Received: 24 September 2024 | Revised: 13 January 2025 | Accepted: 4 February 2025

DOI: 10.1002/ijc.35370

RESEARCH ARTICLE

Cancer Epidemiology

IJC INTERNATIONAL JOURNAL of CANCER | UICC

Exposure to per- and polyfluoroalkyl substances in residential settled dust and risk of childhood acute lymphoblastic leukemia

Catherine Metayer[1] | Libby M. Morimoto[1] | Veronica M. Vieira[2] | Krystal J. Godri Pollitt[3,4] | Scott M. Bartell[2,5,6] | Luann Wong[7] | Thomas M. Young[7]

[1]School of Public Health, University of California, Berkeley, California, USA

[2]Department of Environmental and Occupational Health, University of California, Irvine, California, USA

[3]Department of Epidemiology, Yale University, New Haven, Connecticut, USA

[4]Department of Chemical and Environmental Engineering, Yale University, New Haven, Connecticut, USA

[5]Department of Statistics, University of California, Irvine, California, USA

[6]Department of Epidemiology and Biostatistics, University of California, Irvine, California, USA

[7]Department of Civil and Environmental Engineering, University of California, Davis, California, USA

Correspondence
Catherine Metayer, University of California, Berkeley, 1995 University Avenue, Suite 265, Berkeley, CA 94704, USA.
Email: cmetayer@berkeley.edu

Funding information
National Institute of Environmental Health Sciences, Grant/Award Numbers: P30 ES023513, P42 ES004699, P42ES04705-18, R01ES009137, R01ES032196, R24ES028524; National Cancer Institute contract, Grant/Award Number: N02-CP-11015 (Westat)

Abstract

Per- and polyfluoroalkyl substances (PFAS) are ubiquitous. Young children are commonly exposed to these chemicals via ingestion of settled dust. Several PFAS have been associated with cancers in adults, yet little is known about the risk in children. We investigated whether PFAS concentrations in residential dust were associated with childhood acute lymphoblastic leukemia (ALL). Vacuum bags were collected in homes of 178 children diagnosed with ALL and 204 healthy controls (age 0–7 years) residing in California (2001–2007). Dust samples were sieved and analyzed for 19 PFAS using targeted liquid chromatography mass spectrometry analysis. The effects of individual PFAS and PFAS mixtures were estimated for eight PFAS with at least 50% above the limit of quantification (LOQ) using logistic regression, G-computation, and generalized additive modeling (GAM). In the model mutually adjusting for eight PFAS, a statistically significant association was seen only for *N*-ethyl perfluorooctane sulfonamido acetic acid (EtFOSAA) ($OR_{continuous} = 1.40$, 95% CI = 1.05–1.86 and $OR_{4th\ vs.\ 1st\ quartile} = 2.58$, 95% CI = 1.16–5.71). Using G-computation, the eight PFAS mixture was positively associated with childhood ALL (OR = 1.60, 95% CI = 1.15–2.24), with positive weights for EtFOSAA, perfluoro-*n*-hexanoic acid (PFHxA), perfluoro-1-decanesulfonate (PFDS), and perfluoro-1-octanesulfonate (PFOS), and negative weights for perfluoro-1-hexanesulfonate (PFHxS) and bis(1H,1H,2H,2H-perfluorooctyl)phosphate (6:2 diPAP). Using GAM, the OR for the mixture reached a maximum of 2.24, at the highest value of log10 EtFOSAA and lowest value of log10 PFHxS. Exposure to a mixture of PFAS in settled dust was associated with an overall elevated risk of childhood ALL, with EtFOSAA and PFHxS being the main contributors to the positive and negative weights, respectively.

KEYWORDS

childhood leukemia, environmental exposures, house dust, mixtures, PFAS

What's New?

Because of widespread use and resistance to degradation, per- and polyfluoroalkyl substances (PFAS) are ubiquitous in the environment. For young children, owing in part to crawling and hand-to-mouth behaviors, PFAS exposure is unique. Here, the authors investigated the risk of childhood leukemia in relation to PFAS found in settled dust collected from vacuum bags from homes in California. A mixture of eight PFAS detected in dust was associated with an increased risk of childhood leukemia, with EtFOSAA showing a significant independent association. The findings indicate that residential dust is a source of PFAS exposure and a potential cause of childhood leukemia.

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common cancer in children in industrialized countries.[1] In the United States, the incidence rate has increased over the past four decades especially among Latinx children,[2] suggesting an important role of environmental influences. Per- and polyfluoroalkyl substances (PFAS) are stable man-made chemicals widely used in manufacturing and consumer products since the 1940s. The widespread use of this chemical class that includes over 10,000 compounds has resulted in persistent contamination of soil, drinking water, and indoor surfaces. Perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are legacy PFAS that were largely phased out of U.S. production in the early 2000s. However, their long half-lives in the environment and in human blood, as well as the introduction of replacement PFAS (some of which can degrade to form PFOS or PFOA),[3] have ensured that chemicals from this class continue to impact the public health.[4] In November 2023, the International Agency for Research on Cancer classified PFOA as "*carcinogenic to humans* (*Group 1*)" based on strong mechanistic evidence and limited evidence from observational studies for cancers of the testis and kidney.[5] PFOS was classified as "*possibly carcinogenic to humans* (*Group 2B*)."[5] Epidemiologic studies have yielded inconsistent findings for other cancers including prostate, breast, thyroid, pancreas, and liver.[6] Mechanisms underlying PFAS carcinogenicity may include cytotoxicity, oxidative stress, epigenetic modification, and mediation of immune and hormone pathways.[5]

To date, human studies have mostly focused on PFOS and PFOA and the risks of adult cancers,[6] and less is known about the impact of other legacy and emerging PFAS, especially on childhood cancers. Childhood cancer clusters, including leukemia, brain tumors, and rhabdomyosarcoma, were identified in areas nearby PFAS-contaminated sites in New Hampshire[7] and North Carolina[8] but investigations did not yield statistically significant findings, possibly due to the small numbers of cases.[9] In a Finnish nested case–control study, 19 PFAS were measured in pregnancy blood samples collected from 1986 to 2010 from mothers of 400 children later diagnosed with ALL and of 400 healthy controls.[10] The authors reported increasing risks of early-onset ALL with increasing pregnancy levels of (*N*-methyl perfluorooctane sulfonamido acetic)acid (MeFOSAA). Positive associations were also observed with PFOS in samples collected from 1986 to 1995 when pregnancy blood levels were the highest, and with PFOA among first-born children only; no associations were seen with the other 16 PFAS. Similarly, a California case–control study of retinoblastoma (501 cases and 1121 controls) reported increased risk associated with detection of PFOS and PFOA in archived blood samples that were collected shortly after birth, with some variations in US-born versus Mexico-born mothers; no increased risk was seen with perfluorononanoic acid (PFNA).[11] The immunotoxicity of PFAS is well established, especially in children,[12] and there is strong evidence that inadequate training of a child's immune system contributes to the development of ALL later in life.[13] Altogether, these observations strengthen the need to further investigate the role of PFAS in the development of childhood cancers.

Drinking water and diet are the major sources of PFAS exposure in adults, and mothers may expose their child during pregnancy and breastfeeding.[14,15] Settled dust is another important source of exposure for young children that spend most of their time indoors and engage in crawling and hand-to-mouth activities.[16] Indoor dust has been found to contain detectable levels of PFAS in several studies in the United States[17,18] and other countries.[19–22] Population surveys conducted in the 2000s nationwide[23] and in California[24,25] have also detected PFAS in young children, often at higher levels than adolescents, adults, or their parents, and reported statistically significant, albeit weak, positive associations between some PFAS concentrations in residential dust and children's serum.[24]

The objective of our study was to investigate whether post-natal indoor exposure to PFAS contamination in residential settled dust increases the risk of childhood ALL in an ethnically diverse population in California.

2 | METHODS

2.1 | Study design and population

The California Childhood Leukemia Study (CCLS) is a population-based case–control study conducted in 35 California counties (parent study: 1995–2016) that collected detailed interview data and biospecimens. To complement interviews lacking specificity in terms of exposure assessment, settled dust samples were collected for a subset of households in Northern and Central California (ancillary study: 2001–2007). Details of the design for the parent study have been

TABLE 1 Summary of 33 PFAS measured in all participating households, ordered from the highest to the lowest % detection.

Compound	Abbreviation	Class	Molecular Formula	LOQ	% Detection $N = 382$	Concentration (ng/g)		
						Mean	SD	Range
bis(1H,1H,2H,2H-perfluorooctyl)phosphate	6:2 diPAP	diPAP	C16H9F26O4P	5	100%	562.6	1193.7	(8–9428)
Perfluoro-1-octanesulfonate[a]	PFOS	PFSA	C8HF17O3S	5	95%	218.7	448.5	(5–5180)
Perfluoro-1-decanesulfonate	PFDS	PFSA	C10F21O3S	1	92%	26.5	101.7	(1–1335)
Perfluoro-*n*-octanoic acid	PFOA	PFCA	C8HF15O2	22	75%	251.2	418.1	(23–3508)
Perfluoro-1-hexanesulfonate[a]	PFHxS	PFSA	C6HF13O3S	5	70%	236.7	842.5	(5–9616)
Perfluoro-*n*-heptanoic acid	PFHpA	PFCA	C7HF13O2	13	67%	151.2	304.5	(13–2537)
N-Ethyl perfluorooctane sulfonamido acetic acid[a]	EtFOSAA	PreFAS	C12H8F17NO4S	13	67%	97.9	217.2	(13–2848)
Perfluoro-*n*-hexanoic acid	PFHxA	PFCA	C6HF11O2	12	50%	115.5	274.6	(12–3030)
1H,1H,2H,2H-perfluoro-1-octanesulfonate	6:2 FTS	PreFAS	C8H4F13O3S	35	41%	209.7	451.6	(35–3851)
1H,1H,2H,2H-perfluorodecane sulfonate	8:2 FTS	PreFAS	C10H4F17O3S	16	31%	58.6	87.1	(16–560)
Perfluoro-*n*-nonanoic acid	PFNA	PFCA	C9HF17O2	26	23%	142.5	215.8	(26–1280)
Perfluoro-*n*-decanoic acid	PFDA	PFCA	C10HF19O2	13	21%	90.8	169.4	(14–1090)
Perfluoro-1-pentanesulfonate	PFPeS	PFSA	C5F11O3S	7	19%	26.5	53.9	(7–430)
N-methyl perfluorooctane sulfonamido acetic acid[a]	MeFOSAA	PreFAS	C11H6F17NO4S	14	18%	132.6	123.7	(15–652)
Perfluoro-1-heptanesulfonate	PFHpS	PFSA	C7F15O3S	6	17%	16.8	18.8	(6–122)
Perfluoro-*n*-tetradecanoic acid	PFTeDA	PFCA	C14HF27O2	15	13%	49.2	60.2	(15–268)
Perfluoro-*n*-undecanoic acid	PFUnA	PFCA	C11HF21O2	15	13%	73.7	84.5	(16–437)
Perfluoro-*n*-dodecanoic acid	PFDoA	PFCA	C12HF23O2	13	13%	59.4	83.8	(14–472)
Perfluoro-1-butanesulfonate	PFBS	PFSA	C4F9O3S	6	12%	33.4	61.4	(7–314)
Perfluoro-*n*-pentanoic acid	PFPeA	PFCA	C5HF9O2	30	9%	116.7	143.9	(31–833)
Perfluoro-*n*-tridecanoic acid	PFTrDA	PFCA	C13HF25O2	16	9%	56	61.9	(16–352)
N-methyl perfluoro-1-octanesulfonamide	N-MeFOSA-M	PreFAS	C9H4F17NO2S	3	5%	14.3	28.4	(4–127)
Perfluorooctane sulfonamide	FOSA	FASA	C8H2F17NO2S	14	4%	82.1	148.4	(15–610)
Perfluoro-1-nonanesulfonate	PFNS	PFSA	C9F19O3S	1	1%	6.5	4.8	(2–13)
Perfluoro-*n*-butanoic acid	PFBA	PFCA	C4HF7O2	162	1%	318.7	86	(231–403)
1H,1H,2H,2H-perfluorohexane sulfonate	4:2 FTS	PreFAS	C6H4F9O3S	86	0%	NA	NA	NA
Tetrafluoro(heptafluoropropoxy)propanoic acid	HFPO-DA	PFOS Replacement (GenX)	C6F11O3	500	0%	NA	NA	NA
Dodecafluoro-3H-4,8-dioxanonanoate	NaDONA	PFOS Replacement	C7HF12NaO4	17	0%	NA	NA	NA
9-CHLOROHEXADECAFLUORO-3-oxanonane-1-sulfonate	8:2 Cl-PFESA	PFOS Replacement (F53-B)	C10HClF20O4S	6	0%	NA	NA	NA
11-Chloroeicosafluoro-3-oxaundecane-1-sulfonate	6:2 Cl-PFESA	PFOS Replacement (F51-B)	C8ClF16KO4S	6	0%	NA	NA	NA
2-(*N*-methyl perfluoro-1-octanesulfonamido)-ethanol	N-MeFOSE-M	PreFAS	C11H8F17NO3S	50	0%	NA	NA	NA

(Continues)

TABLE 1 (Continued)

Compound	Abbreviation	Class	Molecular Formula	LOQ	% Detection N = 382	Concentration (ng/g)		
						Mean	SD	Range
N-ethyl perfluoro-1-octanesulfonamide	N-EtFOSA-M	PreFAS	C10H6F17NO2S	3	0%	NA	NA	NA
2-(N-ethyl perfluoro-1-octanesulfonamido)-ethanol	N-EtFOSE-M	PreFAS	C12H10F17NO3S	NA	0%	NA	NA	NA

Abbreviations: diPAP, perfluoroalkyl phosphate; FASA, perfluoroalkyl sulfonamides; LOQ, limit of quantitation; PFCA, perfluoroalkyl carboxylic acids; PFSA, perfluoroalkyl sulfonic acids; PreFAS, fluoroalkyl substance precursors; SD, standard deviation.
[a]Linear and branched.

published previously.[26] Briefly, leukemia cases were identified within 72 h after diagnosis in pediatric hospitals and were eligible if they were ≤15 years of age at diagnosis, had an English or Spanish speaking parent, lived in the study area, and had no previous cancer. Controls (with similar eligibility criteria) were randomly selected from the CA Office of Vital Records (birth registry) and individually matched to each case on date of birth, sex, maternal race, and Latino ethnicity status. Eligibility criteria for the ancillary dust study included children aged 0–7 years at the time of diagnosis for cases (reference date for controls), and families residentially stable since diagnosis/reference date. Households were asked to mail back a vacuum bag from which dust was sieved and stored at −20°C. The mean duration between reference date and dust collection was 1.43 years (1.04 for cases, 1.81 years for controls). The final sample for this analysis included 178 childhood ALL cases and 204 controls, each with at least 2 g of dust in storage.

2.2 | Chemical analysis of settled dust

2.2.1 | Extraction

Concentrations of 33 PFAS in settled dust were measured at the Young Lab in the Department of Civil and Environmental Engineering at the University of California, Davis (Table 1). Dust samples (100 mg) were transferred into glass centrifuge tubes and spiked with a mixture of isotopically labeled surrogate compounds (Table S1). After 10 min, 3 mL of hexane: acetone (3:1 v/v) was added, and the mixture was vortexed for 1 min, followed by 15 min of sonication extraction and centrifugation at 3500 rpm for 5 min. The supernatant was collected into an evaporation tube, and the dust was extracted a second time using 100% acetone following the same procedure. The combined extract was evaporated to 1 mL under nitrogen and filtered through a 0.2 μm PTFE filter. The extract was further evaporated to 0.1 mL and solvent exchanged by adding 1 mL of acetonitrile, which was again evaporated to a final volume of 0.5 mL. A mixture of internal standards was added for analysis by liquid chromatography quadrupole time-of-flight mass spectrometry (LC/Q-TOF-MS). All samples were blinded to case–control status.

2.2.2 | Targeted LC–MS analysis

Chromatographic separation of a 10 μL injection was achieved using an Agilent 1260 Infinity HPLC equipped with a Zorbax Eclipse Plus C18 column in an 18-minute run at a flow rate of 0.35 mL/min with mobile phases of: (a) distilled deionized water plus 1 mM ammonium fluoride, (b) acetonitrile. The Agilent 6530 Q/TOF-MS was run in the 2 GHz extended dynamic range mode at 4 spectra/second. Acquisition was done in data independent All-Ions fragmentation mode using collision energies (CE) of 0, 10, 20, and 40. Quality controls, including matrix spikes and blanks (solvent and method) were run together with samples. Concentrations for all target PFAS were determined using

Agilent Quantitative Analysis (v. B08). Limits of detection (LOD) and limits of quantitation (LOQ) were determined as 3 and 10 times the standard deviation of the lowest detectable standard injection, respectively.

2.3 | Statistical analyses

Eight PFAS were included in our statistical analysis; at least 50% of subjects had measures above the limit of quantification (LOQ) for these chemicals, including perfluoro-*n*-hexanoic acid (PFHxA, 50% > LOQ), perfluoro-*n*-heptanoic acid (PFHpA, 67% > LOQ), perfluoro-*n*-octanoic acid (PFOA, linear, 74% > LOQ), perfluoro-1-hexanesulfonate (PFHxS, linear and branched, 69% > LOQ), perfluoro-1-octanesulfonate (PFOS, linear and branched, 94% > LOQ), (*N*-ethyl perfluorooctane sulfonamido)acetic acid (EtFOSAA, linear and branched, 66% > LOQ), perfluoro-1-decanesulfonate (PFDS, 92% > LOQ), and bis (1H,1H,2H,2H-perfluorooctyl)phosphate (6:2 diPAP, 100% > LOQ). Values below the LOQ were randomly imputed to values between zero and the limit of quantitation using the lognormal distribution of values for each PFAS. Distributions and correlations between PFAS chemicals were assessed. Pearson's chi-square tests were used to compare cases and controls by sociodemographic and birth characteristics. We evaluated each PFAS continuously (log10 transformed) and categorically (quartiles, except for PFHxA which was dichotomized for values above LOQ [reference group]), as well as the sum of all PFAS levels (continuous). Adjusted models included age at diagnosis (continuous), birth year (continuous), sex assigned at birth, race/ethnicity (Latinx vs. non-Latinx), household income (ordinal), and parental highest education (high school or less vs. some college or more). Analytical batch number was not retained in the final models because models with and without adjustment for batch number had similar results. Similarly, additional covariates evaluated as confounders (maternal age, birth order, gestational age, birth weight, and parental smoking status) were found to be unrelated to both the exposures (PFAS) and the outcome (case–control status) and were not included in models. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression to assess the associations between each PFAS and childhood ALL, independently as well as adjusted for all other PFAS. We conducted additional analyses stratified by age at diagnosis (<3 vs. 3+ years), Latinx versus non-Latinx, and residence from birth to dust collection (same home vs. different home) to assess the potential for differential impact of demographic characteristics and duration of exposure. All tests were two-sided, and $p < .05$ indicated statistical significance. All analyses were performed in R (v.4.3.1).

To assess the overall effect of the mixture of eight PFAS with over 50% detection, as well as confirm independent associations observed from classic regression-based approaches, additional methods were used. Quantile G-computation (g-comp), a parametric, generalized linear model-based approach using g-computation, was used to estimate the mixture effect of all assessed PFAS. G-comp estimates the parameters of a marginal structure model by simultaneously increasing all chemicals in the mixture by one quantile, thus permitting non-linear effects of each exposure to the score and estimating a mixture effect.[27] G-comp also provides weights that estimate the relative contribution of each individual PFAS to the mixture. G-comp stratified analyses were also conducted. Cochran *Q* test was used to evaluate heterogeneity between strata, and $p < .05$ indicated statistical significance. R package qgcomp (v.2.15.2) was used to run analyses.

Semi-parametric additive mixture models were also generated using a multivariable loess smooth term for mixtures of continuous PFAS in addition to the adjustment covariates within a generalized additive model (GAM) framework.[28,29] Models were fit using linear terms and non-linear smooths for each PFAS, adjusting for the same covariates, and the model that minimized the AIC was retained as the final GAM. To visualize the relationship between the PFAS and ALL risk, we also predicted the final GAM for varying levels of two PFAS from the 5th to the 95th percentiles, while holding the other PFAS and covariates constant at their median values. These prediction plots provide additional understanding of the magnitude and direction of the effect of PFAS when in combination. R package MapGAM (v.1.3)[30] was used to fit the GAMs and create maps of PFAS mixture effects.

In addition to detailed analyses of the 8 PFAS with >50% detected above LOQ, we parameterized all 33 PFAS measured as below or above LOQ and evaluated associations with ALL individually for each, as well as the total count of detected PFAS chemicals (i.e., the number of PFAS detected above LOQ), using logistic regression models, adjusted with the same socio-demographic factors as listed above.

3 | RESULTS

Children with ALL were more likely to have parents with low education and income levels, compared with controls; cases and controls were otherwise similar with respect to all other demographic characteristics (Table 2). Of the 33 PFAS assessed in dust, 8 were detected in concentrations above the LOQ in at least 50% of homes, and 11 were detected in concentrations above LOQ in 10%–49% of homes. The remaining PFAS that were assessed as part of this study were above LOQ in >0%–9% of homes for 6 PFAS, and 8 were not detected above LOQ in any home (Table 1). In general, concentrations of most PFAS were higher among high SES and non-Latino white households (data not shown). Some PFAS chemicals were moderately to highly correlated with others, including PFOS and PFHxS ($r = .84$), PFOA and PFHxA ($r = .70$), PFOA and PFHpA ($r = .73$), and PFHxA and PFHpA ($r = .83$) (Figure S1). Descriptive statistics (mean, median, standard deviation, minimum value, maximum value, and range) for each of the 8 PFAS with >50% of sample concentrations above the LOQ are shown in Table 1. Average dust concentrations of some PFAS differed for cases vs. controls, although the p-values did not reach statistical significance in crude comparisons via t-tests (Table 3).

In adjusted logistic regression models, the sum of the concentrations of the 8 PFAS detected in at least 50% of homes was associated with an increased risk of childhood ALL; the OR for a 10-fold increase

TABLE 2 Sociodemographic characteristics for cases and controls, California Childhood Leukemia Study (2001–2007).

	Cases ($n = 178$)	Controls ($n = 204$)	p-value
Sex assigned at birth			
Female	77 (43.3%)	84 (41.2%)	.762
Male	101 (56.7%)	120 (58.8%)	
Race			
Hispanic/Latino	71 (39.9%)	62 (30.4%)	.097
Non-Hispanic White	62 (34.8%)	102 (50.0%)	
Non-Hispanic Other	45 (25.3%)	40 (19.6%)	
Birth year			
1982–1996	20 (11.2%)	31 (15.2%)	.24
1997–2001	112 (62.9%)	133 (65.2%)	
2002–2006	46 (25.8%)	40 (19.6%)	
Age at diagnosis/reference (years)			
0–3	66 (37.1%)	78 (38.2%)	.89
4–7	112 (62.9%)	126 (61.8%)	
Parents' highest education attained (combined)			
High school or lower	49 (27.5%)	34 (16.7%)	.02
Some college or more	129 (72.5%)	170 (83.3%)	
Household income			
<$15,000	17 (9.6%)	9 (4.4%)	.01
$15,000–$29,999	28 (15.7%)	14 (6.9%)	
$30,000–$44,999	29 (16.3%)	25 (12.3%)	
$45,000–$59,999	21 (11.8%)	25 (12.3%)	
$60,000–$74,999	14 (7.9%)	21 (10.3%)	
$75,000 or more	69 (38.8%)	110 (53.9%)	
Breastfed			
No	11 (6.2%)	22 (10.8%)	.18
Yes	167 (93.8%)	181 (88.7%)	
Unknown	0 (0%)	1 (0.5%)	

was 1.09 (95% CI: 1.02–1.16) and ORs for the 2nd, 3rd, and 4th quartiles compared with the 1st quartile were 1.48 (95% CI: 0.79–2.77), 2.06 (95% CI: 1.09–2.77), and 2.40 (95% CI: 1.23–4.70), respectively. In models with single PFAS (Table 4), statistically significant increased risks of childhood ALL were observed with dust concentrations of PFHpA, PFOA, PFHxA, PFOS, PFDS, and EtFOSAA when modeled as continuous and/or categorical variables. However, after mutually adjusting for all PFAS, a statistically significant association was seen only for EtFOSAA, whether modeled continuously (OR = 1.40, 95% CI = 1.05–1.86) or categorically, with the highest risk observed for the 4th vs. 1st quartile (OR = 2.58, 95% CI = 1.16–5.71). Stratified analyses for each PFAS did not reveal statistically significant interactions (results not shown). The settled dust concentration of EtFOSAA was not correlated with other chemicals previously found to increase the risk of childhood leukemia in the same CCLS residential dust study, such as PAHs,[31] PCBs,[32] PBDEs,[33] or the herbicide dacthal[34] (Pearson correlation coefficient [absolute value] ≤0.06 for each) (data not shown). Regarding PFAS with <50% detection, the childhood ALL ORs for detect versus non-detect were 2.91 for FOSA (95% CI: 0.98–9.82; $p = .06$; 4% detects) and 1.73 for PFBS (95% CI: 0.94–3.21; $p = .08$; 12% detects), whereas results for other PFAS were either null or inconclusive (Table S2).

Table 5 shows the overall association of the PFAS mixture from the G-computation analysis and the weights for each PFAS on ALL risk. Overall, the PFAS mixture was positively associated with childhood ALL (OR = 1.60, 95% CI = 1.15–2.24). Six of the 8 PFAS in the mixture had positively weighted contributions to ALL risk, with EtFOSAA (weight = 0.2358) and PFHxA (weight = 0.2016) having the strongest positive weights. PFHxS had the strongest negative contribution to the mixture (weight = −0.772), with 6:2 diPAP having a weaker negative weight (−0.228). The magnitude of the association between the PFAS mixture and ALL risk appeared somewhat stronger among children who lived in the same residence since birth (OR = 1.83, 95% CI = 1.16–2.89), were under age 2 at diagnosis (OR = 1.92, 94% CI = 0.92–4.03), and were of Latinx ethnicity (OR = 1.91, 95% CI = 1.32–2.78), although the p-values for heterogeneity were not statistically significant.

TABLE 3 Concentration (ng/g) of 8 PFAS with 50% or more detection overall and by case–control status.

	Overall ($n = 382$)	Cases ($n = 178$)	Controls ($n = 204$)	p-value
6:2 diPAP				
Mean (SD)	563 (1190)	510 (1010)	609 (1330)	.41
Median [Min, Max]	150 [8.00, 9430]	132 [8.00, 9080]	161 [9.00, 9430]	
PFHxA				
Mean (SD)	58.5 (202)	69.1 (254)	52.2 (141)	.43
Median [Min, Max]	10.2 [0, 3030]	14.0 [0.0189, 3030]	10.7 [0.112, 1350]	
PFHpA				
Mean (SD)	102 (259)	115 (290)	93.9 (229)	.44
Median [Min, Max]	28.5 [0, 2540]	29.5 [0.346, 2530]	28.0 [0.170, 2540]	
PFOA				
Mean (SD)	191 (376)	198 (392)	184 (362)	.73
Median [Min, Max]	61.5 [0, 3510]	71.0 [0.505, 3510]	52.0 [0.530, 2560]	
PFHxS				
Mean (SD)	166 (711)	121 (428)	204 (886)	.24
Median [Min, Max]	10.0 [0, 9620]	10.5 [0.0134, 4120]	10.0 [0.0106, 9620]	
PFOS				
Mean (SD)	207 (439)	185 (294)	226 (534)	.34
Median [Min, Max]	52.0 [0, 5180]	55.0 [0.662, 1730]	49.0 [1.82, 5180]	
EtFOSAA				
Mean (SD)	67.1 (183)	84.6 (251)	52.6 (83.3)	.11
Median [Min, Max]	23.0 [0, 2850]	23.5 [0.235, 2850]	23.0 [0.647, 619]	
PFDS				
Mean (SD)	24.4 (97.8)	16.3 (28.6)	31.5 (131)	.11
Median [Min, Max]	7.00 [0, 1340]	7.00 [0.118, 198]	7.00 [0.302, 1340]	
Sum of the PFAS				
Mean (SD)	1380 (2200)	1450 (2520)	1300 (1770)	.48
Median [Min, Max]	579 [41.4, 20,100]	615 [41.4, 20,100]	565 [55.1, 11,500]	

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation; for PFAS abbreviations, refer to Table 2.

The results from the GAMs indicated that associations between childhood ALL risk and log10 transformed PFAS were not all linear. The final model included smooths for log10 PFHxA and log10 PFDS, whereas linear terms were sufficient for the other log10 PFAS chemicals and covariates (Table S3). The direction and magnitude of effects for individual PFAS in the GAM were similar to the G-comp results. Figure 1 presents plots to visualize the effect size and direction of the effect of log10 PFAS on ALL ORs from the GAM. The median of the log prediction values was used as the referent for calculating odds ratios. The plots allowed comparison of the predicted OR range when levels of log10 PFAS increased from the 5th to the 95th percentile. In Figure 1A, we showed the combined effects of log10 EtFOSAA and log10 PFHxS, which were identified in both approaches to be contributing the most to the PFAS mixture. The ORs reached a maximum of 2.24 when predicted at the 95th percentile value of log10 EtFOSAA and the 5th percentile value of log10 PFHxS, and at the median for all other PFAS and covariates. In Figure 1B, we presented the plot of the two non-linear PFAS models. The risk of ALL reached its highest when log10 PFHxA and log10 PFDS levels were at the middle of the distribution and remained consistently elevated at higher dust concentrations. This was in contrast with the other six PFAS, for which the risk changed linearly with log10 PFAS exposure. Unlike the G-comp, the GAM does not produce a single mixture effect estimate. The maximum ORs predicted in Figure 1A,B averaged to 1.77. This was comparable to the OR of 1.60 for the PFAS mixture in the adjusted G-comp.

4 | DISCUSSION

This study is the first to report an elevated risk of childhood ALL with overall levels of PFAS measured in settled dust in residential environments. EtFOSAA was detected in 66% of residences and was most consistently associated with an increased risk of ALL in analyses of individual PFAS and mixture effects. PFHxA, PFDS, and PFOS also contributed to the mixture of PFAS positively associated with

TABLE 4 PFAS concentration (ng/g) and risk of childhood acute lymphoblastic leukemia.

	Cases ($n = 178$)	Controls ($n = 204$)	Single PFAS model			Mutually adjusted PFAS model		
	N (%)	*N* (%)	OR	95% CI	*p*-value	OR	95% CI	*p*-value
6:2 diPAP								
Continuous			1.11	(0.77–1.58)	.58	0.95	(0.65–1.39)	.80
Quartiles								
8.0–71.2	46 (25.8)	50 (24.5)	ref	—				
71.2–150	49 (27.5)	46 (22.5)	1.38	(0.76–2.53)	.29	1.20	(0.62–2.33)	.59
150–510	38 (21.3)	58 (28.4)	0.89	(0.48–1.68)	.73	0.67	(0.34–1.33)	.26
510–9430	45 (25.3)	50 (24.5)	1.31	(0.71–2.42)	.39	1.11	(0.55–2.25)	.77
PFHxA								
Continuous			1.31	(0.99–1.73)	.06	1.01	(0.76–1.34)	.95
Categories								
0.02–12.0	81 (45.5)	110 (53.9)	ref	—				
12.0–39.0	53 (29.8)	43 (21.1)	1.99	(1.17–3.36)	.01	1.66	(0.84–3.29)	.15
39.0–3030	44 (24.7)	51 (25.0)	1.71	(1.00–2.93)	.05	1.40	(0.54–3.64)	.49
PFHpA								
Continuous			1.45	(1.07–1.96)	.02	1.24	(0.86–1.78)	.25
Quartiles								
0.17–8.34	35 (19.7)	61 (29.9)	ref	—				
8.34–28.5	53 (29.8)	42 (20.6)	2.66	(1.43–4.92)	.002	1.66	(0.85–3.27)	.14
28.5–83.5	45 (25.3)	50 (24.5)	2.05	(1.10–3.81)	.02	0.79	(0.33–1.87)	.59
83.5–2540	45 (25.3)	51 (25.0)	2.49	(1.31–4.72)	.01	0.84	(0.27–2.66)	.77
PFOA								
Continuous			1.52	(1.07–2.16)	.02	1.12	(0.75–1.68)	.58
Quartiles								
0.50–21.0	41 (23.0)	55 (27.0)	ref	—				
21.0–61.5	42 (23.6)	53 (26.0)	1.35	(0.73–2.50)	.34	1.15	(0.54–2.46)	.71
61.5–181	50 (28.1)	45 (22.1)	2.28	(1.21–4.29)	.01	2.04	(0.76–5.47)	.16
181–3510	45 (25.3)	51 (25.0)	2.14	(1.12–4.11)	.02	1.93	(0.58–6.42)	.29
PFHxS								
Continuous			1.03	(0.82–1.28)	.83	0.87	(0.67–1.12)	.27
Quartiles								
0.01–3.41	46 (25.8)	50 (24.5)	ref	—				
3.41–10.0	43 (24.2)	53 (26.0)	1.09	(0.60–1.98)	.79	0.70	(0.34–1.41)	.31
10.0–43.2	49 (27.5)	45 (22.1)	1.61	(0.88–2.97)	.13	0.79	(0.35–1.79)	.57
43.2–9620	40 (22.5)	56 (27.5)	1.12	(0.60–2.08)	.72	0.54	(0.21–1.39)	.20
PFOS								
Continuous			1.26	(0.92–1.72)	.14	1.01	(0.63–1.63)	.97
Quartiles								
0.66–17.0	44 (24.7)	56 (27.5)	ref	—				
17.0–52.0	43 (24.2)	49 (24.0)	1.72	(0.93–3.20)	.08	1.67	(0.80–3.49)	.17
52.0–198	45 (25.3)	50 (24.5)	1.79	(0.96–3.34)	.07	1.28	(0.53–3.09)	.58
198–5180	46 (25.8)	49 (24.0)	1.92	(1.02–3.59)	.04	1.36	(0.49–3.79)	.56
EtFOSAA								
Continuous			1.88	(1.25–2.85)	.003	1.40	(1.05–1.86)	.02
Quartiles								
0.24–9.6	43 (24.2)	53 (26.0)	ref	—				

TABLE 4 (Continued)

	Cases ($n = 178$) N (%)	Controls ($n = 204$) N (%)	Single PFAS model			Mutually adjusted PFAS model		
			OR	95% CI	*p*-value	OR	95% CI	*p*-value
9.6–23.0	46 (25.8)	50 (24.5)	1.59	(0.86–2.93)	.14	1.42	(0.73–2.75)	.30
23.0–64.0	42 (23.6)	54 (26.5)	1.76	(0.92–3.37)	.09	1.49	(0.72–3.07)	.28
64.0–2850	47 (26.4)	47 (23.0)	2.78	(1.37–5.62)	.00	2.58	(1.16–5.71)	.02
PFDS								
Continuous			1.34	(0.91–1.97)	.14	1.05	(0.69–1.60)	.81
Quartiles								
0.12–3.0	48 (27.0)	61 (29.9)	ref	—				
3.0–7.0	45 (25.3)	47 (23.0)	1.56	(0.86–2.84)	.15	1.28	(0.66–2.47)	.47
7.0–15.0	40 (22.5)	47 (23.0)	1.66	(0.88–3.12)	.11	1.27	(0.64–2.53)	.49
15.0–1340	45 (25.3)	49 (24.0)	2.11	(1.10–4.05)	.02	1.39	(0.66–2.94)	.39

Note: All logistic regression models are adjusted for age at diagnosis, birth year, sex assigned at birth, race/ethnicity, household income, and parental education. Models for continuous variables use log10 transformed PFAS concentration values.
Abbreviations: CI, confidence interval; OR, odds ratio; for PFAS abbreviations, refer to Table 2.

TABLE 5 G-computation modeling for mixture effect of PFAS on risk of childhood acute lymphoblastic leukemia: Overall and stratified analyses.

		Residence since birth		Age at diagnosis		Ethnicity	
	Overall	Same	Different	0–3 years	4–7 years	Latino	Non-Latino
Mixture effect (OR, 95% CI)							
OR	1.60	1.83	1.50	1.92	1.28	1.91	1.44
95% CI	(1.15–2.24)	(1.16–2.89)	(0.91–2.47)	(0.92–4.03)	(0.87–1.88)	(1.32–2.78)	(1.09–1.90)
p-value	.006	.009	.112	.083	.210	.001	.009
p-value for heterogeneity	—	.56		.34		.23	
Weights							
EtFOSAA	0.286	0.358	0.143	0.2735	0.1789	0.200	0.2752
PFHxA	0.2358	−0.0539	0.373	0.19	0.5139	0.173	0.0782
PFDS	0.2016	−0.0458	0.374	0.1922	0.2077	0.108	0.2497
PFOS	0.1807	0.109	0.11	0.255	−0.0783	0.519	−0.559
PFOA	0.0718	0.123	−0.261	0.0349	0.0995	−0.41591	0.3025
PFHpA	0.0241	0.378	−0.206	0.0544	−0.3785	−0.00711	0.039
PFHxS	−0.772	−0.9003	−0.216	−0.779	−0.435	−0.39335	−0.441
6:2 diPAP	−0.228	0.032	−0.317	−0.221	−0.1082	−0.18363	0.0553

Note: All logistic regression models use log10 transformed PFAS concentration values, and are adjusted for age at diagnosis, birth year, sex assigned at birth, race/ethnicity, household income, and parental education.
Abbreviations: CI, confidence interval; OR, odds ratio; for PFAS abbreviations, refer to Table 2.

childhood ALL risk, whereas PFHxS and, to a lesser extent, 6:2 diPAP contributed to the mixture negatively associated with risk.

EtFOSAA is a byproduct of *N*-methyl perfluorooctane sulfonamidoethanol (N-EtFOSE), which is primarily used in the packaging of consumer products and is a precursor of PFOS. EtFOSAA has been detected in soil and water as well as settled dust in childcare facilities and fire stations.[22] To our knowledge, only one other study measured EtFOSAA in settled dust,[19] and not in relation to cancer risk. Our study reported increased risks of childhood ALL mainly with dust concentrations of EtFOSAA and possibly FOSA, a degradation product of EtFOSAA,[35] although based on a small number of detected values (4%). Associations between blood levels of EtFOSAA and cancer have been previously reported among adults, but not children. In a California cohort study assessing in utero exposure to PFAS from 1957 to 1967, high maternal perinatal serum levels of EtFOSAA and cholesterol combined were found to increase the risk of breast cancer in daughters diagnosed up to age 52.[36] In a cohort study conducted in Finland from 1990 to 2010, data suggested that pre-diagnostic levels of EtFOSAA increased the risk of early-onset thyroid cancer.[37] However, within this Finnish cohort, levels of EtFOSAA measured in

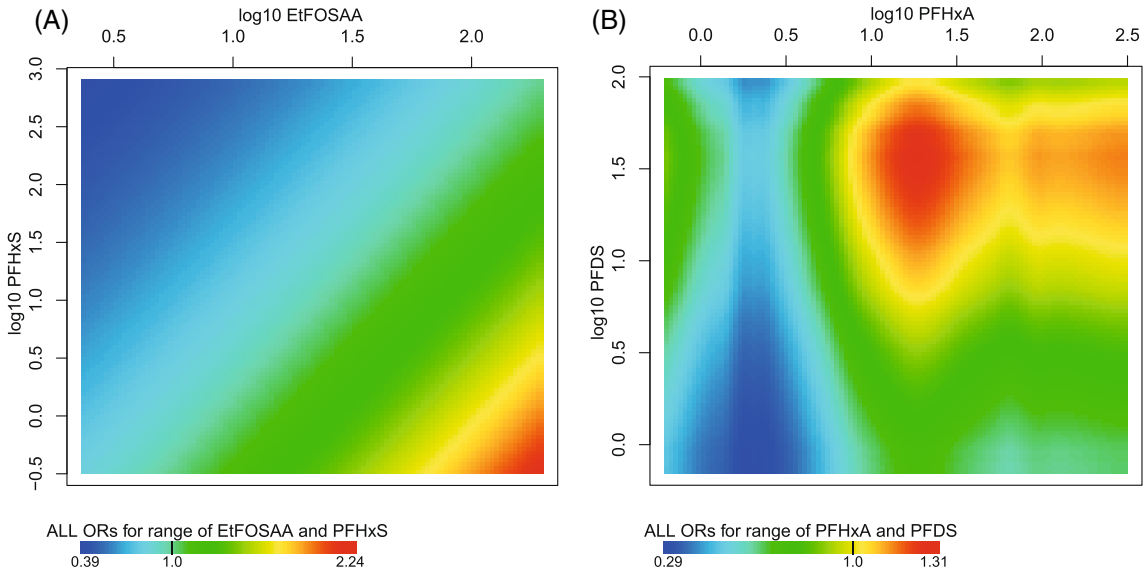

FIGURE 1 Joint effect of PFAS on ALL risk, modelled as generalized additive models. ORs are predicted for median age at blood spot collection; median household income; some college or more for parental education; male sex; Latinx ethnicity; median birthyear. (A) Combined effects of log10 EtFOSAA and log10 PFHxS from the 5th to the 95th percentile and median values for all other PFAS. (B) Combined effects of log10 PFHxA and log10 PFDS from the 5th to the 95th percentile and median values for all other PFAS.

pregnancy blood among mothers of 400 children with ALL and 400 healthy controls were associated with a reduced risk of childhood ALL, whereas high levels of MeFOSAA were associated with an elevated risk among children diagnosed with ALL before 5 years of age. In our study, MeFOSAA was detected in dust samples in only 18% of homes, with no statistically significant difference in concentration by case–control status. Of note, the detection frequencies of MeFOSAA and EtFOSAA in our population were weakly correlated ($r = .12$, $p = .01$). MeFOSAA, a degradation product of MeFOSE that is used in stain and waterproofing of textile and carpet treatments,[38] is found in surface treatment products. Although EtFOSAA and MeFOSAA are both derivatives of precursor FOSAA, results in our California study and the one from Finland do not fully converge, which could be explained by differences in the timing and type of PFAS exposure assessment (pre-natal blood samples vs. postnatal dust samples), composition of the PFAS mixture, as well as differences in environment and population characteristics.

In addition to EtFOSAA, several PFAS measured in the settled dust showed low (PFOA and PFHpA) to moderate (PFHxA, PFDS, and PFOS) positive weight contributing to the mixture effect, even though individual elevated risk estimates did not reach statistical significance. In the Finnish cohort study of childhood ALL, an increased risk was reported with in utero blood levels of PFOS for samples collected from 1986 to 1995 when levels were the highest, and PFNA among first-born children.[10] In our study, the detection level of PFNA was relatively similar in cases (22%) and controls (24%). In another study conducted in California, PFOS and PFOA measured in archived neonatal blood samples were found to increase the risk of retinoblastoma in children, with some differences in risk depending on whether the mother was born in the United States or Mexico, indicating that exposure pathways and levels may vary by population and region.[11] Overall, while there are some similarities across studies, subgroup-specific findings observed for certain PFAS make it difficult to synthesize the results.

PFHxS has been found to increase the risk of certain adult cancers[39,40] and decrease the risk of thyroid cancer.[37,41] In the Finnish cohort study of childhood ALL, there was no association with in utero blood levels of PFHxS, with ORs below or close to 1. In our study, PFHxS was an important contributor to the negative weight in the mixture effect analysis, though the inverse association that was observed in our multiple PFAS adjusted regression model was far from reaching statistical significance. Exposure to PFHxS can occur through multiple sources including food products, notably fish,[42] and consumer products such as carpeting.[43,44] Further exploration of the synergistic effect of multiple PFAS in the current study showed that the risk of childhood ALL rose to 2-fold when dust levels of EtFOSAA were at their highest while levels of PFHxS were at their lowest.

Study of PFAS carcinogenicity has mainly focused on legacy long-chain PFAS such PFOA and PFOS, that were respectively classified in 2023 as "*carcinogenic to humans* (*Group 1*)" and "*possibly carcinogenic to humans* (*Group 2B*)" by the International Agency for Research on Cancer.[5] Using the Key Characteristics of Carcinogens' framework, there is strong evidence that several PFAS induce oxidative stress (*long chain*: PFOS, PFHxS, PFOA, PFNA, PFDA, PFUnA, and PFDoA), modulate receptor-mediated effects (*long chain*: PFOS, PFHxS, PFOA, PFNA, PFDA, and PFUnA; *short chain*: PFBS, PFHxA, and GenX) and are immunosuppressive (*long chain*: PFOS, PFOA, PFDA, and 8:2 FTOH).[45] Immune dysregulation is an established causal pathway in childhood ALL. Indeed, markers of early-life immune stimulation/response such as mode of delivery, social contacts, severity of

infections, and presence of cytomegalovirus and level of L10 cytokines at birth have been found to modulate the risk of childhood ALL.[13,46–48] Therefore early-life exposure to PFAS known to be potent immunosuppressors could further interfere with proper development of a child's immune system leading to subsequent initiation/promotion of leukemia. Markers of oxidative stress at birth have also been documented in children who later developed leukemia.[49] In our study, PFOS and PFNA were associated with increased risk of childhood ALL, while PFHxS reduced risk. All three of these PFAS lead to oxidative stress and immunosuppression, yet the mechanisms by which PFHxS has opposite effects depending on the cancer site remains unclear. Our main result regarding EtFOSAA and increased risk of childhood ALL has not been previously reported, nor was it included in the review of carcinogenic characteristics of PFAS.[45]

Our study presents several strengths and limitations. It is the first to assess the role of several long- and short-chain PFAS in settled dust samples and the development of childhood ALL. We collected vacuum bags that represented a composite of various sources of dust around the homes. We measured 33 different target PFAS substances, including 16 outside the perfluoro-sulfonates and carbolic acids that have been extensively monitored. We conducted mixture effect analyses to increase our understanding of the complex combined impact of multiple chemicals. Our results should be interpreted with caution due to limited sample size, multiple testing, and potential for selection bias. Participating case households had lower socio-economic levels than controls. Although all models were adjusted for race/ethnicity, household income, and education, there could be some residual confounding.

We restricted our sample to children who lived in the same home since diagnosis (for cases)/reference date (for controls) to capture sufficient exposure to dust within the same environment; however, this may have led to a selected group that may not be representative of the general population. Settled dust samples were collected after the diagnosis/reference date, raising issues about temporality. However, our group has measured several other persistent organic compounds such as polychlorinated biphenyls (PCBs) and polybrominated biphenyl ethers (PBDEs) in repeated settled dust samples in the same study population and found that levels were stable for 5–7 years, showing that inter-household variation is larger than the variation over time.[50] Other groups have observed a similar trend in a broad range of semivolatile organic compounds (SVOCs).[51] This suggests that dust provides a household-level estimate of exposure over time (encompassing the prenatal period) and not just a snapshot. We also documented that the dust levels of PCBs and PBDEs correlated with the child's and mother's blood levels.[52,53] Thus, our observations indicating that PCB/PBDE dust levels are good indicators of past exposures and body burden in this study population are likely true for PFAS, which are well-known persistent compounds. Moreover, others have reported significant associations between PFAS concentrations in residential dust and childhood serum in a similar population, although associations were moderate and only observed for a few PFAS examined.[24] Collection of repeated environmental and biological samples should be considered in future studies to improve the assessment of PFAS exposures over time.

Most women in our study breastfed (91%), limiting our ability to examine the impact of breastfeeding on the association between PFAS and childhood leukemia. Additionally, the prevalence of breastfeeding was similar between cases and controls (Table 1). Although breastfeeding is beneficial for immune development and has been associated with a lower risk of childhood leukemia,[54] ingestion of PFAS in breastmilk via maternal exposure to diet and dust is another exposure pathway for children.

In conclusion, our study showed that a mixture of eight PFAS commonly detected in home dust was associated with an increased risk of childhood ALL. Individual PFAS such as EtFOSAA, and possibly PFHxA, PFDS, and PFOS, contributed to the increased risk of childhood ALL, whereas PFHxS contributed to a reduced risk. These findings add to the growing body of evidence that certain PFAS impact the risk of various types of cancer, not just in adults but also in children.

AUTHOR CONTRIBUTIONS

Catherine Metayer: Conceptualization; funding acquisition; supervision; writing – original draft. **Libby M. Morimoto:** Investigation; visualization; writing – original draft; formal analysis. **Veronica M. Vieira:** Formal analysis; funding acquisition; methodology; writing – original draft. **Krystal J. Godri Pollitt:** Methodology; writing – review and editing. **Scott M. Bartell:** Methodology; writing – review and editing. **Luann Wong:** Investigation; methodology; writing – review and editing. **Thomas M. Young:** Conceptualization; investigation; methodology; writing – review and editing.

ACKNOWLEDGMENTS

Research reported in this publication was supported by the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health under Award Number R01ES032196. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dust sample collection and processing in the CCLS was financially supported by NIEHS grants R01ES009137 and P42ES04705-18 (University of California, Berkeley), subcontracts 7590-S-04 (University of California, Berkeley) and 7590-S-01 (Battelle Memorial Institute under National Cancer Institute (NCI) contract N02-CP-11015 (Westat)). Dust analysis at UC Davis was supported in part by NIEHS grants P42 ES004699 and P30 ES023513. Data and resource sharing was supported by NIEHS grant R24ES028524. We thank the families for their participation. We also thank the clinical investigators at the following collaborating hospitals for help in recruiting patients: University of California Davis Medical Center (Dr. Jonathan Ducore), University of California San Francisco (Drs. Mignon Loh and 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 Oakland (Drs. Daniel Kronish and Stacy Month), Kaiser Permanente Roseville (Drs. Kent Jolly

and Vincent Kiley), Kaiser Permanente Santa Clara (Drs. Carolyn Russo, Denah Taggart, and Alan Wong), and Kaiser Permanente San Francisco (Dr. Kenneth Leung). We thank Mary Ward from NCI for her contribution to the primary dust sample collection and processing. Finally, we acknowledge the entire CCLS staff for their effort and dedication.

FUNDING INFORMATION

Research reported in this publication was supported by the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health under Award Number R01ES032196. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dust sample collection and processing in the CCLS was financially supported by NIEHS grants R01ES009137 and P42ES04705-18 (University of California, Berkeley), subcontracts 7590-S-04 (University of California, Berkeley) and 7590-S-01 (Battelle Memorial Institute under National Cancer Institute [NCI] contract N02-CP-11015 [Westat]). Dust analysis at UC Davis was supported in part by NIEHS grants P42 ES004699 and P30 ES023513. Data and resource sharing was supported by NIEHS grant R24ES028524.

CONFLICT OF INTEREST STATEMENT

Scott Bartell serves as a compensated expert witness for PFOA medical monitoring lawsuits in New Hampshire. The terms of this arrangement were reviewed and approved by the University of California, Irvine in accordance with its conflict-of-interest policies. The other authors have no competing interests to declare. All authors certify that their freedom to design, conduct, interpret, and publish research was not compromised by any controlling sponsor.

DATA AVAILABILITY STATEMENT

Data can be made available upon request from the first author, under proper human subjects' research approval.

ETHICS STATEMENT

Consent to participate in the study was obtained from the parents of participating children of the CCLS. The institutional review boards of the University of California, Berkeley, and the California State Department of Health approved the research.

ORCID

Libby M. Morimoto https://orcid.org/0000-0002-1509-739X

REFERENCES

1. Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001-10: a population-based registry study. *Lancet Oncol*. 2017;18:719-731.
2. Barrington-Trimis JL, Cockburn M, Metayer C, Gauderman WJ, Wiemels J, McKean-Cowdin R. Trends in childhood leukemia incidence over two decades from 1992 to 2013. *Int J Cancer*. 2017;140:1000-1008.
3. Liu J, Lee LS, Nies LF, Nakatsu CH, Turcot RF. Biotransformation of 8:2 fluorotelomer alcohol in soil and by soil bacteria isolates. *Environ Sci Technol*. 2007;41:8024-8030.
4. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J Expo Sci Environ Epidemiol*. 2019;29:131-147.
5. Zahm S, Bonde JP, Chiu WA, et al. Carcinogenicity of perfluorooctanoic acid and perfluorooctanesulfonic acid. *Lancet Oncol*. 2024;25:16-17.
6. Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. *Environ Res*. 2021;194:110690.
7. Panikkar B, Lemmond B, Allen L, DiPirro C, Kasper S. Making the invisible visible: results of a community-led health survey following PFAS contamination of drinking water in Merrimack, New Hampshire. *Environ Health*. 2019;18:79.
8. Sun M, Arevalo E, Strynar M, et al. Legacy and emerging perfluoroalkyl substances are important drinking water contaminants in the Cape Fear River watershed of North Carolina. *Environ Sci Technol Lett*. 2016;3:415-419.
9. New Hampshire Department of Health and Human Services, Division of Public Health Services. *Cancer Incidence Report*. New Hampshire Department of Health and Human Services; 2018.
10. Jones RR, Madrigal JM, Troisi R, et al. Maternal serum concentrations of per- and polyfluoroalkyl substances and childhood acute lymphoblastic leukemia. *J Natl Cancer Inst*. 2024;116:728-736.
11. Chen Y, Paul KC, Walker DI, et al. Neonatal per- and polyfluoroalkyl substance exposure in relation to retinoblastoma. *Environ Res*. 2024;240:117435.
12. Ehrlich V, Bil W, Vandebriel R, et al. Consideration of pathways for immunotoxicity of per- and polyfluoroalkyl substances (PFAS). *Environ Health*. 2023;22:19.
13. Wiemels J. Perspectives on the causes of childhood leukemia. *Chem Biol Interact*. 2012;196:59-67.
14. Fromme H, Tittlemier SA, Volkel W, Wilhelm M, Twardella D. Perfluorinated compounds—exposure assessment for the general population in Western countries. *Int J Hyg Environ Health*. 2009;212:239-270.
15. Haug LS, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways to perfluorinated compounds—comparing exposure estimates with biomarkers of exposure. *Environ Int*. 2011;37:687-693.
16. Cohen Hubal EA, Sheldon LS, Burke JM, et al. Children's exposure assessment: a review of factors influencing children's exposure, and the data available to characterize and assess that exposure. *Environ Health Perspect*. 2000;108:475-486.
17. Shin HM, Moschet C, Young TM, Bennett DH. Measured concentrations of consumer product chemicals in California house dust: implications for sources, exposure, and toxicity potential. *Indoor Air*. 2019;30(1):60-75.
18. Strynar MJ, Lindstrom AB. Perfluorinated compounds in house dust from Ohio and North Carolina, USA. *Environ Sci Technol*. 2008;42:3751-3756.
19. Winkens K, Giovanoulis G, Koponen J, et al. Perfluoroalkyl acids and their precursors in floor dust of children's bedrooms: implications for indoor exposure. *Environ Int*. 2018;119:493-502.
20. Moriwaki H, Takatah Y, Arakawa R. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in vacuum cleaner dust collected in Japanese homes. *J Environ Monit*. 2003;5:753-757.
21. Kubwabo C, Stewart B, Zhu J, Marro L. Occurrence of perfluorosulfonates and other perfluorochemicals in dust from selected homes in the city of Ottawa, Canada. *J Environ Monit*. 2005;7:1074-1078.
22. Savvaides T, Koelmel JP, Zhou Y, et al. Prevalence and implications of per- and polyfluoroalkyl substances (PFAS) in settled dust. *Curr Environ Health Rep*. 2021;8:323-335.

23. Kato K, Calafat AM, Wong LY, Wanigatunga AA, Caudill SP, Needham LL. Polyfluoroalkyl compounds in pooled sera from children participating in the National Health and Nutrition Examination Survey 2001–2002. *Environ Sci Technol*. 2009;43:2641-2647.
24. Wu XM, Bennett DH, Calafat AM, et al. Serum concentrations of perfluorinated compounds (PFC) among selected populations of children and adults in California. *Environ Res*. 2015;136:264-273.
25. Eick SM, Goin DE, Cushing L, et al. Mixture effects of prenatal exposure to per- and polyfluoroalkyl substances and polybrominated diphenyl ethers on maternal and newborn telomere length. *Environ Health*. 2021;20:76.
26. Metayer C, Zhang L, Wiemels JL, et al. Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype. *Cancer Epidemiol Biomarkers Prev*. 2013;22:1600-1611.
27. Keil AP, Buckley JP, O'Brien KM, Ferguson KK, Zhao S, White AJ. A quantile-based g-computation approach to addressing the effects of exposure mixtures. *Environ Health Perspect*. 2020;128:47004.
28. Webster T, Vieira V, Weinberg J, Aschengrau A. Method for mapping population-based case-control studies: an application using generalized additive models. *Int J Health Geogr*. 2006;5:26.
29. Vieira V, Webster T, Weinberg J, Aschengrau A, Ozonoff D. Spatial analysis of lung, colorectal, and breast cancer on Cape Cod: an application of generalized additive models to case-control data. *Environ Health*. 2005;4:11.
30. Bai L, Gillen DL, Bartell SM, Vieira VM. Mapping smoothed spatial effect estimates from individual-level data: MapGAM. *R J*. 2020;12(1):32-48.
31. Deziel NC, Rull RP, Colt JS, et al. Polycyclic aromatic hydrocarbons in residential dust and risk of childhood acute lymphoblastic leukemia. *Environ Res*. 2014;133:388-395.
32. Ward MH, Colt JS, Metayer C, et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. *Environ Health Perspect*. 2009;117:1007-1013.
33. Ward MH, Colt JS, Deziel NC, et al. Residential levels of polybrominated diphenyl ethers and risk of childhood acute lymphoblastic leukemia in California. *Environ Health Perspect*. 2014;122:1110-1116.
34. Metayer C, Colt JS, Buffler PA, et al. Exposure to herbicides in house dust and risk of childhood acute lymphoblastic leukemia. *J Expo Sci Environ Epidemiol*. 2013;23:363-370.
35. Zhang W, Pang S, Lin Z, Mishra S, Bhatt P, Chen S. Biotransformation of perfluoroalkyl acid precursors from various environmental systems: advances and perspectives. *Environ Pollut*. 2021;272:115908.
36. Cohn BA, La Merrill MA, Krigbaum NY, et al. In utero exposure to poly- and perfluoroalkyl substances (PFASs) and subsequent breast cancer. *Reprod Toxicol*. 2020;92:112-119.
37. Madrigal JM, Troisi R, Surcel HM, et al. Prediagnostic serum concentrations of per- and polyfluoroalkyl substances and risk of papillary thyroid cancer in the Finnish Maternity Cohort. *Int J Cancer*. 2024;154:979-991.
38. Dassuncao C, Hu XC, Nielsen F, Weihe P, Grandjean P, Sunderland EM. Shifting global exposures to poly- and perfluoroalkyl substances (PFASs) evident in longitudinal birth cohorts from a seafood-consuming population. *Environ Sci Technol*. 2018;52:3738-3747.
39. Moon J, Mun Y. The association between per- and polyfluoroalkyl substances (PFASs) and brain, esophageal, melanomatous skin, prostate, and lung cancer using the 2003-2018 US National Health and Nutrition Examination Survey (NHANES) datasets. *Heliyon*. 2024;10:e24337.
40. Winquist A, Hodge JM, Diver WR, et al. Case-cohort study of the association between PFAS and selected cancers among participants in the American Cancer Society's Cancer Prevention Study II LifeLink Cohort. *Environ Health Perspect*. 2023;131:127007.
41. Li H, Yang M, Yang J, et al. Per- and polyfluoroalkyl substances and the associated thyroid cancer risk: a case-control study in China. *Chemosphere*. 2023;337:139411.
42. EFSA Panel on Contaminants in the Food Chain, Schrenk D, Bignami M, et al. Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA J*. 2020;18:e06223.
43. Beesoon S, Genuis SJ, Benskin JP, Martin JW. Exceptionally high serum concentrations of perfluorohexanesulfonate in a Canadian family are linked to home carpet treatment applications. *Environ Sci Technol*. 2012;46:12960-12967.
44. Zhu Y, Ro A, Bartell SM. Household low pile carpet usage was associated with increased serum PFAS concentrations in 2005-2006. *Environ Res*. 2021;195:110758.
45. Temkin AM, Hocevar BA, Andrews DQ, Naidenko OV, Kamendulis LM. Application of the key characteristics of carcinogens to per and polyfluoroalkyl substances. *Int J Environ Res Public Health*. 2020;17(5):1668. doi:10.3390/ijerph17051668
46. Feng Q, Zhou M, Li S, et al. Interaction between maternal killer immunoglobulin-like receptors and offspring HLAs and susceptibility of childhood ALL. *Blood Adv*. 2022;6:3756-3766.
47. Soegaard SH, Rostgaard K, Skogstrand K, Wiemels JL, Schmiegelow K, Hjalgrim H. Neonatal inflammatory markers are associated with childhood B-cell precursor acute lymphoblastic leukemia. *Cancer Res*. 2018;78:5458-5463.
48. Whitehead TP, Wiemels JL, Zhou M, et al. Cytokine levels at birth in children who developed acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev*. 2021;30:1526-1535.
49. Yano Y, Grigoryan H, Schiffman C, et al. Untargeted adductomics of Cys34 modifications to human serum albumin in newborn dried blood spots. *Anal Bioanal Chem*. 2019;411:2351-2362.
50. Whitehead TP, Brown FR, Metayer C, et al. Polychlorinated biphenyls in residential dust: sources of variability. *Environ Sci Technol*. 2014;48:157-164.
51. Kim K, Shin HM, Wong L, Young TM, Bennett DH. Temporal variability of indoor dust concentrations of semivolatile organic compounds. *Indoor Air*. 2021;31:693-701.
52. Whitehead TP, Crispo Smith S, Park JS, Petreas MX, Rappaport SM, Metayer C. Concentrations of persistent organic pollutants in California children's whole blood and residential dust. *Environ Sci Technol*. 2015;49:9331-9340.
53. Whitehead TP, Crispo Smith S, Park JS, Petreas MX, Rappaport SM, Metayer C. Concentrations of persistent organic pollutants in California women's serum and residential dust. *Environ Res*. 2015;136:57-66.
54. Amitay EL, Keinan-Boker L. Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review. *JAMA Pediatr*. 2015;169:e151025.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Metayer C, Morimoto LM, Vieira VM, et al. Exposure to per- and polyfluoroalkyl substances in residential settled dust and risk of childhood acute lymphoblastic leukemia. *Int J Cancer*. 2025;157(1):103-115. doi:10.1002/ijc.35370