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Flame retardants and their metabolites in the homes and urine of pregnant women residing in California (the CHAMACOS cohort)

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HIGHLIGHTS

- We measured flame retardants (FRs) in dust and urine from pregnant women.
- We detected Firemaster® 550 and organophosphate FRs in almost all the dust samples.
- The maximum TCEP and TDCIPP dust levels were among the highest ever reported.
- Metabolites of TDCIPP and triphenyl phosphate were detected in >75% of urine samples.
- Results are valuable to assess trends in PFR exposure and risk in pregnant women.

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ABSTRACT

Organophosphate flame retardants (PFRs), used in consumer products since the 1970s, persist in the environment. Restrictions on penta-polybrominated diphenyl ether (PBDE) flame retardants resulted in increased use of Firemaster® 550 (FM® 550), and the organophosphate triesters: tris(1,3- dichloro-2-propyl) phosphate (TDCIPP); tris(chloropropyl) phosphate (TCIPP); tris(2-chloroethyl) phosphate (TCEP); and triphenyl phosphate (TPHP). The objectives of this study were to (1) identify determinants of flame retardants (4 PFRs, PentaBDEs and FM® 550) in house dust, (2) measure urinary PFR metabolites in pregnant women, and (3) estimate health risks from PFR exposure. We measured flame retardants in house dust (n = 125) and metabolites in urine (n = 310) collected in 2000–2001 from Mexican American women participating in the CHAMACOS birth cohort study in California. We detected FM® 550 and PFRs, including two (TCEP and TDCIPP) known to the state of California to cause cancer, in most dust samples. The maximum TCEP and TDCIPP dust levels were among the highest ever reported although the median levels were generally lower compared to other U.S. cohorts. Metabolites of TDCIPP (BDCIPP: bis(1,3-dichloro-2-propyl) phosphate) and TPHP (DPHP: diphenyl phosphate) were detected in 78% and 79% of prenatal urine samples, respectively. We found a weak but positive correlation between TPHP in dust and DPHP in 124 paired prenatal urine samples (Spearman rho = 0.17; p = 0.06). These results provide information on PFR exposure and risk in pregnant women from the early 2000's and are also valuable to assess trends in exposure and risk given changing fire safety regulations and concomitant changes in chemical flame retardant use.

1. Introduction

Organophosphate flame retardants (PFRs) are environmentally persistent chemicals (X Zhang et al., 2016) that have been used in consumer products since the 1970s. Restrictions on the use of the penta-polybrominated diphenyl ether (PBDE) flame retardant mixture in Europe (2002), the U.S. (2005) and other countries resulted in increased use of PFRs as replacements, including the organophosphate triesters [tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), tris(chloropropyl) phosphate (TCIPP), tris(2-chloroethyl) phosphate (TCEP), and triphenyl phosphate (TPHP)] (Stapleton et al., 2011; van der Veen and de Boer, 2012). These chemicals are

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Abbreviations

BEH-TEBP	bis(2-ethylhexyl) tetrabromophthalate
EH-TBB	(2-ethylhexyl) 2,3,4,5-tetrabromobenzoate
PBDE	polybrominated diphenyl ether
ip-PDPP	isopropylphenyl diphenyl phosphate
TCEP	tris(2-chloroethyl) phosphate
TCIPP	tris(chloropropyl) phosphate
TDCIPP	tris(1,3-dichoro-2-propyl) phosphate
TPHP	triphenyl phosphate

applied to polyurethane foams, often found in furniture, child car seats, and related products, to meet federal and state flammability standards (Stapleton et al., 2012). TPHP is also used as a plasticizer, and has recently been identified as a common ingredient in nail polish (Mendelsohn et al., 2016). Additional current use flame retardants, such as Firemaster® 550, a mixture that contains two brominated compounds, (2-ethylhexyl) 2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl) tetrabromophthalate (BEH-TEBP) as well as TPHP and isopropylphenyl diphenyl phosphate (ip-PDPP), are also used as replacements for PBDEs in some applications. These chemicals are ubiquitous in the home environment of families and children worldwide (Ali et al., 2012a, 2012b; Bergh et al., 2011; Cequier et al., 2015; Dodson et al., 2012; Schreder et al., 2015). PFRs have been measured in >95% of house dust samples collected in the United States (Stapleton et al., 2009), as well as in the foam of numerous baby products and in infant and adult urine, indicating direct human exposure (Hoffman et al., 2014, 2015a; Stapleton et al., 2011). Recent studies have also reported PFRs in child care environments (Bergh et al., 2011; Bradman et al., 2014; Fromme et al., 2014).

There is growing concern about the potential health effects of PFR exposure. For example, several recent toxicological studies have linked TPHP exposure with reproductive and developmental toxicity, neurotoxicity, metabolic disruption, endocrine effects, and genotoxicity (Du et al., 2016; Mendelsohn et al., 2016; Q Zhang et al., 2016). TPHP has also been found to induce significant estrogenic activity *in vitro* (Krivoshiev et al., 2016; Zhang et al., 2014). Further, two of the most widely used PFRs (TCEP and TDCIPP) are identified as carcinogens by the state of California (OEHHA, 2011; State of California, 2016).

The impact of flame retardants on human health is under scrutiny. The state of California recently passed legislation that changes furniture flammability standards that resulted in widespread flame retardant use in the U.S., and also requires that consumer products are labeled if they contain flame retardant chemicals (State of California, 2014; Zota et al., 2008). And while animal and *in vitro* studies suggest that PFRs may affect neurodevelopment through non-cholinergic mechanisms similar to some organophosphate pesticides (Dishaw et al., 2011; Levin et al., 2002; Slotkin et al., 2007; Slotkin and Seidler, 2007, 2012), no human health studies focusing on vulnerable populations such as pregnant women and children have been completed. In this study, we assessed PFR and FM® 550 contamination in homes and exposures to pregnant women living in California, where exposures are likely to be high due to historical flammability standards.

2. Materials and methods

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) is a longitudinal birth cohort study of predominantly low-income, Mexican-American families living in California's Salinas Valley. Detailed methods for CHAMACOS have been published previously (Eskenazi et al., 2004, 2006). Eligible pregnant women (≥18 years old, < 20 weeks gestation, Spanish- or English-speaking, qualifying for low-income health insurance, and planning to deliver at the public hospital) were recruited between October 1999 and October 2000 from community clinics.

2.1. Study interviews and home visits

Participants' demographic and household information were collected through personal interviews conducted in English or Spanish by bilingual, bicultural staff. Women were interviewed twice during pregnancy (at ~ 13 and 26 weeks gestation) and home environmental assessments were conducted between the first and second prenatal interviews. Information obtained from the questionnaire and home environmental assessment included years residing in the U.S., education, family income, housing density, quality of housekeeping, number of pieces of stuffed furniture present (chairs, couches, love seats), and percentage of floors covered with wall-to-wall carpeting (Bradman et al., 2005). During the home inspections, subjective measures such as quality of housekeeping (excellent, average or poor/less clean) and presence of extremely worn carpet (yes/no) were recorded by trained study staff.

2.2. Dust sample collection and analysis

Dust sample collection occurred during prenatal CHAMACOS home visits in 2000–2001 (mean (SD) gestational age = 17 (5.6) weeks; n = 125). The dust sampling methods followed procedures described in the American Society for Testing Materials (ASTM) Standard Practice D 5438-05. Dust samples were collected from at least 1 m squared using the High Volume Small Surface Sampler (HVS3) with a cyclone that extracted particles ≥5.0 μm (Harnly et al., 2009; Roberts et al., 1991). Bulk dust was sieved to ≤150 μm and stored at −80C until analysis. Samples were analyzed for four PFR triesters (TCEP; TDCIPP; TCIPP; and TPHP) and two brominated components of FM® 550 (EH-TBB and BEH-TEBP) using gas chromatography – mass spectrometry either in electron impact mode (EI) or electron capture negative ionization mode (GC/ECNI-MS) (Stapleton et al., 2009). Eight congeners that comprise the penta-BDE mixture were also measured (BDE28, BDE47, BDE66, BDE85/155, BDE99, BDE100, BDE153 and BDE154) and summed for statistical analyses (Stapleton et al., 2014). Both dust concentrations (i.e., ng/g) and dust loading (i.e., ng/m^2) were determined. Across all analytes, average recoveries based on measurements of internal standards ranged from 81 to 158%. See Supplementary Material (SM), Tables S1–S3 for detailed sampling, laboratory, and analytical QA/QC results.

2.3. Urine sample collection and analysis

Urine collection occurred during the 2nd prenatal study visit (mean (SD) gestational age = 26 (2.4) weeks; n = 310). Samples were kept at −80 °C in the CHAMACOS biorepository and then transported on dry ice for the analysis at Duke University. We measured four PFR urinary metabolites: bis(1,3-dichloro-2-propyl) phosphate (BDCIPP); isopropylphenyl phenyl phosphate (ip-PPP); tert-butylphenyl phenyl phosphate (tb-PPP); and diphenyl phosphate (DPHP). Samples were also analyzed for bis(1-chloro-2-propyl) phosphate (BCIPP), the metabolite of TCIPP, however, BCIPP was not detected in any samples (detection frequency (DF) = 0%). Analyses were performed using negative electrospray ionization liquid chromatography-tandem mass spectrometry (LC/MS-MS) (Butt et al., 2014).

The method detection limits (MDLs) for urinary metabolite analyses (BCIPP, BDCIPP, DPHP, ip-PPP and tb-PPP) ranged from 0.03 to 0.33 ng/ml and the average internal standard recoveries for dDPHP and dBDCIPP were 79% and 116%, respectively (See SM Table S4). Results were standardized by specific gravity (ng/ml) (Harley et al., 2016). (Creatinine-adjusted metabolite levels and metabolite levels unadjusted for dilution are presented in SM Tables S5–S6.) On average, the prenatal urine samples were collected 9.4 (5.0) weeks after the dust samples.

2.4. Data analysis

Concentrations < MDL for urine and dust were imputed as the MDL divided by the square root of 2 (Hornung and Reed, 1990). We computed summary statistics of PFRs, EH-TBB, BEH-TEBP and ∑penta-BDE flame retardant levels in dust for 125 women, and PFR (BDCIPP, DPHP, ip-PPP, and tb-PPP) metabolite levels in urine for 310 women. Dust concentrations and loadings were $\log_{10}$-transformed for statistical analysis. We computed within-sample Pearson correlations for individual flame retardants measured in dust (n = 125). In addition, Pearson correlations and ANOVA were used to assess bivariate associations between the PFR, FM® 550 and ∑penta-BDE ($\log_{10}$-transformed) dust levels and loading and demographic information (e.g., years residing in the U.S., education, household income, etc.) and housing characteristics (e.g., number of pieces of stuffed furniture in the home, presence of any carpet, housing density, quality of housekeeping, etc.) (See SM Table S7). We used multivariate regression modeling to examine associations between PFR, EH-TBB and BEH-TEBP levels in dust with potential determinants of concentration and loading including: number of pieces of stuffed furniture in the home, housing density (number of people per room), year of home construction, quality of housekeeping (excellent vs. average or less clean) and presence of extremely worn carpet (yes/no). Final multivariate regression models were adjusted for household income (below the poverty threshold vs. above); maternal birth country (Mexico/other vs. U.S.), time in the U.S. (years) and smoking during pregnancy (yes/no). These covariates were selected *a priori* based on previous literature (Bradman et al., 2005, 2014; Castorina et al., 2011) and bivariate analyses. For ease of interpretation, we converted beta coefficients and 95% confidence intervals into measurements of percent change in dust levels associated with a one-unit increase in the predictor variable using the formula: percent change = 100 × (antilog(β)-1) (Ruotsalainen et al., 1993).

For PFR analytes, we calculated Spearman correlation coefficients (rho) to determine the associations between continuous household dust concentrations and loadings (TDCIPP and TPHP) and urinary metabolite (BDCIPP and DPHP) levels for the 124 women with both dust and urine measurements. Spearman correlation coefficients were also used to determine the associations between the four measured urinary metabolites (BDCIPP, DPHP, ip-PPP and tb-PPP). All analyses were conducted in STATA 13 (StataCorp, College Station, TX).

2.5. Non-cancer risk estimation based on PFRs in dust and urinary BDCIPP levels

We conducted a screening-level risk assessment to evaluate PFR exposures to pregnant women. We estimated pregnant women's doses for TCEP and TDCIPP, which have established health-based reference values (ATSDR, 2012). The non-dietary ingestion exposure-dose estimates for TCEP and TDCIPP were derived from the median, 95th % and maximum dust concentrations. Assuming a dust intake rate of 30 mg per day (U.S. EPA, 2011), we used standard equations relating concentration, intake rate and the mean body weight measured at 26 weeks gestation (73.9 kg) for the CHAMACOS cohort (ATSDR, 2005). We assumed that gastrointestinal absorption of these compounds was 100%. Detailed information on the dose calculations based on dust measurements is presented in the SM.

TDCIPP dose estimates were also calculated based on pregnant women's urinary BDCIPP levels using Equation (1). Assuming steady state conditions, we estimated a full day's urinary excretion of metabolites based on single-void urine samples using creatinine as an index of total daily urinary output volume (Castorina et al., 2003). Toxicokinetic studies of TDCIPP and its metabolites in rodents have found that approximately 69% of TDCIPP is excreted as urinary BDCIPP (ATSDR, 2012; Lynn et al., 1981). In the absence of human experimental data, however, we assumed that 100% of the absorbed dose is excreted as the urinary metabolite.

$$D_{TDCIPP} = \frac{\left(\frac{C_{BDCIPP}}{MW_{BDCIPP}} \times MW_{TDCIPP} \times \frac{Cr_{ex}}{Cr_{conc}} \right)}{BW} \quad (1)$$

where, D_{TDCIPP} is the estimated TDCIPP dose (μg/kg/day), C_{BDCIPP} is the urinary metabolite level (μg/L), MW_{TDCIPP} and MW_{BDCIPP} is the molecular weight of the PFR and corresponding metabolite (μg/μmol), Cr_{ex} is the expected daily creatinine excretion (g/day), Cr_{conc} is the average creatinine concentration of the urine samples (g/L), and BW is the average cohort body weight at 26 weeks gestation (kg). See SM for further information on the dose calculations.

Dose estimates (μg/kg/day) were compared to ATSDR minimum risk levels (MRLs) for TCEP and TDCIPP (ATSDR, 2012). If the ratios were greater than 1, the exposure exceeds the respective health-based exposure benchmark.

2.6. No significant risk levels (NSRLs) for cancer

Under California's Proposition 65, the Office of Environmental Health Hazard Assessment (OEHHA) has set “Safe Harbor Levels” called No Significant Risk Levels (NSRLs) for carcinogenic substances, defined as the daily intake level posing a one in 100,000 (10^{-5}) excess risk of cancer over a lifetime (OEHHA, 2001); the NSRL for TDCIPP is 5.4 μg/day (OEHHA, 2011). While TCEP is known by the state of California to cause cancer, an NSRL has not yet been established for the compound (State of California, 2016). We estimated TDCIPP doses (μg/day) based on both pregnant women's house dust levels and urinary BDCIPP levels, and compared each individual estimate to the NSRL using the methods described above and in the SM. We compared the median, 95th % and maximum dose estimates to the NSRL for TDCIPP.

3. Results and discussion

3.1. Demographic characteristics

Eighty-five percent of the pregnant women in this analysis were born in Mexico, with 48% having spent <5 years in the United States. The mean age = 26 years (sd = 5.2), nearly all were renters and lived within 200% of the federal poverty level (Bradman et al., 2005). Twenty-eight percent were employed as farm fieldworkers during pregnancy and 81% had at least one household member who worked in agriculture. Additional demographic information on this population has been published previously (Eskenazi et al., 2004).

3.2. Flame retardant dust levels

Table 1 presents the concentrations of flame retardants measured in dust from 125 homes. EH-TBB and BEH-TEBP were

Table 1
Concentrations of organophosphate and PBDE flame retardants and Firemaster® 550 constituents measured in prenatal house dust (CHAMACOS cohort; n = 125).

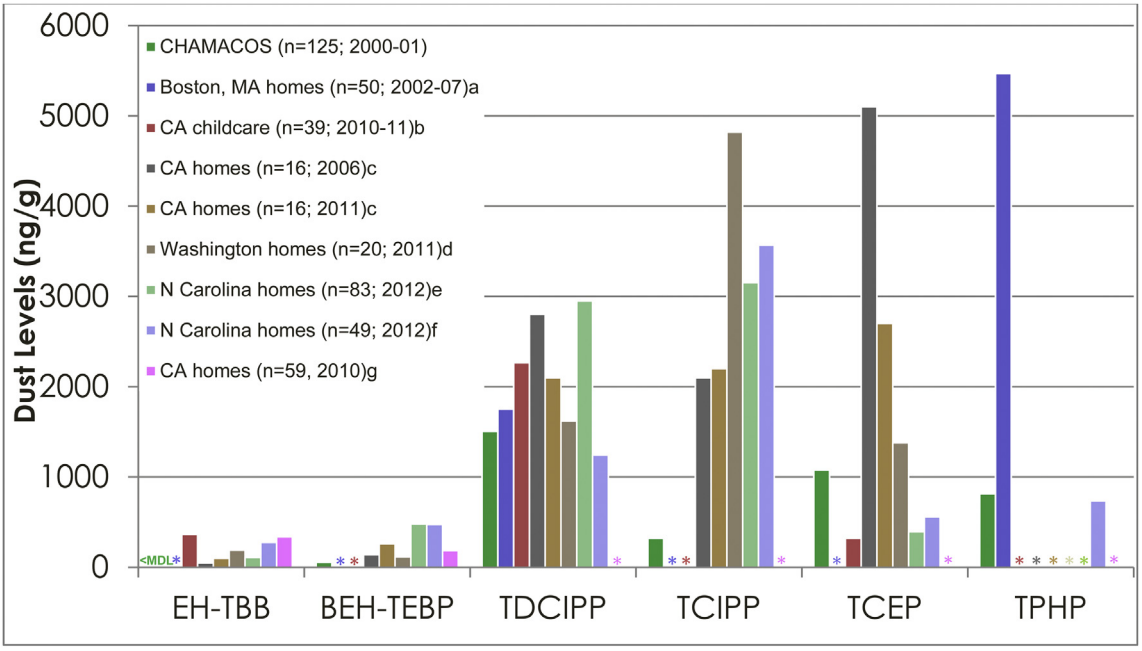
		Concentration (ng/g)						
Flame retardant	DF (%)	GeoMean (95% CI)	Min	p25	p50	p75	p90	Max
TCEP	100	1067 (857.9, 1326)	111.6	414.7	1079	2216	5070	157,000
TDCIPP	100	2021 (1582, 2581)	180.9	852.3	1506	4201	8615	2,140,000
TCIPP	97.6	410.4 (308.7, 545.7)	<MDL	121.5	319.6	1082	3901	56,560
TPHP	100	813.5 (676.6, 978.2)	46.1	447.2	766.6	1374	2188	76,780
EH-TBB	45.6	6.1 (5.0, 7.5)	<MDL	<MDL	<MDL	12.6	27.6	310.9
BEH-TEBP	97.6	64.9 (51.6, 81.6)	<MDL	34.6	56.4	131.0	323.9	7811
∑ Penta-BDEs[a]	100	3706 (2835, 4843)	180.3	1229	3575	9777	26,120	396,800

Abbreviations: Tris (2-chloroethyl) phosphate (TCEP); Tris (1,3-dichoro-2-propyl) phosphate (TDCIPP); Tris (1-chloro-2-propyl) phosphate (TCIPP); Triphenyl phosphate (TPHP); (2-ethylhexyl) 2,3,4,5-tetrabromobenzoate (EH-TBB); bis(2-ethylhexyl)tetrabromophthalate (BEH-TEBP).
NOTE: EH-TBB and BEH-TEBP are brominated components found in Firemaster® 550 (FM® 550), the latter compound being a brominated analogue of di(2-ethylhexyl) phthalate (DEHP).
[a] ∑ Penta-BDE congeners: sum of BDE28, BDE47, BDE66, BDE85/155, BDE99, BDE100, BDE153 and BDE154 (Stapleton et al., 2014).

detected in 45.6% and 97.6% of samples, respectively. Levels of EH-TBB and BEH-TEBP (median (range) = <MDL (<MDL-310.9) and 56.4 (<MDL-7811) ng/g, respectively) were much lower than the PFR compounds. The maximum TCEP and TDCIPP dust levels were among the highest ever reported although, in general, the median levels were lower in CHAMACOS compared to other U.S. cohorts (median (range) = 1079 (112.1–157,000) ng/g and 1506 (181.3–2,140,000) ng/g, respectively) (Bradman et al., 2014; Brown et al., 2014; Dodson et al., 2012; Hoffman et al., 2015b; Meeker and Stapleton, 2010; Schreder and La Guardia, 2014; Stapleton et al., 2014). In comparison to international studies, CHAMACOS TCEP and TDCIPP medians were slightly lower than reported levels in Japan and Sweden (Bergh et al., 2011; Kanazawa et al., 2010) and were similar to or higher than levels reported in studies from Belgium, New Zealand, Pakistan and Spain (Ali et al., 2012a, 2012b; Brommer et al., 2012; Garcia et al., 2007; Van den Eede et al., 2011). Fig. 1 presents median flame retardant levels in CHAMACOS dust compared to other published U.S. studies (Bradman et al., 2014; Brown et al., 2014; Dodson et al., 2012; Hoffman et al., 2015b; Meeker and Stapleton, 2010; Schreder and La Guardia, 2014; Stapleton et al., 2014). CHAMACOS sampling occurred in 2000–2001, before the PBDE phase out, while sampling in the other studies was more recent. For example, the highest medians reported for TDCIPP and TCIPP found in U.S. dust samples were collected in 2012 (Stapleton et al., 2014) and 2011 (Schreder and La Guardia, 2014), respectively.

Median (range) penta-BDE levels in dust (e.g., BDE47 = 1007 (19.2–126,600) ng/g; BDE99 = 1597 (79.0–98,870) ng/g; and BDE100 = 283.8 (16.1–64,340) ng/g) were similar to the PFR compounds. These penta-BDE congener levels were similar to those we previously reported for 28 California urban and rural homes sampled in 2006 (Quirós-Alcalá et al., 2011).

The five PFRs were weakly to moderately correlated with each other (rho = 0.09–0.45; $p < 0.05$) (Table 2). As expected, the two



* Star indicates analyte not measured.
Note: Year of sample collection is provided in parentheses.

Fig. 1. Median PFR and Firemaster® 550 levels in dust (CHAMACOS 2000-01) compared to other studies. [a] Meeker and Stapleton, 2010; [b] Bradman et al., 2014; [c] Dodson et al., 2012 (Two sampling periods); [d] Schreder and La Guardia, 2014; [e] Stapleton et al., 2014; [f] Hoffman et al., 2015b; [g] Brown et al., 2014.

Table 2
Pearson correlations of PFR, FM® 550 constituent and ∑penta-BDE[a] concentrations in house dust (n = 125).

	TCEP	TDCIPP	TCIPP	TPHP	EH-TBB	BEH-TEBP	∑Penta-BDEs
TCEP	1						
TDCIPP	0.27*	1					
TCIPP	0.45**	0.09*	1				
TPHP	0.33**	0.20*	0.34**	1			
EH-TBB	0.13	−0.05	0.17	0.29**	1		
BEH-TEBP	0.18*	0.06	0.28*	0.30**	0.46**	1	
∑Penta-BDEs	0.31**	0.24**	0.34**	0.66**	0.18*	0.12	1

*p < 0.05; **p < 0.001.
[a] ∑ Penta-BDE congeners: sum of BDE28, BDE47, BDE66, BDE85/155, BDE99, BDE100, BDE153 and BDE154.

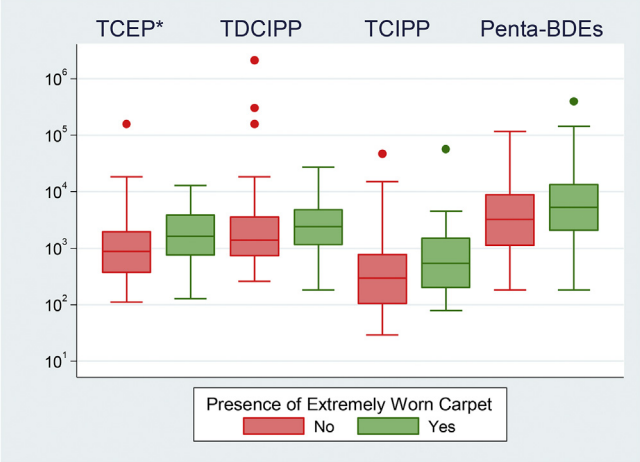
FM® 550 components (EH-TBB and BEH-TEBP) were significantly correlated with each other (r = 0.46; p < 0.001) (Table 2). TPHP was strongly correlated with ∑penta-BDE congeners (r = 0.66; p < 0.001). This finding was not surprising as TPHP and penta-BDEs are often found together in furniture (Stapleton et al., 2011, 2012). Before the PBDE phase out, manufacturers often used penta-BDE in combination with TPHP to maintain certain properties of the foam (color, texture, etc.).

Flame retardant dust loading (ng/m^2) levels are presented in the SM (Table S8). The highest dust loadings were found for TCEP and ∑penta-BDEs (medians = 7063 ng/m^2 and 22,560 ng/m^2, respectively). PFR dust loadings were more strongly correlated than the dust concentrations (rho = 0.40–0.67; p < 0.001) (SM Table S9). The strongest dust loading correlations was found for TPHP and ∑penta-BDE (r = 0.78; p < 0.001). The loading of the two FM® 550 components (EH-TBB and BEH-TEBP) were also strongly correlated with each other (rho = 0.73; p < 0.001).

We observed excellent or average housekeeping quality for 90% of homes despite high measures of housing disrepair (Bradman et al., 2005). In our bivariate analyses, we found significantly higher levels of TCEP with the presence of extremely worn carpets (GM (95th CI): 1543 (1052, 2262) ng/g vs 913.5 (702.8, 1187) ng/g; p < 0.05) (Fig. 2). In addition, TCIPP (GM (95th CI): 603.8 (376.9, 967.4) ng/g vs 348.9 (245.2, 496.5) ng/g) and ∑penta-BDE (5347 (3033, 9428) ng/g vs 3176 (2357, 4279) ng/g) dust levels were also higher with the presence of extremely worn carpets, albeit not significantly (p = 0.08). Dust loadings of TCEP, TCIPP and TPHP were all significantly higher with the presence of extremely worn carpets (SM Table S10).

TCEP levels in dust were significantly associated with the presence of extremely worn carpets (p < 0.05) in multivariate regression models adjusted for household poverty; resident density, maternal country of birth, number of years living in the U.S., smoking, number of pieces of stuffed furniture in the home, and quality of housekeeping (see Table 3). TCEP dust levels were 90.6% (95% CI: 13.1%, 221%) higher in homes with "extremely worn carpets" (n = 37) compared to other homes (n = 88). Multivariate TCEP dust loading model results were very similar. TCEP dust loadings were 132.1% (95% CI: 9.9%, 390.1%) higher in homes with "extremely worn carpets" compared to other homes (see SM Table S11). No other significant associations were found between dust levels or loadings and potential determinants of dust flame retardant levels in multivariate models.

The approximate ratio of EH-TBB/BEH-TEBP in FM® 550 is 3:1 (by mass) and according to the MSDS for FM® 550, the brominated compounds contribute approximately 50% of the mixture whereas the remaining 50% is comprised of isopropylated triaryl phosphate isomers and TPHP (Stapleton et al., 2008). In the CHAMACOS dust samples, the ratio of EH-TBB/BEH-TEBP ranged from 0.01 to 7.2, with a mean value of 0.31, possibly suggesting different sources with different relative compositions of EH-TBB and BEH-TEBP. Sources of BEH-TEBP other than FM® 550 such as its use in polyvinyl chloride (PVC) are plausible (Andersson et al., 2006). Other studies have reported higher BEH-TEBP levels compared to EH-TBB in older dust samples, suggesting that BEH-TEBP has been used for some time, and the presence of EH-TBB is more likely related to the more recent use of FM® 550 (Stapleton et al., 2008). BEH-TEBP is the primary ingredient in a flame retardant formulation known as DP-45 (and likely others) used in cables, wirings, etc. (Covaci et al., 2011) and thus may be an additional source of BEH-TEBP in house dust.



* ANOVA p<0.05 (TCEP); p=0.08 (TCIPP and ∑Penta-BDEs)

Fig. 2. Carpet wear and flame retardant levels in house dust.

3.3. Urinary metabolite levels

Table 4 presents urinary flame retardant metabolite concentrations for 310 pregnant women from the CHAMACOS cohort. Metabolites of TDCIPP (BDCIPP) and TPHP (DPHP) were detected in 77% and 79% of urine samples. Compared to PFR exposure assessed in 349 pregnant women from North Carolina in the early 2000s (Hoffman et al., 2017), the median (max) PFR metabolite levels in the CHAMACOS cohort were lower (BDCIPP: 0.4 (53.1) ng/ml, DPHP: 0.9 (54.1) ng/ml) than the North Carolina study (BDCIPP: 1.9 (140) ng/ml, DPHP: 1.3 (112) ng/ml). The relatively high urinary PFR levels reported by Hoffman et al., 2017 were not expected as sample collection for the study occurred before the phase out of the penta-BDE flame retardant mixture (Stapleton et al., 2012).

Table 3
Change in log-transformed TCEP levels in dust sampled during pregnancy with "presence of extremely worn carpet (Yes vs. No)" using linear regression model (n = 115).[a]

	TCEP % change (95% CI)	*p*-value
Presence of "extremely worn carpet" (Yes/No)	**90.6 (13.1, 221)**	**0.02**
Household income (at or below poverty threshold vs. > threshold)	−16.6 (−47.9, 33.6)	0.45
Housing density (<1 vs. ≥1 person per room)	62.5 (−30.2, 278)	0.26
Smoking during pregnancy (yes vs.no)	−85.0 (−96.7, −31.6)	0.02
Birth country (U.S. vs. Mexico/other)	−57.1 (−83.1, 9.0)	0.08
Years in the U.S. prior to delivery	−1.4 (−5.5, 3.0)	0.53
Number of pieces of stuffed furniture (≥3 vs < 3)	−0.8 (−23.2, 28.1)	0.95
Quality of housekeeping (excellent vs average or poor)	9.4 (−16.5, 43.5)	0.51

[a] Model $R^2 = 0.12$.

Table 4
Maternal prenatal urinary PFR metabolite levels (CHAMACOS cohort; n = 310).

Flame retardant	Metabolite[a]	>MDL[b] (%)	Concentration (ng/ml) specific gravity standardized					
			GeoMean (95% CI)	p25	p50	p75	p90	Max
TDCIPP	BDCIPP	77.7	0.28 (0.23, 0.34)	0.15	0.41	0.82	1.58	53.07
TPHP	DPHP	79.4	0.93 (0.82, 1.06)	0.51	0.93	1.65	3.41	54.13
ip-PDPP	ip-PPP[c]	71.6	0.33 (0.30, 0.36)	<MDL	0.34	0.60	1.01	5.47
tb-PDPP	tb-PPP	15.2	0.03 (0.03, 0.04)	<MDL	<MDL	<MDL	0.14	0.97

Abbreviations: MDL = method detection limit; CI = confidence interval; BDCIPP = bis(1,3-dichloro-2-propyl) phosphate; DPHP = diphenyl phosphate; ip-PPP = isopropylphenyl phenyl phosphate; tb-PPP = tert-butylphenyl phenyl phosphate.
[a] Samples were also analyzed for BCIPP, the metabolite of TCIPP, but BCIPP was not detected (DF = 0%).
[b] Mean (SD) method detection limits (ng/ml): BCIPP = 0.13 (0.04); BDCIPP = 0.03 (0.01); DPHP = 0.33 (0.10); ip-PPP = 0.14 (0.04); tb-PPP = 0.08 (0.04).
[c] Presumed metabolite of ip-PDPP, a component of FM® 550 (although can be used as a plasticizer in other applications).

The presumed urinary metabolite (ip-PPP) of isopropylphenyl diphenyl phosphate (ip-PDPP) was detected in 72% of samples (median = 0.34 ng/ml). The compound ip-PDPP is a component of FM® 550, although it can also be used as a plasticizer in other applications. The urinary metabolite (tb-PPP) of tert-butylphenyl diphenyl phosphate (tb-PDPP), not present in FM® 550, was detected in just 15% of samples (median < MDL). The three frequently detected urinary metabolites (DF > 70%) were weakly correlated, suggesting exposures co-occur (Spearman rho range = 0.16–0.30; $p < 0.05$) (see SM Table S12).

Previous studies have demonstrated that the concentrations of PFRs in household dust are weakly correlated with levels of their metabolites in human urine samples (Dodson et al., 2014; Hoffman et al., 2015b), suggesting that dust exposure is not the predominant pathway of exposure. We found no correlation between TDCIPP in dust and its metabolite BDCIPP in prenatal urine (Spearman rho = 0.04, $p = 0.65$), but we observed a weak positive correlation between TPHP in dust and specific-gravity normalized DPHP in 124 paired prenatal urine samples (rho = 0.17; $p = 0.06$). Correlations were slightly stronger when urinary DPHP levels were not corrected for urinary dilution (rho = 0.26; $p < 0.05$). These findings were similar to TPHP/DPHP and TDCIPP/BDCIPP correlations reported in a recent study of 53 homes in North Carolina (Hoffman et al., 2015b), where TPHP in dust was weakly correlated with uncorrected DPHP in adult urine (rho = 0.15) and not correlated with TDCIPP in dust and uncorrected BDCIPP in adult urine (rho = 0.05). These authors did observe significant correlations between TPHP in dust and adult hand wipes (rho = 0.37; $p < 0.01$) (Hoffman et al., 2015b). Dodson et al. (2014) also reported weakly positive nonsignificant correlations between urine and dust concentrations for urinary BDCIPP and TDCIPP levels in dust (Dodson et al., 2014). One limitation of our study is that the environmental and biological samples were not collected on the same day. However, the flame retardant compounds measured in this study persist in the environment, and their presence in dust represents the potential for long-term human exposure.

3.4. Non-cancer risk estimation based on PFRs in dust and urinary BDCIPP metabolite

Pregnant women's oral dose estimates derived from TCEP and TDCIPP levels in dust did not exceed chronic MRL values. The TCEP median and maximum oral dose estimates (0.0004 and 0.064 μg/kg/day, respectively) were several orders of magnitude lower than TCEP's chronic MRL (200 μg/kg/day) (ATSDR, 2012). Similarly, the TDCIPP median and maximum oral dose estimates (0.0006 and 0.87 μg/kg/day, respectively), were much lower than TDCIPP's chronic MRL (20 μg/kg/day).

Additionally, we estimated pregnant women's TDCIPP dose based on their urinary BDCIPP levels (median and max = 0.0001 and 0.01 μg/kg/day, respectively). These dose estimates were orders of magnitude lower than TDCIPP's chronic MRL (20 μg/kg/day).

3.5. No significant risk level (NSRL) for cancer

Pregnant women's oral dose estimates derived from the two highest TDCIPP levels in dust (64.2 and 9.0 μg/day) exceeded the NSRL for cancer of 5.4 μg/day (ratios = 11.9 and 1.7, respectively) (OEHHA, 2016). In total, 1.6% of dose estimates (2 of 125) exceeded the NSRL. The median and 95th % TDCIPP dose estimates (0.05 and 0.49 μg/day, respectively) were much lower than the cancer benchmark.

Pregnant women's TDCIPP dose estimates estimated from the median and maximum urinary BDCIPP levels (0.006 and 0.80 μg/day, respectively), did not exceed the NSRL of 5.4 μg/day (ratios = 0.001 and 0.15, respectively). The lack of human toxicokinetic data for TDCIPP is a source of uncertainty and may have resulted in an underestimation of dose. Toxicokinetic studies of TDCIPP and its metabolites in rodents found 69% of TDCIPP is excreted as urinary BDCIPP (ATSDR, 2012; Lynn et al., 1981); whereas we assumed 100% was excreted as the urinary metabolite. Further, as no pharmacokinetic data exist for prenatal exposure to these compounds, we made no attempt to estimate fetal exposure and potential risk. Future studies are

needed to assess potential health risks of prenatal PFR exposure.

4. Conclusions

This study demonstrates that even years before the phase out of PBDE flame redardants, alternative flame retardant chemicals were being used in California resulting in significant human exposure. For example, urinary metabolites of PFRs were measured in >70% of participating pregnant women fifteen years ago, and the parent compounds were measured in >95% of dust samples, indicating widespread home contamination. Dose estimates derived from maximum TDCIPP levels measured in dust indicated that exposures may have exceeded benchmarks based on carcinogenicity. These results provide information on PFR exposure and risk in pregnant women from the early 2000's, and will also be valuable to assess trends in exposure and risk over time given changing fire safety regulations and concomitant changes in chemical flame retardant use.

We observed significantly higher levels of TCEP dust levels and loading in multivariate models when the carpet was reported to be “extremely worn” in the home. Given the high level of crowding, poor housing quality, and lack of maintenance by landlords in this population's housing stock (Bradman et al., 2005), housekeeping quality is often not in the control of participants; “extremely worn” carpets were often old, warranting replacement, which is the landlord's responsibility. We believe the degree of carpet wear reflected age and time to accumulate contaminants. When possible, good housekeeping and dust reduction may reduce exposures to residents, but better maintenance of house quality by property owners is needed to minimize indoor contamination and potential exposure. In a future paper, we will examine prenatal flame retardant exposures and potential neurodevelopmental outcomes in CHAMACOS children.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemosphere.2017.03.076.

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