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Dust-metal Loadings and the Risk of Childhood Acute Lymphoblastic Leukemia

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Abstract

We evaluated the relationship between the risk of childhood acute lymphoblastic leukemia (ALL) and levels of metals in carpet dust. A dust sample was collected from the homes of 142 ALL cases and 187 controls participating in the California Childhood Leukemia Study using a high volume small surface sampler (2001–2006). Samples were analyzed using microwave-assisted acid digestion in combination with inductively-coupled plasma mass spectrometry for arsenic, cadmium, chromium, copper, lead, nickel, tin, tungsten, and zinc. Eight metals were detected in at least 85% of the case and control homes; tungsten was detected in less than 15% of homes. Relationships between dust-metal loadings (μg metal per m^2 carpet) and ALL risk were modeled using multivariable logistic regression, adjusting for the child's age, sex, and race/ethnicity and confounders, including household annual income. A doubling of dust-metal loadings was not associated with significant changes in ALL risk [odds ratio (95% confidence interval): arsenic: 0.94 (0.83, 1.05), cadmium: 0.91 (0.80, 1.04), chromium: 0.99 (0.87, 1.12), copper: 0.96 (0.90, 1.03), lead: 1.01 (0.93, 1.10), nickel: 0.92 (0.80, 1.07), tin: 0.93 (0.82, 1.05), and zinc: 0.91 (0.81, 1.02)]. Our findings do not support the hypothesis that metals in carpet dust are risk factors for childhood ALL.

Keywords

Childhood acute lymphoblastic leukemia; Dust; Environmental exposure; Lead; Metals

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INTRODUCTION

Leukemia is the most common cancer in children under the age of 15, accounting for about a third of such malignancies (Ross and Spector, 2006). Approximately 2,200 children aged 0–14 are diagnosed with leukemia in the United States each year (4.3 cases per 100,000) and acute lymphoblastic leukemia (ALL) comprises about 80% of these cases (Buffler et al., 2005). Established risk factors for ALL include prenatal exposure to x-rays, therapeutic radiation, and specific genetic syndromes. Incidence of ALL peaks from ages 2–5 (Ross and Spector, 2006), suggesting that prenatal or early-life exposures play an important role in the development of the disease. Moreover, incidence of ALL is highest in industrialized countries (Ross and Spector, 2006), which could indicate that environmental exposures contribute to ALL risk. Indeed epidemiological investigations have implicated certain environmental contaminants as possible risk factors for childhood leukemia, as summarized in meta-analyses for pesticides (Turner et al., 2010; Van Maele-Fabry et al., 2011), tobacco smoke (Chang, 2009; Liu et al., 2011), traffic-related air pollution (Boothe et al., 2014), and solvents and paints (Colt and Blair, 1998). Metals are likewise commonplace in the industrialized world and arsenic, cadmium, hexavalent chromium, and nickel have been classified as human carcinogens, primarily of the lung (IARC, 2006; IARC, 2012a; IARC, 2012b; IARC, 2012c; IARC, 2012d).

There is limited and inconsistent support for the hypothesis that prenatal or early life exposures to specific metals may increase the risk of childhood ALL. The most convincing evidence is for lead, as two studies have shown that paternal occupational exposure to lead is associated with childhood acute myeloid leukemia (Buckley et al., 1989) and ALL (Miligi et al., 2013). There are also case studies of one adult human (Crosby, 1977) and one juvenile primate (Krugner-Higby et al., 2001) who ingested large quantities of lead and subsequently developed myeloid leukemia. Other studies have indicated that maternal occupational exposure to metals is associated with childhood leukemia (Shu et al., 1988; Buckley et al., 1989; McKinney et al., 2003) and that maternal residence near a metal smelter during pregnancy is associated with childhood cancer in her offspring (Wulff et al., 1996). High water levels of arsenic and tungsten were considered possible causes for the clustering of ALL cases in Fallon, Nevada, but no association was found (Rubin et al., 2007; Sheppard et al., 2007). Likewise, high water levels of arsenic, trichloroethylene, tetrachloroethylene, and chloroform were considered possible causes for the clustering of ALL cases in Woborn, Massachusetts, but a non-significant association between maternal exposure to contaminated water during pregnancy and leukemia in her offspring was observed [odds ratio=8.33, confidence interval=0.73–94.67 (Costas et al., 2002)]. In each of the above studies only a small number of leukemia cases (or parents thereof) were exposed to metals. To date, the largest evaluation of the relationship between exposure to metals and ALL was a population-based case-control study that estimated levels of arsenic, cadmium, chromium, lead, and zinc in the drinking water of 491 cases and 491 controls *in utero* and after birth until diagnosis (Infante-Rivard et al., 2001). The investigators reported no significantly increased risks of ALL associated with average metal levels in drinking water from either period; however, ALL cases were more likely than controls to have cumulative postnatal zinc levels above the 95th percentile (odds ratio=2.48, confidence interval=0.99–6.24).

Children may be exposed to metals via inhalation, breastfeeding, dermal absorption, drinking water, dietary ingestion, or non-dietary ingestion of soil or dust (ATSDR, 2007). Inadvertent ingestion of settled dust is the major route of exposure to lead for many children, as demonstrated by the observed correlation between interior dust-lead loadings and children's blood-lead levels in numerous studies (Lanphear et al., 1998). Similar relationships between dust-metal levels and biological-metal levels have been reported for arsenic (Hartwell et al., 1983), cadmium (Hartwell et al., 1983; Hogervorst et al., 2007), copper (Callan et al., 2013), chromium (Stern et al., 1998), nickel (Creason et al., 1975), and tin (Creason et al., 1975). Dust is likely to be an important source of metal exposures for young children, who spend much of their time on the floor and have frequent hand-to-mouth activity (Cohen Hubal et al., 2000).

Historically, the two major sources of lead that have resulted in exposure to the general population have been lead-based paint and leaded gasoline (Bellinger and Bellinger, 2006). Additionally, mining or smelting operations, iron or steel industries, coal or oil combustion, pesticide or fertilizer applications, cigarette smoke, and municipal waste incineration can also be important sources of lead and other metals (ATSDR, 2007). Many factors have been shown to influence lead levels in house-dust samples, including lead paint in the home, bare soil outside the home, the presence of a fireplace, home characteristics (age, condition, type, building materials, ventilation, recent remodeling), resident characteristics (employment in a lead-exposed job, race, income, smoking habits), neighborhood population density; and household density (Baker et al., 1977; Culbard et al., 1988; Kim and Fergusson, 1993; Thorton et al., 1994; Sutton et al., 1995; Meyer et al., 1999; Dixon et al., 2005; Egeghy et al., 2005; Gaitens et al., 2009; Rasmussen et al., 2013). Dust levels of other metals may also be influenced by some of these factors.

As part of the California Childhood Leukemia Study (CCLS), we collected carpet-dust samples from homes of ALL cases and controls and analyzed loadings and concentrations of 9 metals.

METHODS

Study population

The CCLS is a population-based case–control study of childhood leukemia conducted in the San Francisco Bay area and California Central Valley that seeks to identify genetic and environmental risk factors for childhood leukemia. Cases 0–14 years of age were ascertained from pediatric clinical centers; controls, matched to cases on date of birth, sex, Hispanic ethnicity, and maternal race, were selected from the California birth registry. Dust samples were collected from a subset of study homes as one strategy for assessing environmental exposures. Case and control participants who were enrolled in the study from December 1999 through November 2007 were eligible for dust collection if they were 0–7 years old and lived in the same home they had occupied at the time of diagnosis (or a similar reference date for controls). The participation rate for the main study was 86% for both cases and controls. Among 324 leukemia cases and 407 controls eligible for dust sampling, 296 leukemia cases (91%), including 269 ALL cases, and 333 controls (82%) participated. We obtained written informed consent from each child's primary caretaker and study protocols

were approved by the institutional review boards at the University of California, Berkeley and the National Cancer Institute.

Dust collection

Dust samples were collected from CCLS homes using the high volume small surface sampler (HVS3) and household vacuum cleaners from 2001–2007, as previously described (Colt et al., 2008). From 2001–2006, dust was collected using both sampling methods and samples that were collected with the standardized HVS3 protocol (ASTM, 2005) were used preferentially in chemical analyses. HVS3 dust samples were collected from a carpet or rug in the room where the child spent the most time while awake (commonly the family room) and stored in the dark at −20 °C prior to chemical analysis. One major advantage of collecting dust with the HVS3 is that the sampling area was measured; thus, chemical concentrations (*i.e.*, mass of chemical per mass of dust) and chemical loadings (*i.e.*, mass of chemical per area sampled) were calculated. Our primary statistical analysis employed metal loadings obtained from HVS3-collected dust samples (142 cases, 187 controls), because dust-lead loadings are thought to be more useful indicators of childhood lead exposures than dust-lead concentrations (Lanphear et al., 1995). In addition, we also evaluated the relationship between ALL risk and dust-metal concentrations. These secondary statistical analyses were performed for HVS3-collected dust samples (142 cases, 187 controls) as well as for HVS3 and vacuum dust samples combined (241 cases, 293 controls).

Each case household was enrolled in the study at the time of diagnosis and, subsequently, each control household was enrolled as close to the diagnosis/reference date as possible. Case and control households participated in an initial in-home interview, and dust sampling was conducted during a second home visit. The median time between diagnosis/reference date and the dust sampling visit was 1.34 years, and the interval was longer for controls (median: 1.55 years, range: 0.58–4.21 years) than for cases (median: 0.97 years, range: 0.38–3.36 years), due to the additional time required for control enrollment. We expected that chemical levels measured after the diagnosis/reference date would reflect chemical levels in the home during the etiologically-relevant time periods of the children's lives, based on our evaluation of the temporal variability of persistent organic contaminants in dust samples collected from CCLS homes in two dust sampling rounds separated by 3–8 years (Whitehead et al., 2013a; Whitehead et al., 2013b; Whitehead et al., 2014).

Chemical analysis

A multi-residue analysis scheme was used to analyze organic and inorganic chemicals from several compound classes at Battelle Memorial Institute (Columbus, OH), as previously described (Colt et al., 2008). We selected nine metals for analysis that were classified as known or probable human carcinogens (arsenic, cadmium, chromium, lead and nickel), were used in soldering or welding (copper, tin and zinc), and were of interest in a childhood cancer cluster investigation (tungsten). Dust samples were sieved using a 100-mesh metal-free sieve to obtain the fine (<150 μm) fraction of dust. For analysis of metals, conventional microwave-assisted acid digestion was combined with inductively-coupled plasma/mass spectrometry (ICP/MS). A portion (0.2 g) of fine dust was digested in 10 mL of ultra-pure nitric acid in a Teflon microwave digestion vessel. Once capped, the vessels were heated to

150°C and digested for three hours. After cooling, the digest was transferred to a 50 mL conical tube and diluted to 50 mL with deionized water; this volume was divided and further diluted by a factor of 10X and 100X. Solutions were analyzed in reverse order of dilution (*i.e.*, 100X first) and matched to the calibration range. The ICP/MS was calibrated daily using an 8 to 11 point calibration curve ranging in concentrations from 0.1 to 2,500 μg/mL. Internal standards of scandium, terbium, and yttrium were added in-line to samples and standards, and used for quantification and to correct for variations in instrument response. Quantification was performed using a linear regression analysis of the calibration curve data. Sample batches consisted of 35 to 37 participant samples, a method blank, one standard reference material (NIST SRM 2583), and participant samples in triplicate, one of which was spiked to give 2.5 μg/L of each analyte in the extract (except zinc, which was spiked to give 25 μg/L).

Interviews

Parents initially participated in structured in-home interviews designed to ascertain demographic and other information potentially relevant to childhood leukemia. Subsequently, in a second interview that included dust collection, respondents were asked additional questions designed to ascertain information about sources of residential chemical exposures. Together, the two interviews covered several topics relevant to this analysis, including potential sources of metal exposures in the home (*i.e.*, cigarette smoking at home and fireplace use); factors potentially impacting dust loadings (*i.e.*, age of sampled carpet, household vacuum cleaning frequency, residents' shoe removal habits, pet ownership, number of children in the household, presence of bare soil outside the home, and residence age/type); as well as household annual income (see Supplemental Table S1 for interview questions). Parental occupational exposures to metals were assessed as probable, possible, or not likely using job-specific modules designed to elicit parent-reported information on the tasks performed at work, as previously described (Reinier et al., 2004). Examples of jobs with probable metal exposures were welders, painters, electricians, mechanics, and construction workers (see Supplemental Table S2 for details regarding parental occupational exposure to metals).

Some participants were unable or unwilling to complete all aspects of the interviews. To maximize statistical power in regression analyses, we replaced missing interview data using population averages. There were three variables with missing data for at least ten observations: traffic density (52 missing observations replaced with 33,000 veh-mi/mi^2/day), residence construction date (43 missing observations replaced with 1972), and household annual income (11 missing observations replaced with $45,000–$59,000). Compared to models that used imputed data, relationships between ALL risk and metal loadings were similar in models using data from the subset of participants with complete covariate information (data not shown).

Geographic information

We grouped residences into six geographic regions by county: the metropolitan San Francisco Bay Area (Alameda, Contra Costa, Santa Clara, San Francisco, and San Mateo counties); the northern San Francisco Bay Area (Marin, Napa, Solano, and Sonoma

counties); the Sacramento Valley (Butte, Colusa, Glenn, Sacramento, Sutter, Yolo, and Yuba counties); the Sierra Mountains (Amador, Calaveras, El Dorado, Mariposa, Nevada, Placer, and Tuolumne counties); the San Joaquin Valley (Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, Tulare counties); and the California central coast (Monterey, San Benito, San Luis Obispo, and Santa Cruz counties). We used a global positioning device to determine the latitude and longitude for each residence. We linked each location to the corresponding U.S. Census block and categorized each residence as urban, suburban, or rural based on the Census Bureau's delineations (U.S. Census Bureau,). We estimated ambient air metal concentrations at a census tract resolution using results from the U.S. Environmental Protection Agency (EPA) 2005 National-Scale Air Toxics Assessment (U.S. Environmental Protection Agency, 2009). The U.S. EPA assessment employed a National Emissions Inventory to estimate ambient air concentrations of 5 metals (*i.e.*, arsenic, cadmium, chromium, lead, and nickel) attributable to emissions from major stationary sources (*e.g.*, power plants), area sources (*e.g.*, commercial buildings), and mobile sources (*e.g.*, automobiles). Traffic density was estimated as described previously (Gunier et al., 2006). Briefly, traffic density within 500 meters of the home was the sum, for all roads in the buffer, of road length multiplied by average daily traffic count, divided by the buffer area (United States Department of Transportation, Office of Highway Policy Information, 2003). Outdoor soil-metal concentrations for each of the nine metals were estimated at each residence location using data from the U.S. Geological Survey's Geochemical Landscapes Project (Smith et al., 2013). The publicly available survey data includes 258 measurement sites in California with a sampling density of approximately 1 site per 1,600 square kilometers. We used simple kriging (ArcGIS, ESRI, Redlands, CA) to estimate soil-metal concentrations at a depth of 0–5 cm over the extent of the study area.

Statistical analysis

We assigned all values below the method reporting limit (MRL, see Table 1) a concentration equal to MRL/v2 (Hornung and Reed, 1990). For each metal, we modeled the relationship between ALL odds and $\log_2$-transformed metal loadings using a multivariable logistic regression model (Proc Logistic, SAS v. 9.2, Cary, NC). Based on the regression coefficients, we estimated odds ratios associated with a doubling of metal loadings in carpet dust. By design, at the time of enrollment, CCLS cases and controls were matched by child's age, sex, and race/ethnicity. However, due to the additional eligibility criteria used for dust sampling, matched statistical analyses were not possible. As such, we present odds ratios adjusted for the matching factors of child's age, sex, and race/ethnicity.

Based on previous investigations of the determinants of dust-lead levels (Baker et al., 1977; Culbard et al., 1988; Kim and Fergusson, 1993; Thorton et al., 1994; Sutton et al., 1995; Meyer et al., 1999; Dixon et al., 2005; Egeghy et al., 2005; Gaitens et al., 2009; Rasmussen et al., 2013), we evaluated the following factors as potential confounders of the relationship between metal loadings and ALL risk: household annual income, residence age, residence type, residence location, residents' shoe removal habits, number of children in the household, residents' cigarette smoking habits, residents' fireplace use, parental occupational exposure to metals, parental employment as a welder, presence of pets, presence of bare soil outside the residence, traffic density, urban density, estimated outdoor

soil-metal concentrations, estimated outdoor air-metal concentrations, household vacuum cleaning frequency, age of sampled carpet, season of dust sampling, and year of dust sampling. For each metal, we compared the regression coefficient from the logistic model adjusted for matching factors (β_1) to the regression coefficient from the logistic model adjusted for matching factors plus one possible confounder ($\beta 1^*$). If the difference between the two coefficients [*i.e.*, abs(β_1 - β_1*)] was greater than 20% of the standard error of β_1 [*i.e.*, $^{0.2*SE(\beta_1)}$], we included the confounder in the final multivariable logistic regression model for that metal. This process was repeated for each metal and each potential confounder.

By design, at the time of dust collection, each participant lived in the same home they had occupied at the time of diagnosis (or a similar reference date for controls). However, some participants moved into the index home shortly before the diagnosis/reference date. Moreover, carpet age was not used as an eligibility criterion for participation, so some dust samples were collected from carpets that were not in place prior to the time of diagnosis/reference. In secondary statistical analyses we restricted our regression models to exclude (1) any participant that moved into the index home less than one year before the diagnosis/reference date (N = 19 cases, 30 controls) and (2) any participant with a dust sample collected from a carpet or rug that was not in the index home for at least one year prior to the diagnosis/reference date (N = 27 cases, 50 controls). To evaluate the possibility of risk modification by socioeconomic status, secondary statistical analyses also included regression models stratified by annual household income.

RESULTS

Table 1 shows the summary statistics of metal loadings in dust samples collected by HVS3 from homes of 142 cases and 187 controls. Eight of nine metals were detected in at least 85% of both case and control homes. The one exception was tungsten, which was detected in only 10% of the case homes and 13% of the control homes. As such, tungsten loadings are not discussed further. The median, 25th percentile, and 75th percentile of metal loadings from control homes were generally similar or higher than those from the case homes. Two exceptions were the 25th percentile of lead loadings and the 75th percentile of tin loadings, which were higher for case homes.

Supplemental Table S3 shows Spearman rank correlation coefficients between dust-metal loadings as well as between dust-metal loadings and dust loadings (*i.e.*, grams of dust collected per square meter of carpet). Dust loadings were highly correlated with arsenic, cadmium, chromium, copper, lead, and nickel loadings (r_s: 0.81–0.91); whereas, correlations were lower for zinc (r_s=0.68) and tin (r_s=0.45). Likewise, arsenic, cadmium, chromium, copper, lead, and nickel loadings were more highly correlated with each other (r_s: 0.75–0.88) than with zinc loadings (r_s: 0.62–0.70) or tin loadings (r_s: 0.39–0.52).

Supplemental Table S4 shows bivariate relationships between metal loadings and possible metal loading determinants. Lower household annual income and older residence age were associated with higher loadings of all metals. Cigarette smoking at home and increased traffic density in the 500 m surrounding the home were associated with higher loadings of

specific metals. In contrast, the practice of removing shoes at the entrance of the residence was associated with lower loadings for 6 of 8 metals. Compared to carpets sampled from 2001–2003, carpets sampled from 2004–2006 had lower loadings for 5 of 8 metals. Additionally, homes from the San Joaquin Valley had higher loadings of arsenic and cadmium than homes from the metropolitan San Francisco Bay Area. Homes with a parent that was probably exposed to metals at work (N=23) and homes with a parent employed as a welder (N=11) had higher loadings of cadmium, lead, and zinc than homes without a parent exposed to metals at work, although these differences were not significant in bivariate analysis. Supplemental Table S5 highlights the determinants of metal loadings that remained significant (p<0.05) in multivariable models. With the exception of traffic density, each of the bivariate relationships noted above remained significant in at least one multivariable model.

Table 2 shows the characteristics of the case and controls. The age and gender distribution were similar for cases and controls. In contrast, a larger proportion of the control children were non-Hispanic, White compared to the case children (50% vs. 36%, p-value=0.04). Among the determinants of metal loadings discussed above, residence age, shoe removal, and year of dust sampling were similarly distributed between the cases and controls. In contrast, control households were more likely than case households to have an income of at least $75,000 (50% vs. 34%, p-value=0.003). Case residences were more likely than control residences to be located in the San Joaquin Valley (37% vs. 24%, p-value=0.001). Case residences were more likely than control residences to have estimated outdoor soil-copper concentrations below the population median (58% vs. 45%, p-value=0.02). Finally, cases were also less likely than controls to live in single-family residences (80% vs. 89%, p-value=0.02).

Table 3 shows the number of case and control homes in each quartile of metal loadings and corresponding crude odds ratios. There were no significantly elevated or decreased odds ratios and no monotonically increasing trends in odds ratios by metal loading quartile. Odds ratios decreased monotonically by quartile of copper loadings. Table 4 shows that metal loadings were not associated with ALL risk for any metal in logistic regression models that adjusted for child's age, sex, and race/ethnicity or in fully adjusted models.

Table 5 shows the regression results for multivariable logistic models that evaluated the relationship between ALL and $\log_2$-tansformed metal concentrations. We observed a significant negative association between cadmium concentrations and ALL risk for all dust samples combined [odds ratio (95% confidence interval): 0.84 (0.72, 0.99)]. Otherwise, metal concentrations were not associated with ALL risk. For models that included HVS3 samples only, odds ratios calculated with metal concentrations tended to be higher than odds ratios calculated with metal loadings, most notably for chromium and nickel [odds ratio (95% confidence interval): chromium: 1.23 (0.97, 1.57), and nickel: 1.30 (0.90, 1.88)].

Supplemental Table S6 shows the relationship between ALL and $\log_2$-tansformed metal loadings, stratified by income. For participants with household annual income below $75,000, metal loadings were not associated with ALL risk. Moreover, when the lower income group was further stratified into five smaller groups, there was no evidence of

increasing odds ratios across decreasing income strata (data not shown). For participants with household annual income of at least $75,000, increasing loadings of arsenic, cadmium, nickel, tin, and zinc were associated with decreasing ALL risk. When evaluating the relationship between ALL and $\log_2$-tansformed metal loadings for participants that moved into the index home more than one year before the diagnosis/reference date and for participants with carpets/rugs that predate diagnosis/reference by more than one year, results were similar to the results from the models using all HVS3 samples (data not shown).

DISCUSSION

This is the first study published in the peer-reviewed literature to assess the relationship between dust-metal loadings in children's homes and the risk of childhood ALL. We found no evidence that case homes had higher dust-metal loadings than control homes, or that dust-metal loadings were associated with ALL risk. Our findings do not support the hypothesis that early childhood exposure to metals present in carpet dust is a risk factor for childhood ALL.

A Canadian population-based case-control study estimated metal levels in the drinking water of 491 cases and 491 controls and found no association with ALL risk (InfanteRivard et al., 2001). Other studies (Shu et al., 1988; Buckley et al., 1989; McKinney et al., 2003; Miligi et al., 2013) that have shown associations between parental occupational exposures to metals and the risk of childhood leukemia were equivocal, because metal exposures were not directly assessed via environmental or biological measures and because significant results were based on a small number of parents of children with leukemia that were exposed to metals (*i.e.*, $5 \leq N \leq 44$). In contrast, our analysis was based on a relatively large study population (*i.e.*, 142 ALL cases and 187 controls) and we evaluated ALL risk using specific and objective measures of environmental metal levels as surrogates for childhood metal exposures.

Given that children may also be exposed to metals via inhalation, breastfeeding, and diet, one limitation of our analysis is that we did not use biological measurements to assess children's exposure to metals. However, it is well established that ingestion of settled dust is a major route of exposure to lead for children, as numerous investigators have reported correlations between interior dust-lead loadings and children's blood-lead levels (Lanphear et al., 1998). Likewise, dust loadings of other metals analyzed here should also be useful surrogates for biological intake (Creason et al., 1975; Hartwell et al., 1983; Stern et al., 1998; Hogervorst et al., 2007; Callan et al., 2013), especially for young children, who spend much of their time on the floor and have frequent hand-to-mouth activity (Cohen Hubal et al., 2000). In the CCLS, we have previously demonstrated a positive relationship between ALL risk and carpet-dust concentrations of polychlorinated biphenyls (Ward et al., 2009), the herbicide chlorthal (Metayer et al., 2013), polybrominated diphenyl ethers (Ward et al., 2014), and polycyclic aromatic hydrocarbons (Deziel et al., 2014). The major advantage of assessing exposures to metals using dust measurements is that dust collection is less invasive than collection of biological materials such as blood, especially for young children. Moreover, a dust measurement should provide a long-term average of in-home metal contamination with little day-to-day temporal variability, as evidenced by longitudinal dust

measurements of lead (Egeghy et al., 2005) and persistent organic contaminants (Whitehead et al., 2013a; Whitehead et al., 2013b; Whitehead et al., 2014).

Another limitation of our study was that the case population had significantly lower income than the control population. Because lower income was associated with higher metal loadings, there was a potential to observe spurious positive risk estimates. However, odds ratios were null with and without adjustment for income in multivariable logistic regression models. Moreover, we stratified multivariable logistic regression models by income and observed only negative or null risk estimates (Supplemental Table S6). We interpret with caution the observed negative risk estimates for the subgroup of participants with household annual income greater than $75,000. Due to the lack of biological plausibility, we suspect that exposure to metals in carpet dust does not truly confer a protective effect for childhood ALL; rather, we suggest that this observation may be a chance finding.

In summary, our analysis assessing the relationship between dust-metal loadings in children's homes and the risk of childhood ALL does not support the hypothesis that metals in carpet dust are risk factors for childhood ALL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary statistics of metal loadings (μg/m^2) in dust samples collected by high volume small surface sampler from California Childhood Leukemia Study homes (2001-2006).

Metal	MRL, μg/m^2	Cases, *N*=142		Controls, *N*=187	
		% > MRL	Median (IQR), μg/m^2	% > MRL	Median (IQR), μg/m^2
Arsenic	0.12	99	4.0(1.5, 9.4)	99	4.5(1.9, 11)
Cadmium	0.12	100	2.1(0.76, 4.9)	100	2.4(0.93, 5.5)
Chromium	1.2	100	57(25, 120)	98	57(25, 120)
Copper	0.12	92	110(48, 220)	94	130(50, 290)
Lead	0.12	98	48(21, 120)	96	59(19, 120)
Nickel	1.2	100	48(21, 100)	100	52(23, 110)
Tin	6.1	87	4.0(1.0, 13)	86	4.1(1.2, 11)
Tungsten	0.012	10	<MRL(<MRL, <MRL)	13	<MRL(<MRL, <MRL)
Zinc	1.2	99	480(220, 1300)	99	570(280, 1400)

MRL=Method reporting limit, IQR = inter-quartile range

Table 2

Characteristics of acute lymphoblastic leukemia cases and controls participating in the California Childhood Leukemia Study with dust collected by high volume small surface sampler (2001–2006).

Possible confounders	ALL Cases, *N*=142 (%)	Controls, *N*=187 (%)	χ^2-test *p*-value
Child's age at diagnosis/reference date			
<1	2 (1)	7 (4)	
1 to <2	17 (12)	26 (14)	
2 to 5	78 (55)	106 (57)	
>5	45 (32)	48 (26)	0.40
Child's sex			
Male	82 (58)	105 (56)	
Female	60 (42)	82 (44)	0.77
Child's race/ethnicity			
Hispanic	58 (41)	56 (30)	
Non-Hispanic, White	51 (36)	93 (50)	
Non-Hispanic, African American	3 (2)	6 (3)	
Non-Hispanic, Asian	19 (13)	14 (7)	
Non-Hispanic, other race(s)	11 (8)	18 (10)	0.04
Household annual income			
<$75,000	91 (66)	90 (50)	
≥$75,000	46 (34)	91 (50)	0.003
Residence age			
Built before 1980	63 (54)	95 (56)	
Built 1980 or later	54 (46)	74 (44)	0.69
Residence location			
Metropolitan San Francisco Bay Area	59 (42)	73 (39)	
Northern San Francisco Bay Area	12 (8)	22 (12)	
Sacramento Valley	4 (3)	20 (11)	
San Joaquin Valley	53 (37)	44 (24)	
California central coast	13 (9)	16 (9)	
Sierra Mountains	1 (1)	12 (6)	0.001
Residence type			
Single family home	113 (80)	165 (89)	
Duplex/Townhouse	14 (10)	7 (4)	
Apartment/Condominium	8 (6)	12 (6)	
Mobile home	7 (5)	2 (1)	0.02
Residents usually remove shoes			
Yes	40 (28)	64 (34)	
No	101 (72)	122 (66)	0.25
Parent is employed as a welder			
No	135 (95)	183 (98)	
Yes	7 (5)	4 (2)	0.16

Possible confounders	**ALL Cases, *N*=142 (%)**	**Controls, *N*=187 (%)**	**χ^2-test *p*-value**
Estimated outdoor soil-Cu concentrations			
<27 μg/g	81 (58)	83 (45)	
≥27 μg/g	58 (42)	100 (55)	0.02
Year of dust sampling			
2001 to 2003	68 (48)	90 (48)	
2004 to 2006	74 (52)	97 (52)	0.97

Table 3

Crude odds ratios (95% confidence intervals) for acute lymphoblastic leukemia by quartiles of metal loadings in dust samples collected by high volume small surface sampler from California Childhood Leukemia Study homes (2001–2006).

Metal	Loadings, μg/m^2	Cases, *N*(%)	Controls, *N*(%)	Odds Ratio (Confidence Interval)
Arsenic	<1.9	43(30)	47(25)	1.0
	1.9–4.5	35(25)	47(25)	0.81(0.45, 1.49)
	4.5–11	31(22)	47(25)	0.72(0.39, 1.33)
	≥11	33(23)	46(25)	0.78(0.43, 1.44)
Cadmium	<0.93	40(28)	47(25)	1.0
	0.93–2.4	38(27)	47(25)	0.95(0.52, 1.73)
	2.4–5.5	31(22)	47(25)	0.78(0.42, 1.44)
	≥5.5	33(23)	46(25)	0.84(0.46, 1.56)
Chromium	<25	36(25)	47(25)	1.0
	25–57	37(26)	47(25)	1.03(0.56, 1.89)
	57–120	32(23)	47(25)	0.89(0.48, 1.66)
	≥120	37(26)	46(25)	1.05(0.57, 1.94)
Copper	<50	40(28)	47(25)	1.0
	50–130	39(27)	47(25)	0.98(0.54, 1.77)
	130–290	36(25)	47(25)	0.90(0.49, 1.65)
	≥290	27(19)	46(25)	0.69(0.37, 1.30)
Lead	<19	32(23)	47(25)	1.0
	19–59	47(33)	47(25)	1.47(0.80, 2.69)
	59–120	26(18)	47(25)	0.81(0.42, 1.57)
	≥120	37(26)	46(25)	1.18(0.63, 2.20)
Nickel	<23	38(27)	47(25)	1.0
	23–52	38(27)	47(25)	1.00(0.55, 1.83)
	52–110	31(22)	47(25)	0.82(0.44, 1.52)
	≥110	35(25)	46(25)	0.94(0.51, 1.74)
Tin	<1.2	37(26)	47(25)	1.0
	1.2–4.1	34(24)	47(25)	0.92(0.50, 1.70)
	4.1–11	28(20)	47(25)	0.76(0.40, 1.43)
	≥11	43(30)	46(25)	1.19(0.65, 2.16)
Zinc	<280	48(34)	47(25)	1.0
	280–570	27(19)	47(25)	0.56(0.30, 1.05)
	570–1400	32(23)	47(25)	0.67(0.37, 1.22)
	≥1400	35(25)	46(25)	0.75(0.41, 1.35)

[a] Dust-metal loading categories are based on the quartiles among controls

Table 4

Adjusted odds ratios (95% confidence intervals) for acute lymphoblastic leukemia associated with a doubling of metal loadings in dust samples collected by high volume small surface sampler from California Childhood Leukemia Study homes (2001–2006).

Metal	Models adjusted for matching factors[a]	Fully adjusted models[b]
Arsenic	0.99 (0.89, 1.10)	0.94 (0.83, 1.05)
Cadmium	0.98 (0.87, 1.10)	0.91 (0.80, 1.04)
Chromium	1.04 (0.92, 1.17)	0.99 (0.87, 1.12)
Copper	0.98 (0.92, 1.04)	0.96 (0.90, 1.03)
Lead	1.03 (0.95, 1.12)	1.01 (0.93, 1.10)
Nickel	0.99 (0.87, 1.14)	0.92 (0.80, 1.07)
Tin	1.00 (0.89, 1.12)	0.93 (0.82, 1.05)
Zinc	0.95 (0.86, 1.06)	0.91 (0.81, 1.02)

[a] Matching factors were child's age at diagnosis/reference date, child's sex, and child's race/ethnicity

[b] Fully adjusted models include matching factors plus the following determinants of dust-metal loadings that confounded the relationship between ALL risk and dust-metal loadings.

As: Household annual income, residence location

Cd: Household annual income, residence location, year of dust sampling

Cr: Household annual income, residence location, residents' shoe removal habits

Cu: Household annual income, residence location, estimated outdoor soil-Cu concentrations

Pb: Household annual income

Ni: Household annual income, residents' shoe removal habits, residence type

Sn: Household annual income, residence location, resident employed as welder

Zn: Household annual income, residence location

Table 5

Odds ratios (95% confidence intervals) for acute lymphoblastic leukemia associated with a doubling of metal concentrations in dust samples collected by high volume small surface sampler (HVS3) and household vacuum cleaners from California Childhood Leukemia Study homes (2001-2007).

Metal	HVS3 Samples, N = 142 cases, 187 controls		HVS3 and Vacuum Samples, N = 241 cases, 293 controls	
	Models adjusted for matching factors[a]	Fully adjusted models[b]	Models adjusted for matching factors[a]	Fully adjusted models[c]
Arsenic	0.99 (0.81, 1.20)	0.99 (0.81, 1.20)	0.92 (0.81, 1.03)	0.92 (0.81, 1.03)
Cadmium	0.96 (0.78, 1.18)	0.92 (0.74, 1.13)	0.85 (0.73, 0.99)*	0.84 (0.72, 0.99)*
Chromium	1.16 (0.94, 1.43)	1.23 (0.97, 1.57)	1.09 (0.94, 1.28)	1.15 (0.97, 1.35)
Copper	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)
Lead	1.06 (0.95, 1.18)	1.06 (0.95, 1.18)	1.03 (0.94, 1.13)	1.03 (0.94, 1.13)
Nickel	1.03 (0.75, 1.43)	1.30 (0.90, 1.88)	0.92 (0.74, 1.14)	0.99 (0.79, 1.26)
Tin	1.03 (0.85, 1.23)	1.03 (0.85, 1.24)	0.98 (0.87, 1.10)	1.00 (0.88, 1.13)
Zinc	0.94 (0.83, 1.08)	0.97 (0.84, 1.12)	0.94 (0.83, 1.07)	0.98 (0.86, 1.11)

*Indicates the estimated odds ratio is significantly different than 1.0 (p-value<0.05)

[a]Matching factors were child's age at diagnosis/reference date, child's sex, and child's race/ethnicity

[b]Models were adjusted for matching factors plus the following determinants of dust-metal concentrations that confounded the relationship between ALL risk and dust-metal concentrations.

As: (no additional adjustment)

Cd: Year of dust sampling, number of children in the household

Cr: Residence location, household annual income, estimated soil-Cr concentrations Cu: (no additional adjustment)

Pb: (no additional adjustment)

Ni: Residence location, household annual income, number of children in the household, estimated soil-Ni concentrations

Sn: Residence location, season of dust sampling

Zn: Residence location, household annual income, year of dust sampling, residence type

[c]Models were adjusted for matching factors plus the following determinants of dust-metal concentrations that confounded the relationship between ALL risk and dust-metal concentrations.

As: (no additional adjustment)

Cd: Residence location, number of children in the household

Cr: Residence location, household annual income, estimated soil-Cr concentrations

Cu: Household annual income, sampling method

Pb: (no additional adjustment)

Ni: Residence location, household annual income, estimated soil-Ni concentrations

Sn: Year of dust sampling

Zn: Household annual income, year of dust sampling, number of children in the household, estimated soil-Zn concentrations