date and sample collection was longer in vacuum controls compared to HVS3 controls (>1.5years: 71% and 54%, respectively). In the participants with vacuum dust, concentrations of PAHs increased with increasing duration between diagnosis/reference and sampling (not shown), making that variable a strong confounder.

Among those with HVS3 dust, we observed no significant associations with ALL and dust concentrations of individual PAHs (OR per log ng/g), summed PAHs, and the PAH TEQ, though the OR (95% CI) for benzo[*b*]fluoranthene was marginally significantly increased (1.20 [0.95, 1.52] (Table 4). However, the ORs for benzo[*b*]fluoranthene were significantly elevated in the second (1.89 [1.04–3.42]) and third tertiles (1.89 [1.03–3.47]) compared to the lowest tertile; the OR for indeno[1,2,3-cd]pyrene was significantly elevated in the second tertile (1.77 [1.01, 3.11]), but not the third (Table 5). We did not observe any other associations with ALL risk and the tertiles of individual PAHs, summed PAHs, or the PAH TEQ.

Cases with vacuum dust tended to have marginally higher PAH concentrations than controls (Table 2), which after adjustment for the duration variable in multivariable models, yielded significantly elevated ORs (Tables 4 and 6). Among the participants with vacuum dust, the ORs (95% CI) for ALL increased significantly with each log ng/g increase in indeno[1,2,3-*cd*]pyrene (1.81 [1.04–3.16]), dibenzo[*a,h*]anthracene (1.98 [1.11–3.55]), and the TEQ (2.35 [1.18–4.69]) (Table 5). For example for indeno[1,2,3-*cd*]pyrene, there was a 1.81-fold increase in risk with each 2.72-fold increase in the concentration. We also observed positive associations of borderline significance for benzo[a]pyrene (1.42 [0.96–2.12]) and benzo[*k*]fluoranthene (1.71 [0.91–3.22]). The ORs for ALL were significantly elevated in both tertiles above the reference for indeno[1,2,3-*cd*]pyrene, the summed PAHs, and the TEQ, and in one tertile above the reference for benzo[*a*]pyrene (Table 5). Of these, the ORs increased monotonically across the tertiles only for the summed PAHs and the TEQ. Compared to the lowest tertile of summed PAHs, ORs (95% CI) were 3.21 (1.12–9.23) and 4.30 (1.30–14.2) in the second and third tertiles, respectively. For the PAH TEQ, ORs (95% CI) were 3.38 (1.10–10.4) and 6.44 (1.86–22.2), for the second and third tertiles, respectively. The Spearman correlations among the PAHs that were associated with ALL in the vacuum samples were modest (0.31–0.56).

Through our stratified analyses in the HVS3 subset, we investigated, to the extent possible, whether the heterogeneity in ORs by sample type could be explained by the demographic or temporal factors that differed by sample type as reported in Table 3 (i.e., sex, season of dust sampling, duration between reference/diagnosis and sampling, year of sampling, and

income) (Supplemental Table S.1). We observed only small differences in ORs for individual PAHs, summed PAH, and PAH TEQ by season (summer/fall vs. winter/spring), year (2001–2004 vs. 2005–2006), and household income (<$60,000 vs. $60,000) with considerable overlap between 95% CIs. In addition, we mapped the locations of case and control homes by sample type and, based on visual inspection, did not observe any spatial patterns in the location of the homes (not shown). ORs (95% CI) were higher among those with dust samples collected 1.5 years of reference/diagnosis (n=152 cases, 97 controls) compared to those with samples collected > 1.5 years after reference/diagnosis (n=33 cases, 115 controls), with the strongest positive associations for benzo[*b*]fluoranthene (1.4 [1.1–1.9]), benzo[*k*]fluoranthene (1.3 [0.98–1.7]), and indeno[1,2,3-*cd*]pyrene (1.3 [0.98–1.7]) (Table S.1). Though we had limited numbers to do stratified analyses within the vacuum subset, we calculated ORs and 95% CIs in the subgroup with durations between reference/diagnosis and sampling 1.5 years (60 cases, 27 controls) and observed positive associations with ALL risk and concentrations of benzo[*a*]pyrene (1.5 [1.0, 2.4]), indeno[1,2,3-*cd*]pyrene (1.9 [1.0, 3.5]), and the PAH TEQ (2.0 [1.0, 4.0]).

4. DISCUSSION

For the participants whose dust was collected by the HVS3, we observed mostly null results. We observed significant positive associations between risk of childhood ALL and concentrations of benzo[*b*]fluoranthene and indeno[1,2,3-*cd*]pyrene in HVS3 dust in at least one tertile above the reference group, though the ORs did not increase monotonically across the tertiles. We also observed positive associations for some PAHs among those with samples collected within 1.5 years of diagnosis/reference. In contrast, in the smaller subset of participants whose dust was obtained from the home vacuum, we observed statistically significant or borderline significant positive associations with benzo[*a*]pyrene, dibenzo[*a,h*]anthracene, benzo[*k*]fluoranthene, indeno[1,2,3-*cd*]pyrene, the summed PAHs, and the PAH TEQ, which weights the PAH concentrations by their carcinogenicity. The ORs increased significantly and monotonically across the tertiles for the summed PAHs and the TEQ. We observed these positive associations after adjustment for the duration between the diagnosis/reference and sampling dates, but not in unadjusted models. We also observed positive associations for some PAHs in unadjusted models of participants with samples collected within 1.5 years of the diagnosis/reference date.

Results from case-control studies of childhood leukemia and ALL provide limited evidence that exposure to certain sources of PAHs increases risk. For example, case-control studies from North and South America and the United Kingdom have shown an increased risk of childhood leukemia if a parent had an occupation operating motor vehicles or with exposure to motor vehicle exhaust (Castro-Jimenez and Orozco-Vargas, 2011; Colt and Blair, 1998; McKinney et al., 2003). In contrast, a case-control study in China did not observe any association between ALL and maternal occupational exposure to coal tar, petroleum products, or PAH, as self-reported in a detailed interview. Most cohort and case-control studies examining the effect of maternal smoking on childhood leukemia have not observed significant associations (Castro-Jimenez and Orozco-Vargas, 2011; Chang, 2009; Chang et al., 2006; Klebanoff et al., 1996). However, paternal smoking has been consistently associated with increased risk (Milne et al., 2012). Results from epidemiologic studies of

proximity to traffic and risk of childhood leukemia have been inconsistent, with the weight of evidence supporting no association (Raaschou-Nielsen and Reynolds, 2006), including an earlier analysis from the Northern California Childhood Leukemia Study (Reynolds et al., 2004). Smoking and traffic often involve co-exposures to other chemicals, including the known leukemogen benzene, making it difficult to draw conclusions specifically about the contribution of PAHs.

Molecular studies demonstrate that an association between PAH exposure and risk of childhood cancer is biologically plausible. In a study conducted in New York City, Bocskay et al. (2005) reported an association between prenatal exposure to airborne carcinogenic PAHs and frequency of chromosomal aberrations in cord blood, though no association was seen between PAH-DNA adducts and aberrations. Orjuela et al. (2012) reported that urinary metabolite levels of the PAH naphthalene were associated with occurrence and frequency of chromosomal aberrations, including translocations, in 5-year-olds in New York City. Naphthalene is generally well-correlated with other individual PAHs and total PAHs in occupational and environmental sources (Rappaport et al., 2004) (Deziel et al., 2013).

The heterogeneity in risk estimates between HVS3 and vacuum dust samples may be due to differences in the timing of sample collection. Due to a change in the sampling protocol, nearly all vacuum samples were collected toward the end of the study, from July 2006 to November 2007, mainly in summer and fall. The results from our stratified analyses within the larger HVS3 subset suggest that the observed heterogeneity is not attributable to calendar year (2001–2004 versus 2005–2006), season, demographic, or spatial factors.

Another possible explanation for the heterogeneity in risk estimates due to dust collection type may be related to the different protocols used for dust collection. The HVS3 is operated at a specific velocity and flow rate by trained data collectors following a uniform protocol. There is more potential for variability in the vacuum dust samples because participants differ in their frequency of cleaning and emptying bags, and vacuum cleaners vary with respect to their motors and flow rates. The additional variability among the participant vacuum cleaners would be expected to add imprecision to the risk estimates (Colt et al., 2008) and therefore does not explain the higher ORs observed among the participants with vacuum dust. The HVS3 samples were collected from the room where the child spent the most time while awake. The vacuum cleaner dust was collected from an average of 5 rooms and therefore may be more representative of exposures in the entire home. Spearman correlations between PAH concentrations in vacuum bag and HVS3 dust samples were stronger in an earlier study in a different population that sampled with the HVS3 in all rooms in which the home vacuum had been used and only included bagged vacuum cleaners (range: 0.85–0.94) (Colt, 1998), compared to the more recent study (0.55–0.81) (Colt et al., 2008). The relevance of each collection method to the child's exposure may depend on each child's activity patterns.

One advantage of the HVS3 method is that it allows for the calculation of loading, i.e. the amount of chemical per square meter of carpet (ng/m^2), which has been suggested to be a more relevant metric for predicting children's exposures to other contaminants, such as lead

(Lanphear et al., 1995). However, we observed similar associations with ALL for concentrations and loadings.

PAH concentrations in vacuum samples (and to lesser extent in HVS3 samples) tended to increase with increasing duration between diagnosis/reference and sample date; however, the reasons for this relationship are not clear as we observed no temporal trends in PAHs. We observed higher ORs in individuals with HVS3 samples collected within 1.5 years of diagnosis/reference compared to those with samples collected more than 1.5 years after diagnosis/reference. In addition, restricting our analyses to vacuum cases and controls with duration between diagnosis/reference and sampling of 1.5 years or less resulted in statistically significant ORs for benzo[*a*]pyrene, indeno[1,2,3-*cd*]pyrene, and the PAH TEQ, consistent with the associations observed in adjusted models for the full vacuum subset. Samples collected less than 1.5 years after diagnosis/reference may be more representative of concentrations at the etiologically relevant time period compared to those collected after a longer period of time; regression analyses restricted to these samples may better estimate the true risk of ALL. However, the cut-point of 1.5 years was based on sample size, and we were not able to evaluate the consistency of these findings using other cut-points.

The use of residential dust as an exposure metric offers several strengths. Measurements of PAHs in dust are objective and independent of self-report. Dust collection allows for quantification of specific PAHs, which may reflect tobacco smoking in the home (Maertens et al., 2004), proximity to heavy traffic (Chuang et al., 1999), and infiltration of outdoor air (Whitehead et al., 2011). Dust collection also provides the ability to quantify other potentially carcinogenic compounds, strengthening our analysis by allowing us to adjust for concentrations of PCBs and dacthal, chemicals previously linked to ALL. In addition, because PAHs levels in dust within the same homes are generally correlated in samples collected within 3 to 8 years, PAH levels in dust samples collected after diagnosis are likely to be reflective of past PAH exposures (Whitehead et al., 2013). A limitation of using dust as an exposure indicator is that residential dust may not capture all sources of exposure to children. Chuang et al. estimated that dietary ingestion is the dominant route of exposure in low-income children, contributing 66% of total daily dose, compared to 24% for non-dietary ingestion of dust and soil and 10% from inhalation (Chuang et al., 1999). Though the children in our study represent a wide range of incomes, it is clear that by using dust as an exposure indicator, we may be overlooking an important route of exposure.

Some limitations should be considered in the interpretation of our findings. We had small sample size, and the protocol change to vacuum samples resulted in different associations with risk compared to the HVS3 subset, which we were not able to explain. Also, because our study population was limited to participants who did not move after diagnosis/reference date, if PAH levels differ between residentially stable versus non-residentially stable households, our results may not be generalizable to the broader population.

In conclusion, though we did not observe significant associations between ALL and increasing concentrations of PAHs in residential dust in the larger subset of participants with dust collected from the standardized HVS3 method, the observed elevated risks for multiple PAHs in the smaller subset of participants with dust collected from household vacuum

cleaners warrants further exploration. Additional methodologic work is needed to understand which dust collection approach better represents PAH exposure in children. In addition, inclusion of samples from other media (air, diet) or the use of biomarkers could help clarify the association between PAHs and childhood ALL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

ABBREVIATIONS

ALL	acute lymphoblastic leukemia
PAHs	polycyclic aromatic hydrocarbons
HVS3	high volume small surface sampler
TEQ	toxic equivalence
OR	odds ratio
95% CI	95% confidence interval

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Highlights

We examined a link between dust polycyclic aromatic hydrocarbons and child leukemia.

Dust was collected using a specialized sampler or home vacuum cleaner.

No increased leukemia risk observed when dust collected with specialized sampler.

Leukemia risk associated with polycyclic aromatic hydrocarbons in dust from vacuum.

Reason for different results by dust collection method deserves further study.

Table 1

Distributions of PAH concentrations (ng/g) from HVS3 samples in cases and controls: The Northern California Childhood Leukemia Study 2001–2007.

PAH	IARC Group[a]	TEF[b]	Detection Limit (DL)	Cases (n=185) %<DL	% Interference	Median (IQR)[c]	%<DL	% Interference	Controls (n=212) Median (IQR)c
Benzo[a]pyrene	1	1	2	1.6	4.3	37.9 (19.5, 78.6)	1.9	1.9	41.0 (17.7, 87.0)
Dibenzo[a,h]anthracene	2A	5	2	7.6	1.1	12.7 (6.32, 28.7)	9.9	0.9	13.1 (6.10, 29.2)
Benzo[a]anthracene	2B	0.1	2	1.1	0.0	26.6 (12.8, 45.6)	0.9	0.5	23.5 (12.2, 43.7)
Benzo[b]fluoranthene	2B	0.1	2	0.0	0.5	63.8 (36.7, 132)	0.5	1.4	54.0 (30.3, 112)
Benzo[k]fluoranthene	2B	0.1	2	0.0	0.5	49.6 (23.9, 101)	0.0	3.3	41.9 (20.9, 83.5)
Chrysene	2B	0.01	2	0.0	0.5	70.8 (39.7, 148)	0.0	0.0	66.7 (38.9, 114)
Indeno[1,2,3-cd]pyrene	2B	0.1	2	0.0	0.0	54.5 (34.3, 111)	0.5	0.0	51.0 (29.2, 105)
Coronene	3	NA[d]	4	2.7	4.9	96.8 (55.0, 163)	1.9	5.7	104 (52.2, 164)
Dibenzo[a,e]pyrene	3	NA[d]	4	1.6	1.1	24.2 (15.4, 44.8)	0.5	1.4	25.3 (15.1, 52.5)
Summed PAHs	--	--	--	--	--	490 (320, 818)	--	--	476 (309, 726)
PAH TEQ	--	--	--	--	--	139 (70, 266)	--	--	153 (70.9, 261)

[a] Group 1, known human carcinogen, Group 2A, probable human carcinogen; Group 2B possible human carcinogen; Group 3, not classifiable (IARC, 2010)

[b] Based on Nisbet and LaGoy 1992

[c] Subsitutes first imputed value

[d] Not Applicable; insufficient data to determine a TEF

HVS3, high volume small surface sampler; IARC, International Agency for Research on Cancer; IQR, inter-quartile range; PAH, polycyclic aromatic hydrocarbons; TEF, toxic equivalency factor; TEQ, toxic equivalence.

Table 2

Distributions of PAH concentrations (ng/g) from vacuum samples in cases and controls: The Northern California Childhood Leukemia Study 2001–2007.

PAH	IARC Group[a]	TEF[b]	Detection Limit (DL)	Cases (n=66)			Controls (n=94)		
				%< DL	% Interference	Median (IQR)	%< DL	% Interference	Median (IQR)
Benzo[a]pyrene	1	1	2	4.5	0.0	41.0 (21.7, 70.1)	2.1	3.2	40.3 (17.2, 74.0)
Dibenzo[a,h]anthracene	2A	5	2	3.0	1.5	15.8 (9.6, 26.0)	3.2	0.0	16.2 (10.3, 23.8)
Benzo[a]anthracene	2B	0.1	2	3.0	0.0	28.5 (16.2, 45.1)	0.0	0.0	23.9 (13.8, 49.6)
Benzo[b]fluoranthene	2B	0.1	2	0.0	0.0	71.7 (32.4, 142)	0.0	0.0	56.2 (32.0, 131)
Benzo[k]fluoranthene	2B	0.1	2	0.0	0.0	34.3 (22.4, 61.5)	0.0	2.1	33.3 (19.4, 54.6)
Chrysene	2B	0.01	2	0.0	0.0	87.3 (55.7, 134)	0.0	0.0	76.4 (43.4, 152)
Indeno[1,2,3-cd]pyrene	2B	0.1	2	0.0	0.0	58.4 (37.6, 95.5)	0.0	0.0	46.2 (28.4, 95.4)
Coronene	3	NA[d]	4	7.6	1.5	75.0 (51.2, 127)	0.0	0.0	86.1 (51.2, 154)
Dibenzo[a,e]pyrene	3	NA[d]	4	4.5	0.0	40.3 (20.8, 68.6)	1.1	0.0	34.2 (17.7, 62.4)
Summed PAHs	--	--	--	--	--	504 (364, 743)	--	--	475 (315, 903)
PAH TEQ	--	--	--	--	--	162 (107, 207)	--	--	150 (91.9, 227)

[a]Group 1, known human carcinogen, Group 2A, probable human carcinogen; Group 2B possible human carcinogen; Group 3, not classifiable (IARC, 2010)

[b]Based on Nisbet and LaGoy 1992

[c]Subsitutes first imputed value

[d]Not Applicable; insufficient data to determine a TEF

IARC, International Agency for Research on Cancer; IQR, inter-quartile range; PAH, polycyclic aromatic hydrocarbons; TEF, toxic equivalency factor; TEQ, toxic equivalence.

Table 3

Characteristics of ALL cases and controls by dust sample type (HVS3 and vacuum): the Northern California Childhood Leukemia Study, 2001–2007.

Demographic factors	HVS3		Vacuum	
	Cases (n=185)	Controls (n=212)	Cases (n=66)	Controls (n=94)
	No. (%)	No. (%)	No. (%)	No. (%)
Child age (yr) at diagnosis/reference				
<1	4 (2)	9 (4)	1 (2)	3 (3)
1–<2	24 (13)	27 (13)	8 (12)	14 (15)
2–5	102 (55)	126 (59)	39 (59)	55 (59)
>5	55 (30)	50 (24)	18 (27)	22 (23)
Sex[b]				
Male	105 (57)	117 (55)	40 (61)	64 (68)
Female	80 (43)	95 (45)	26 (39)	30 (32)
Race/ethnicity				
Hispanic	73 (39)	68 (32)	21 (32)	21 (22)
Non-Hispanic White	70 (38)	102 (48)	23 (35)	49 (52)
Non-Hispanic Black or Other	42 (23)	42 (20)	22 (33)	24 (26)
Annual household income				
< $30,000	45 (24)	32 (15)	11 (17)	11 (12)
$30,000–59,999	65 (35)	55 (26)	17 (26)	20 (21)
$60,000+	75 (41)	125 (59)	38 (57)	63 (67)
Season of dust sampling				
Winter	59 (32)	36 (17)	3 (5)	6 (6)
Spring	50 (27)	87 (41)	4 (6)	4 (4)
Summer	47 (25)	43 (20)	35 (53)	42 (45)
Fall	29 (16)	46 (22)	24 (36)	42 (45)
Age of home				
Built 1980 or later	69 (37)	88 (42)	27 (41)	35 (37)
Built before 1980	86 (47)	103 (49)	34 (51)	50 (53)
Unknown	30 (16)	21 (10)	5 (8)	9 (10)
Type of residence				
Single family	147 (79)	186 (88)	53 (80)	82 (87)
Other	38 (21)	26 (12)	13 (20)	12 (13)
# Cigarettes smoked in household in month before dust sampled				
None	174 (94)	200 (94)	65 (98)	91 (97)
>=1 cigarette/day	11 (6)	12 (6)	1 (2)	3 (3)
Duration between diagnosis/reference and sampling				
<= 1.5 Year	152 (82)	97 (46)	60 (91)	27 (29)
>1.5 Years	33 (18)	115 (54)	6 (9)	67 (71)
Year Interview/Sampling				

Demographic factors	HVS3		Vacuum	
	Cases (n=185)	Controls (n=212)	Cases (n=66)	Controls (n=94)
	No. (%)	No. (%)	No. (%)	No. (%)
2001–2002	62 (34)	62 (29)	1 (2)	0 (0)
2003–2004	90 (49)	90 (42)	2 (3)	4 (4)
2005–2006	33 (18)	60 (28)	33 (50)	41 (44)
2007	0 (0)	0 (0)	30 (45)	49 (52)

ALL, acute lymphoblastic leukemia; HVS3, high volume small surface sampler; PAH, polycyclic aromatic hydrocarbon.

Table 4

Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association of log-transformed PAH concentrations and risk of ALL for HVS3 and vacuum samples.

PAH	HVS3 OR (95% CI)		Vacuum OR (95% CI)	
	Adjusted for Matching Factors[a,b]	Fully Adjusted OR (95% CI)[a,c]	Adjusted for Matching Factors[a,b]	Fully Adjusted OR (95% CI)[a,c]
Benzo[a]pyrene	0.99 (0.83, 1.17)	0.98 (0.81, 1.19)	1.06 (0.78, 1.45)	1.42 (0.95, 2.12)
Dibenzo[a,h]anthracene	1.00 (0.84, 1.18)	0.98 (0.80, 1.19)	1.05 (0.70, 1.58)	1.98 (1.11, 3.55)
Benzo[a]anthracene	1.06 (0.87, 1.30)	1.04 (0.83, 1.30)	1.03 (0.72, 1.48)	1.17 (0.72, 1.89)
Benzo[b]fluoranthene	1.21 (0.98, 1.49)	1.20 (0.95, 1.52)	1.10 (0.78, 1.55)	1.30 (0.83, 2.05)
Benzo[k]fluoranthene	1.14 (0.92, 1.40)	1.16 (0.91, 1.47)	1.31 (0.83, 2.06)	1.71 (0.91, 3.22)
Chrysene	1.09 (0.87, 1.36)	1.05 (0.82, 1.35)	0.96 (0.65, 1.43)	1.16 (0.67, 2.00)
Indeno[1,2,3-cd]pyrene	1.12 (0.91, 1.38)	1.09 (0.87, 1.38)	1.25 (0.84, 1.85)	1.81 (1.04, 3.16)
Coronene	1.04 (0.84, 1.30)	0.95 (0.74, 1.21)	0.86 (0.56, 1.30)	1.08 (0.64, 1.82)
Dibenzo[a,e]pyrene	0.99 (0.79, 1.25)	0.92 (0.71, 1.19)	1.21 (0.79, 1.83)	1.52 (0.89, 2.58)
Summed PAHs	1.10 (0.84, 1.42)	1.04 (0.77, 1.39)	1.06 (0.63, 1.78)	1.72 (0.84, 3.52)
PAH TEQ	0.98 (0.80, 1.20)	0.96 (0.76, 1.20)	1.11 (0.69, 1.77)	2.35 (1.18, 4.69)

[a] OR for association with 1-unit increase in the PAH concentration on the natural log scale (i.e., with 2.72-fold increase on the untransformed scale).

[b] Effect estimates are adjusted for child's age, sex, and race/ethnicity.

[c] Effect estimates are adjusted for child's age, sex, race/ethnicity, and duration between reference/diagnosis and sampling.

ALL, acute lymphoblastic leukemia; HVS3, high volume small surface sampler; PAH, polycyclic aromatic hydrocarbons; TEQ, toxic equivalence.

Table 5

Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association of PAH concentrations in dust collected from HVS3 samples and risk of ALL.

PAH	Tertile max (ng/g)	Cases	Controls	OR	95% CI
Benzo[*a*]pyrene	24.9	63	70	1.00	
	58.3	63	71	1.22	(0.70, 2.13)
	1948	59	71	0.93	(0.53, 1.60)
Dibenzo[*a,h*]anthracene	7.91	54	70	1.00	
	21.4	74	71	1.50	(0.86, 2.61)
	393	57	71	1.07	(0.61, 1.88)
Benzo[*a*]anthracene	15.0	58	70	1.00	
	34.1	60	71	1.15	(0.65, 2.01)
	834	67	71	1.19	(0.69, 2.07)
Benzo[*b*]fluoranthene	36.5	45	70	1.00	
	81.9	66	71	1.93	(1.08, 3.45)
	2450	74	71	1.81	(1.03, 3.17)
Benzo[*k*]fluoranthene	27.1	54	70	1.00	
	65.4	59	71	0.99	(0.56, 1.75)
	814	72	71	1.35	(0.78, 2.35)
Chrysene	49.1	64	70	1.00	
	95.0	55	71	0.89	(0.51, 1.55)
	1547	66	71	1.01	(0.59, 1.74)
Indeno[1,2,3-*cd*]pyrene	34.3	46	70	1.00	
	85.9	78	71	1.77	(1.01, 3.11)
	2371	61	71	1.37	(0.77, 2.43)
Coronene	65.3	63	70	1.00	
	129	48	71	0.75	(0.42, 1.34)
	666	74	71	0.99	(0.58, 1.70)
Dibenzo[*a,e*]pyrene	17.6	60	70	1.00	
	40.1	71	71	1.27	(0.73, 2.21)
	611	54	71	0.81	(0.46, 1.43)
Summed PAHs	359	59	70	1.00	

PAH	Tertile max (ng/g)	Cases	Controls	OR	95% CI
	622	60	71	1.02	(0.59, 1.79)
	11170	66	71	1.16	(0.67, 2.00)
PAH TEQ	87.9	61	70	1.00	
	220	67	71	1.26	(0.72, 2.18)
	4574	57	71	0.87	(0.50, 1.52)

[a] Effect estimates are adjusted for child's age, sex, race/ethnicity, and duration between reference/diagnosis and sampling.

ALL, acute lymphoblastic leukemia; HVS3, high volume small surface sampler; PAH, polycyclic aromatic hydrocarbons; TEQ, toxic equivalence.

Table 6

Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association of PAH concentrations in dust from vacuum samples and risk of ALL.

PAH	Tertile max (ng/g)	Cases	Controls	OR^a	95% CI
Benzo[*a*]pyrene	22.3	19	31	1.00	
	63.2	27	31	3.05	(1.02, 9.10)
	622	20	32	2.48	(0.81, 7.63)
Dibenzo[*a,h*]anthracene	12.7	26	31	1.00	
	21.3	19	31	1.51	(0.53, 4.33)
	241	21	32	2.43	(0.80, 7.37)
Benzo[a]anthracene	14.9	14	31	1.00	
	35.5	27	31	1.54	(0.53, 4.50)
	521	25	32	2.06	(0.69, 6.13)
Benzo[*b*]fluoranthene	39.0	23	31	1.00	
	81.6	16	31	0.54	(0.19, 1.58)
	871	27	32	1.47	(0.53, 4.10)
Benzo[*k*]fluoranthene	22.6	17	31	1.00	
	44.5	28	31	1.81	(0.63, 5.21)
	282	21	32	2.71	(0.87, 8.49)
Chrysene	50.6	13	31	1.00	
	128	35	31	2.47	(0.86, 7.06)
	1117	18	32	2.00	(0.64, 6.22)
Indenol[1,2,3-*cd*]pyrene	33.9	12	31	1.00	
	80.0	31	31	4.94	(1.63, 15.0)
	1188	23	32	4.24	(1.34, 13.4)
Coronene	60.4	23	31	1.00	
	130	28	31	1.70	(0.60, 4.80)
	591	15	32	1.36	(0.44, 4.19)
Dibenzo[*a,e*]pyrene	22.1	24	31	1.00	
	46.8	17	31	1.81	(0.59, 5.51)
	713	25	32	1.72	(0.63, 4.69)
Summed PAHs	359	14	31	1.00	

PAH	Tertile max (ng/g)	Cases	Controls	OR[a]	95% CI
	643	30	31	3.21	(1.12, 9.23)
	5242	22	32	4.30	(1.30, 14.2)
PAH TEQ	114	18	31	1.00	
	188	25	31	3.38	(1.10, 10.4)
	2097	23	32	6.44	(1.86, 22.2)

[a]Effect estimates are adjusted for child's age, sex, race/ethnicity, and duration between diagnosis/reference and sampling.

ALL, acute lymphoblastic leukemia; PAH, polycyclic aromatic hydrocarbons; TEQ, toxic equivalence.