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Exposure to Organophosphate Flame Retardant Chemicals in the U.S. General Population: Data from the 2013-2014 National Health and Nutrition Examination Survey

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Abstract

Background: Use of organophosphate flame retardants (OPFRs) including tris(1,3-dichloro-2-propyl) phosphate, triphenyl phosphate, tris(1-chloro-2-propyl) phosphate, and tris-2-chloroethyl phosphate, in consumer products is on the rise because of the recent phase out of polybrominated diphenyl ether (PBDE) flame retardants. Some of these chemicals are also used as plasticizers or lubricants in many consumer products.

Objectives: To assess human exposure to these chlorinated and non-chlorinated organophosphates, and non-PBDE brominated chemicals in a representative sample of the U.S. general population 6 years and older from the 2013–2014 National Health and Nutrition Examination Survey (NHANES).

Methods: We used solid-phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry after enzymatic hydrolysis of conjugates to analyze 2,666 NHANES urine samples for nine biomarkers: diphenyl phosphate (DPHP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), bis-(1-chloro-2-propyl) phosphate (BCIPP), bis-2-chloroethyl phosphate (BCEP), di-n-butyl phosphate (DNBP), di-p-cresylphosphate (DpCP), di-o-cresylphosphate (DoCP), dibenzyl phosphate (DBzP), and 2,3,4,5-tetrabromobenzoic acid (TBBA). We calculated the geometric mean (GM) and distribution percentiles for the urinary concentrations (both in micrograms per liter [μg/L] and in micrograms per gram of creatinine). We only calculated GMs for analytes with an overall weighted frequency of detection >60%. For those analytes, we also a) determined weighted Pearson correlations among the log10-transformed concentrations, and b) used regression models to evaluate associations of various demographic parameters with urinary concentrations of these biomarkers.

Results: We detected BDCIPP and DPHP in approximately 92% of samples, BCEP in 89%, DNBP in 81%, and BCIPP in 61%. By contrast, we detected the other biomarkers much less frequently: DpCP (13%), DoCP (0.1%), TBBA (5%), and did not detect DBzP in any samples. Concentration ranges were highest for DPHP (<0.16–193 μg/L), BDCIPP (<0.11–169 μg/L), and BCEP (<0.08–110 μg/L). Regardless of race/ethnicity, 6–11 year old children had significantly

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higher BCEP adjusted GMs than other age groups. Females had significant higher DPHP and BDCIPP adjusted GM than males, and were more likely than males to have DPHP concentrations above the 95th percentile (odds ratio = 3.61; 95% confidence interval, 2.01–6.48).

Conclusions: Our results confirm findings from previous studies suggesting human exposure to OPFRs, and demonstrate, for the first time, widespread exposure to several OPFRs among a representative sample of the U.S. general population 6 years of age and older. The observed differences in concentrations of certain OPFRs biomarkers by race/ethnicity, in children compared to other age groups, and in females compared to males may reflect differences in lifestyle and exposure patterns. These NHANES data can be used to stablish a nationally representative baseline of exposures to OPFRs and when combined with future 2-year survey data, to evaluate exposure trends.

1. Introduction:

Flame retardants are substances added to plastics, furniture, upholstery, electrical equipment, electronic devices, textiles and other consumer goods to reduce product flammability and to comply with strict government fire safety standards and regulations. Polybrominated diphenyl ethers (PBDEs) were the most popular flame retardants used in the United States (EPA 2014); (de Wit 2002) until recently, when the pentaBDE and octaBDE products were voluntarily withdrawn from the U.S. market (2004); and the production, import, and sale of decaBDE ended in 2013 because of concerns related to persistence, bioaccumulation, and potential adverse health effects (Tullo 2003; EPA 2009; Betts 2008). Alternative replacements to PBDEs include chlorinated and non-chlorinated organophosphate flame retardants (OPFRs) such as tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), tris(1-chloro-2-propyl) phosphate (TCIPP), tris(2-chloroethyl) phosphate (TCEP), triphenyl phosphate (TPHP), tricresyl phosphates (TCPs), tributyl phosphate (TNBP), and tribenzyl phosphate (TBzP) (van der Veen and de Boer 2012; Bergman et al. 2012; EPA 2015). Of interest, some OPFRs can also be used as plasticizers or lubricants (van der Veen and de Boer 2012; Covaci et al. 2011; Solbu et al. 2007; Andresen et al. 2004). Furthermore, OPFRs are often used together and in combination with other non-PBDE brominated chemicals (e.g., 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB)) in popular commercial formulations of contemporary flame retardants such as Firemaster® 550 and Firemaster® BZ-54 (Bearr et al. 2012; Carignan et al. 2013; EPA 2015).

OPFRs and other contemporary flame retardants have been detected in indoor environments, including dust (Ali et al. 2012; Ali et al. 2013; Stapleton et al. 2008; Stapleton et al. 2009; Mizouchi et al. 2015), hand wipes (Hoffman et al. 2015b; Stapleton et al. 2014), baby products (Stapleton et al. 2011), and furniture foam (Stapleton et al. 2009). Ingestion, inhalation, and dermal contact are potential routes of human exposure to OPFRs (Hou et al. 2016; Schreder et al. 2016). Reported OPFR levels in indoor environments are comparable or higher than levels of PBDEs (Dodson et al. 2012).

In laboratory studies, OPFRs readily metabolize to their dialkyl or diaryl phosphates and to a variety of hydroxylation products (Van den Eede et al. 2013; Van den Eede et al. 2015; Van den Eede et al. 2016; Su et al. 2014); EH-TBB rapidly metabolizes to 2,3,4,5-

tetrabromobenzoic acid (TBBA) in humans and rats (Roberts et al. 2012). Urinary metabolites of several flame retardants, which have been detected in American adults and children (Hoffman et al. 2014; Hoffman et al. 2015b; Jayatilaka et al. 2017; Butt et al. 2014), have been used as biomarkers of exposure to these contemporary flame retardants. Data collected from several epidemiological studies suggest that urinary concentrations of bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), a metabolite of TDCIPP, have increased considerably since 2002 (Hoffman et al. 2017b); samples collected in 2014 and 2015 had BDCIPP concentrations that were more than 15 times higher than those collected in 2002 and 2003. These studies also showed significant increases in diphenyl phosphate (DPHP) urinary concentrations albeit much smaller than for BDCIPP (Hoffman et al. 2017b). Worldwide organophosphate esters production volumes increased from ~100,000 tonnes/year in 1992 to 341,000 tonnes/year in 2007 (Greaves and Letcher 2017). For example, in the United States, production of TCPP, TDCPP and TCEP increased from below 14,000 tonnes/year in the mid-1980s to ~38,000 tonnes/year in 2012 (Schreder et al. 2016).

Little is known about the potential health effects of these emerging contaminants. OPFRs have been associated with adverse reproductive/developmental and neurological effects in animals (van der Veen and de Boer 2012; Dishaw et al. 2011; Baldwin et al. 2017). For example, studies in zebrafish suggest that OPFRs have a role in developmental neurotoxicity and altered behavior at early life stages perhaps because of their structural similarities to organophosphate pesticides (Dishaw et al. 2011; Dishaw et al. 2014; Oliveri et al. 2015) . In vitro, exposure of PC12 cells to TDCIPP and TCEP decreased cell growth, increased apoptosis, altered morphology and produced significant changes in the gene and protein levels (Ta et al. 2014). Of interest, TDCIPP and TCEP are included in the Proposition 65 list of chemicals known to cause cancer (OEHHA 2016a) and The European Chemicals Agency has designated TCEP as a “substance of very high concern” because of its reproductive toxicity, chronic and acute aquatic life effects, and suspected carcinogenicity (ECHA 2017).

Furthermore, certain OPFRs may also affect human health (Hoffman et al. 2017c). For example, higher dust levels of TCEP were associated with increased odds of papillary thyroid cancer (Hoffman et al. 2017c); several OPFRs in floor dust were associated with higher prevalence of atopic dermatitis (TDCIPP), or of asthma and allergic rhinitis (TNBP) (Araki et al. 2014). Furthermore, TPHP exposure may be associated with increased levels of total thyroxine, especially in women (Preston et al. 2017). OPFR exposure was also associated with measurable differences in social behaviors among 3–5 year old children (Lipscomb et al. 2017); children with higher OPFR exposures exhibited poorer social skills, as measured by externalizing behavior and responsibility, which play an important role in a child’s ability to succeed academically and socially. Therefore, it is important to know how much of these compounds or their metabolites are present in humans.

Because of the increased use of contemporary flame retardants in consumer products and the chemicals potential adverse health effects, interest exist in understanding the extent of human exposure. Biomonitoring of contemporary flame retardants will help us understand the extent of exposure to these chemicals and will provide the information needed to set up reference ranges which may be used to evaluate future exposures. In this manuscript, we report for the first time the urinary concentrations of nine contemporary flame retardant

metabolites in a representative sample of the U.S. general population 6 years of age and older, stratified by age group, sex, and race/ethnicity.

2. Materials and Methods

2.1. Study Population:

The National Health and Nutrition Examination Survey (NHANES) is the result of the National Health Survey Act of 1956, which granted legislative authorization for a continuing survey to provide current statistical data on the amount, distribution, and effects of illness and disability in the United States (CDC 2014). NHANES, conducted continuously since 1999 by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), includes direct household interviews with demographic, socioeconomic, dietary, and health-related questions, physical examinations and collection of clinical samples. Some of these samples are used to assess exposure to environmental chemicals.

For this study, we analyzed 2,666 spot urine samples collected from a random one-third subset of 2013–2014 NHANES participants six years of age and older to maintain the representative design of the survey. NCHS Research Ethics Review Board reviewed and approved the study protocol. All respondents gave informed written consent to participate in the survey; parents or guardians provided consent for participants younger than 18 years (CDC 2017).

2.2. Urinary Concentrations of OPFRs and Other Alternative Flame Retardant Biomarkers:

The urine specimens were collected, aliquoted, and shipped on dry ice to the CDC`s National Center for Environmental Health where they were stored at −70 ^{0}C until analysis. We quantified nine urinary biomarkers: BDCIPP, bis(1-chloro-2-propyl) phosphate (BCIPP), bis(2-chloroethyl) phosphate (BCEP), DPHP, di-p-cresylphosphate (DpCP), di-o-cresylphosphate (DoCP), dibutyl phosphate (DNBP), dibenzyl phosphate (DBzP), and TBBA. The analytical method, described in detail elsewhere (Jayatilaka et al. 2017), relies on an enzymatic hydrolysis of urinary conjugates of the target biomarkers in 400 μL urine, automated off-line solid phase extraction, separation by reversed phase high-performance liquid chromatography, and detection by isotope dilution-electrospray ionization tandem mass spectrometry (Jayatilaka et al. 2017). Calibration standards, reagent blanks, and NHANES study samples were analyzed with urine-based quality control (QC) materials. The approximate concentrations of the target analytes were 4 ng/mL (QCL) and 15 ng/mL (QCH)(Jayatilaka et al. 2017). The limits of detection (LODs) were 0.05 μg/L (DoCP, DpCP, DNBP, DBzP, and TBBA), 0.08 μg/L (BCEP), 0.10 μg/L (BCIPP), 0.11 μg/L (BDCIPP), and 0.16 μg/L (DPHP). The precision of measurements, expressed as the relative standard deviation of multiple measures of the QC materials, ranged from 2.7% to 7.5%, depending on the target biomarker and concentration range. The method accuracy, calculated from the recovery at three spiking levels (0.5; 5.0 and 25 ng/mL), ranged from 93.5% to 108%, depending on the analyte and concentration (Jayatilaka et al. 2017).

2.3. Statistical Analysis

We analyzed the data using Statistical Analysis System (SAS) (version 9.3; SAS Institute Inc., Cary, NC) and SUDAAN (version 11, Research Triangle Institute, Research Triangle Park, NC). SUDAAN incorporates sample weights and design variables to account for the complex, clustered design of NHANES. For concentrations below the LOD, we imputed a value equal to the LOD divided by the squared root of 2 (Hornung and Reed 1990).

We stratified age, self-reported in years at the last birthday, in four groups: 6–11, 12–19, 20–59, and ≥60 years. Based also on self-reported data we defined four race/ethnicity groups: non-Hispanic black, non-Hispanic white, all Hispanic, and Other. We calculated the geometric mean (GM) and distribution percentiles for the urinary concentrations (both in micrograms per liter [μg/L] and in micrograms per gram of creatinine [μg/g creatinine]) using the survey sampling weights, which account for unequal selection probabilities caused by the cluster design and the oversampling of certain groups. We only calculated GMs for analytes with an overall weighted frequency of detection >60%. For those same analytes, we also determined weighted Pearson correlations among the $\log_{10}$-transformed concentrations (not corrected for creatinine).

We used analysis of covariance to examine the associations of age group (6–11, 12–19, 20–59, ≥60), sex, race/ethnicity (four above categories), $\log_{10}$ creatinine, and all possible two way interaction terms on the log-transformed concentrations of the target analytes detected in >60% of participants. We calculated the adjusted GM concentrations of these five biomarkers (in μg/L). We log-transformed the concentrations of the target analytes and creatinine because their distributions were right-skewed.

For each analyte, to reach the final multivariate logistic regressions model, we used backward elimination including all the two-way interaction terms, with a threshold of $P < 0.05$ for retaining the variable in the model, using Satterwaite-adjusted F statistics. We evaluated for potential confounding by adding back into the model each of the excluded variables one by one and examining changes in the β coefficients of the statistically significant main effects. If addition of one of these excluded variables changed a β coefficient by ≥ 10%, the variable was re-added to the model.

Last, we conducted weighted multiple logistic regressions to examine the likelihood of having concentrations above the 95th percentile (an arbitrary value we selected as example of higher than average concentrations) for the five biomarkers detected in >60% participants with sex, age group, race/ethnicity, and creatinine, variables selected on the basis of statistical, demographic, and biologic considerations.

3. Results

We quantified urinary concentrations of nine contemporary flame retardant metabolites in 2,666 NHANES 2013–2014 samples. In Tables 1–5, we present the GM concentrations, select percentiles, and detection frequencies stratified by age group, sex, and race/ethnicity for BDCIPP, DPHP, BCEP, DNBP, and BCIPP. We detected BDCIPP and DPHP in approximately 92% or participants, BCEP in 89%, DNBP in 81%, and BCIPP in 61%. By

contrast, we detected the other biomarkers much less frequently: DpCP (13%), DoCP (0.1%), TBBA (5%), and did not detect DBzP in any samples (Tables S1-S4). We also detected BDCIPP, DPHP and BCEP at the highest concentrations with concentrations ranging from <0.11 μg/L to 169 μg/L, <0.16 μg/L to 193 μg/L, and <0.08 μg/L to 110 μg/L, respectively. DNBP and BCIPP concentrations were not as high and ranged from < 0.05μg/L −70.3 μg/L and <0.10 μg/L to 46.7 μg/L, respectively.

Bivariate Pearson`s correlation analysis (Table 6) showed statistically significant correlations ($P < 0.0001$) between the log-transformed concentrations of DPHP and BDCIPP (Pearson correlation coefficient (r) = 0.45) and BCEP (r = 0.36), and between log-transformed concentrations of BDCIPP and BCEP (r = 0.41), DNBP (r = 0.29), and BCIPP (r = 0.28).

DPHP:

The final DPHP linear regression model included sex, race, age, sex*age (P=0.0157), sex*race (P=0.0099) and log creatinine (Table 7). Females had significant higher adjusted GM than males, regardless of race and age group (P=0.0262 for 12–19 years old; P<0.001 for 20–59 years old, ≥60 years, and for all races), except among the 6–11 year olds. Among males, non-Hispanic whites had higher adjusted GM concentrations than Hispanics (P=0.03) and non-Hispanic blacks (P=0.007). By contrast, among females, Hispanics (P=0.003) and non-Hispanic whites (P=0.0004) had higher adjusted GMs than females of Other races. Adjusted GMs showed a significant downward trend as age increased. Regardless of sex, 6–11 year old children had higher adjusted GMs than adolescents 12–19 years of age (P<0.001), who, in turn, had higher adjusted GMs than adults 20–59 years (P<0.001). However, we observed no differences between adjusted GMs for younger adults (20–59 years) and older adults (≥60 years).

In the final multivariate logistic analysis, $\log_{10}$ creatinine (P <0.001), sex (P=0.0003), and age (P<0.001) were significantly associated with the likelihood of DPHP exceeding the 95th percentile (Table S6). Children were 6.6 times more likely than persons 60 years and older to have DPHP concentrations above the 95th percentile (adjusted odds ratio [OR] = 6.6; 95% CI, 2.5–17.2); we observed no other statistically significant differences by age. Females were 3.6 times more likely than males to have concentrations of DPHP above the 95th percentile (adjusted OR = 3.61; 95% CI, 2.01–6.48).

BDCIPP:

The final BDCIPP linear regression model included race, sex (P=0.004), age, age*race (P=0.0037), and log creatinine (P<0.001) (Table 7). Females had significant higher adjusted GMs than males (P=0004). Adjusted GMs showed a significant downward trend as age increased. However, between Hispanics and non-Hispanic blacks, we observed no differences between adolescents and adults 20–59 years old; among persons of Other race, we observed no difference between younger (20–59 years) and older (≥60 years) adults. Among children and adolescents, non-Hispanic whites had significantly higher adjusted GMs than Hispanics (P=0.02, 0.04, for 6–11 years and 12–19 years, respectively) and non-Hispanic blacks (P=0.0001, 0.014, for 6–11 years and 12–19 years, respectively). By contrast, for adults 20–59 years old, Hispanics and non-Hispanic whites had significantly

higher adjusted GMs than non-Hispanic blacks (P <0.01 for both Hispanic and non-Hispanic whites) and persons of Other race (P<0.01 for Hispanic and P=0.001 for non-Hispanic white).

In the final multivariate logistic analysis, $\log_{10}$ creatinine (P <0.0001) and age (P<0.0001) were significantly associated with the likelihood of BDCIPP exceeding the 95th percentile. Children 6–11 years of age were 10.74 times more likely than adults 60 years and older to have BDCIPP concentrations above the 95th percentile (adjusted OR = 10.74; 95% CI, (4.42– 26.1); we observed no statistically significant differences among other age groups.

BCEP:

Race, sex, age, sex*age (P=0.004), and age*race (P=0.04) were significant in the final BEtCP linear regression model (Table 7). Regardless of race/ethnicity, children had significantly higher adjusted GMs than adolescents (P=0.047, 0.005, 0.0343, and 0.015 for Hispanics, non-Hispanic whites, non-Hispanic blacks, and persons of Other race, respectively) who, in turn, had significantly higher adjusted GMs than adults 20–59 years old (P=0.0002, <0.001, 0.0007, and 0.0027 for Hispanic, non-Hispanic whites, non-Hispanic blacks, and Other race persons, respectively). Except for people in the Other race/ethnicity group, children had significantly higher adjusted GMs than adults 60 years and older (P=0.0008, <0.001, 0.01 for Hispanics, non-Hispanic whites, and non-Hispanic blacks, respectively).

Among children, non-Hispanic whites (P=0.0056) and Other race persons (P=0.0411) had significantly higher adjusted GMs than non-Hispanic blacks. Among adolescents, Hispanics had significantly higher adjusted GMs than non-Hispanic blacks (P=0.0435). For the 20–59 years olds, non-Hispanic whites had higher adjusted GMs than non-Hispanic blacks (P=0.0367). Regardless of sex, children and adolescents had significantly higher adjusted GMs than adults 20–59 years old (P <0.01). We observed a significant sex difference for the 20–59 years olds (P=0.0111), but not for the other age groups.

In the final multivariate logistic analysis, $\log_{10}$ creatinine (P<0.001) and age (P<0.02) were significantly associated with the likelihood of BCEP concentrations exceeding the 95th percentile. Children, but not adolescents or adults 20–59 years of age, were more likely than adults 60 years and older to have BCEP concentrations exceeding the 95th percentile (adjusted OR = 2.05; 95% CI, 1.07 −3.93).

DNBP:

The final DNBP linear regression model included race (P<0.001), sex (P=0.0005), and age (P<0.001) (Table 7). Females had significant higher adjusted GMs than males (P=0.0005). Non-Hispanic whites (P=0.0003), non-Hispanic blacks (P<0.001), and Hispanics (P=0.0173) had significantly higher adjusted GMs than persons of Other race/ethnicity. Children had adjusted GMs significantly higher than all other age groups; other differences did not reach statistical significance.

In the final multivariate logistic analysis, $\log_{10}$ creatinine (P<0.001) and age (P=0.001) were significantly associated with the likelihood of DNBP exceeding the 95th percentile.

Children, but not adolescents or adults 20–59 years of age, were more likely than adults 60 years and older to have concentrations of DNBP exceeding the 95th percentile (adjusted OR = 3.6; 95% CI, 1.98 −6.5).

BCIPP:

Race and age were significant in the final BCIPP linear regression model (Table 7). Non-Hispanics whites and persons of Other race had higher adjusted GMs than non-Hispanic blacks (P=0.0003 and 0.0005 for non-Hispanics whites and Other race, respectively) and All Hispanics (P=0.0057 and 0.0169 for non-Hispanics whites and Other race, respectively). Children had significantly higher adjusted GMs than all other age groups (all P <0.001); differences among the other age groups did not reach statistical significance.

The final logistic multivariate analysis included $\log_{10}$ creatinine (P<0.001) and age (P<0.003). Children (OR = 3.57; 95% CI,1.97–6.45) and adults 20–59 years old (OR = 1.58, 95% CI, 1.03–2.43) were more likely than adults ≥60 years of age to have concentrations of BCIPP above the 95th percentile; we observed no other age-related differences.

4. Discussion

For the first time, we present nationally representative data for five OPFRs among Americans 6 years of age and older. We detected BDCIPP, DPHP, BCEP, DNBP in >80% and BCIPP in >60% of the samples analyzed which suggests widespread exposure to the precursors of these OPFRs. Depending on the OPFR metabolite, concentration ranges spanned 3–4 orders of magnitude. These results are in agreement with previous research involving convenience samples of non-occupationally exposed populations (Jayatilaka et al. 2017; Cooper et al. 2011; Dodson et al. 2014; Meeker et al. 2013b; Butt et al. 2014), in which BDCIPP and DPHP were also the most frequently detected biomarkers. Moreover, in U.S. house dust the parent compounds of BDCIPP and DPHP, TDCIPP and TPHP, respectively, were detected in 96% and 98% of the samples (Stapleton et al. 2009). Similarly, in a recent study, TPHP, TCIPP, TDCIPP and TCEP were detected in more than 60% of the silicone wristbands worn by preschoolers (Kile et al. 2016); with TPHP and TDCIPP detected in more than 89% of the samples. Several studies reported TNBP concentrations in dust, and the levels vary considerably (Luongo and Ostman 2016; Ouyang et al. 2017; García et al. 2007). Although dust concentrations among countries/studies must be compared cautiously because important considerations (e.g., year of sample collection, collection protocols, handling and storage of the samples) may differ, the existing data suggest that house dust could be a source of human exposure to TNBP and other OPFRs. Of interest, we infrequently detected DpCP, TBBA, and DoCP, and we did not detect DBzP in any of the samples. These relatively low detection frequencies, even though LODs were the same (0.05 μg/L) and the lowest among all nine biomarkers measured, suggest limited human exposures to their corresponding parent compounds or that pharmacokinetic factors are different (e.g., the measured analytes are not the best biomarkers of exposure).

The lower detection frequency of BCIPP compared to BDCIPP was unexpected considering the presence of relatively similar levels of their corresponding precursors TCIPP and TDCIPP in house dust (Dodson et al. 2012; Carignan et al. 2013; Stapleton et al. 2009;

Stapleton et al. 2014). However, in a recent study of 21 U.S. mother-toddler pairs, BDCIPP was detected in all individuals, whereas BCIPP was only detected in 8% (Butt et al. 2014). The relatively low BCIPP concentrations compared to BDCIPP may relate to a low yield of BCIPP from TCIPP, as suggested by in vitro metabolism studies with human liver microsomes and S9 fractions (Van den Eede et al. 2013; Van den Eede et al. 2016). Although BCIPP was the major metabolite formed by liver enzymes, Van den Eede et al. suggested that detecting BCIPP in urine can be difficult because of analytical challenges and possible pharmacokinetic processes interfering with its elimination in urine, such as protein binding, storage in tissues or other excretion pathways (Van den Eede et al. 2016). Nevertheless, we ruled out analytical difficulties as responsible for the lower detection frequency of BCIPP because the detection limits for both BDCIPP and BCIPP in our method are comparable (0.11 vs 0.10 μg/L).

The moderate correlation between concentrations of DPHP and DBCIPP and, of interest, weaker correlations between DPHP and BCEP, BDCIPP and BCEP, and BDCIPP and BCIPP might reflect the ubiquity of the parent compounds for a wide variety of commercial applications or the combined use of the parent compounds in commerce. TDCIPP is the most common flame retardant for polyurethane foam used in upholstered furniture, automotive products, carpet padding and gymnastic equipment (EPA 2015; Cooper et al. 2016), and some children's products such as toys, strollers, car seats, nursing pillows, and sleeping products, including nap mats, sleep positioners, travel beds, bassinets, portable crib mattresses, and play pens (OEHHA 2016b). TCEP was identified in upholstered polyurethane foam baby products such as car seats, baby carriers, and changing table pads (Stapleton et al. 2011). TCEP is also found as a 10% impurity in Albemarle's Antiblaze V6 (Stapleton et al. 2012), used in automobile foams. On the other hand, TCIPP, the parent compound of BCIPP, is mainly used as a flame retardant in rigid and flexible polyurethane foam (FPUF) used in upholstered FPUF baby products such as car seats, baby carriers, and changing table pads (Stapleton et al. 2011). TCIPP is often used as replacement of TCEP. Besides being a component of several flame retardant mixtures including Firemaster® 550, TPHP is predominantly used as an additive in hydraulic fluids and to regulate pore size in concrete (Andresen et al. 2004; Solbu et al. 2007). TPHP was also identified in a computerized indoor office environment with the computer video display units as the source of emission (Carlsson et al. 2000). Additionally, TPHP is often listed as ingredient in nail polish to increase flexibility and improve adhesion on the nail (Mendelsohn et al. 2016). DPHP is the main metabolite of TPHP (Sasaki et al. 1984) but is also a metabolite of multiple OPFRs, including 2-ethylhexyldiphenyl phosphate (Nishimaki-Mogami et al. 1988) and tert-butylphenyl diphenylphosphate (Heitkamp et al. 1985), and DPHP itself has been used as an additive in industrial applications, typically as a catalyst for resin manufacturing (Makiguchi et al. 2011; Makiguchi et al. 2013). Therefore, the detection of DPHP in a person's urine can result from exposure to several OPFRs as well as direct contact with DPHP.

Differences in exposure sources may explain the weak correlations we observed between BDCIPP and DNBP. TNBP is predominantly used as plasticizer in the manufacture of plastics and vinyl resins, as an antifoam agent for concrete (Andresen et al. 2004), and as additive in hydraulic fluids to enhance their properties (Solbu et al. 2007). TNBP is also

used as an additive in concrete and glue, and may be present in putty (Marklund et al. 2005). We speculate that DNBP in urine might be associated with exposure to TNBP from recent renovations.

Conclusions about particular exposures are hard to draw from the correlations among urinary biomarkers because there are many possible household sources of flame retardants and limited information is available on OPFRs exposure sources and metabolism. Biotransformation and kinetics studies of several organophosphate triesters are limited to one in vitro study in herring gulls using a hepatic microsomal metabolism assay that suggested the fastest depletion rate for TNBP followed by TCIPP, TPHP, and lastly by TDCIPP (Greaves et al. 2016). The same investigators also reported that halogenated OP triesters hydrolyze to their respective diesters more efficiently (TDCIPP (90%) and TCIPPP (56%)) than non-halogenated OP triesters (TPHP (15%) and TNBP (14%)) (Greaves et al. 2016); these differences may reflect dissimilarities in metabolism pathways.

We note that concentrations of DPHP, BDCIPP, DNBP, and BCIPP differ by sex. In general, females had higher adjusted GMs of these OPFR metabolites than males, which may reflect differences in exposure patterns and/or metabolism by sex. Of interest, not only did females had higher adjusted GM concentrations of DPHP, but females were also 3.6 times more likely than males to have concentrations of DPHP above the 95th percentile. Together, these findings suggest that females experience higher exposures to TPHP, perhaps from higher use of nail polish by women compared to men because TPHP is a known ingredient in nail polish (Mendelsohn et al. 2016). The higher concentrations of TPHP among NHANES females agree with the results from recent studies in which DPHP urinary concentrations in women were 43% higher than (Preston et al. 2017) or almost twice (Hoffman et al. 2015b) those of men; however, concentrations of BDCIPP were not (Hoffman et al. 2015b).

We also observed that concentrations of certain OPFRs differed by race/ethnicity. Racial differences may relate to lifestyle, diet, and use of OPFRs-containing products. Last, the detection of OPFR metabolites in children suggests that exposure occurs at young ages. Additionally, higher concentrations of OPFRs in children compared to other age groups suggest that exposures in children are higher than in adults, assuming there are no differences in pharmacokinetics. This finding is in agreement with other studies in which concentrations in children were higher than in adults, particularly for BDCIPP and DPHP (Butt et al. 2014; Van den Eede et al. 2015; Cequier et al. 2014; Cequier et al. 2015; Butt et al. 2016; Hoffman et al. 2015a; Hoffman et al. 2017a). Several studies in the United States showed detectable and variable levels of various flame retardants in indoor dust (Stapleton et al. 2009; Meeker et al. 2013b; Hoffman et al. 2015b; Schreder and La Guardia 2014). In fact, one of these studies showed that household dust might be an important source of exposure to TDCIPP but not TPHP (Meeker et al. 2013a). Others showed mean TCIPP dust levels three times higher than those of TDCIPP and TCEP (Schreder and La Guardia 2014), while Stapleton et al. showed that TPHP dust concentrations were 5–11 times higher than TDCIPP and TCIPP (Stapleton et al. 2009). The higher likelihood of children 6–11 years of age having BDCIPP, DPHP, BCEP, DNBP and BCIPP concentrations above the 95th percentile compared to other age groups can be related to children’s playing patterns and on their relatively low body weights which result in higher exposures. Because of children’s

play habits, many opportunities exist for exposure through dermal adsorption, inhalation, and ingestion of dust containing OPFRs.

5. Conclusion

We present the first nationally representative assessment of exposure to several contemporary flame retardants among Americans 6 years of age and older. We found that exposure to several OPFRs is widespread with BDCIPP, DPHP, BCEP, DNBP, and BCIPP detected in the majority of the samples analyzed. These data can be used to stablish a nationally representative baseline of exposures to OPFRs and when combined with more 2-year survey data, to evaluate trends in exposure. Adjusted GMs of OPFR metabolites were higher in females than males, which may reflect lifestyle differences affecting exposure patterns. The detection of OPFR metabolites in children suggests that exposure occurs at young ages. Higher concentrations of OPFRs in children compared to other age groups might reflect that exposures in children are higher than in adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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7. References

Ali N, Ali L, Mehdi T, Dirtu AC, Al-Shammari F, Neels H, Covaci A (2013) Levels and profiles of organochlorines and flame retardants in car and house dust from Kuwait and Pakistan: implication for human exposure via dust ingestion. Environment international 55:62–70. doi:10.1016/j.envint.2013.02.001 [PubMed: 23523855]

Ali N, Dirtu AC, Van den Eede N, Goosey E, Harrad S, Neels H, t Mannetje A, Coakley J, Douwes J, Covaci A (2012) Occurrence of alternative flame retardants in indoor dust from New Zealand: indoor sources and human exposure assessment. Chemosphere 88 (11):1276–1282. doi:10.1016/j.chemosphere.2012.03.100 [PubMed: 22551874]

Andresen JA, Grundmann A, Bester K (2004) Organophosphorus flame retardants and plasticisers in surface waters. The Science of the total environment 332 (1–3):155–166. doi:10.1016/j.scitotenv.2004.04.021 [PubMed: 15336899]

Araki A, Saito I, Kanazawa A, Morimoto K, Nakayama K, Shibata E, Tanaka M, Takigawa T, Yoshimura T, Chikara H, Saijo Y, Kishi R (2014) Phosphorus flame retardants in indoor dust and their relation to asthma and allergies of inhabitants. Indoor air 24 (1):3–15. doi:10.1111/ina.12054 [PubMed: 23724807]

Baldwin KR, Phillips AL, Horman B, Arambula SE, Rebuli ME, Stapleton HM, Patisaul HB (2017) Sex Specific Placental Accumulation and Behavioral Effects of Developmental Firemaster 550 Exposure in Wistar Rats. Scientific reports 7 (1):7118. doi:10.1038/s41598-017-07216-6 [PubMed: 28769031]

Bearr JS, Mitchelmore CL, Roberts SC, Stapleton HM (2012) Species specific differences in the in vitro metabolism of the flame retardant mixture, Firemaster® BZ-54. Aquatic Toxicology 124:41–47. doi:http://dx.doi.org/10.1016/j.aquatox.2012.06.006 [PubMed: 22889877]

Bergman A, Ryden A, Law RJ, de Boer J, Covaci A, Alaee M, Birnbaum L, Petreas M, Rose M, Sakai S, Van den Eede N, van der Veen I (2012) A novel abbreviation standard for organobromine,

organochlorine and organophosphorus flame retardants and some characteristics of the chemicals. Environment international 49:57–82. doi:10.1016/j.envint.2012.08.003 [PubMed: 22982223]

Betts K (2008) Court bans widely used flame retardant. Environmental science & technology 42 (11): 3910. doi:10.1021/es0871199 [PubMed: 18589943]

Butt CM, Congleton J, Hoffman K, Fang M, Stapleton HM (2014) Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. Environmental science & technology 48 (17):10432–10438. doi:10.1021/es5025299 [PubMed: 25090580]

Butt CM, Hoffman K, Chen A, Lorenzo A, Congleton J, Stapleton HM (2016) Regional comparison of organophosphate flame retardant (PFR) urinary metabolites and tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey. Environment international 94:627–634. doi:10.1016/j.envint.2016.06.029 [PubMed: 27397928]

Carignan CC, McClean MD, Cooper EM, Watkins DJ, Fraser AJ, Heiger-Bernays W, Stapleton HM, Webster TF (2013) Predictors of tris(1,3-dichloro-2-propyl) phosphate metabolite in the urine of office workers. Environment international 55:56–61. doi:10.1016/j.envint.2013.02.004 [PubMed: 23523854]

Carlsson H, Nilsson U, Ostman C (2000) Video display units: an emission source of the contact allergenic flame retardant triphenyl phosphate in the indoor environment. Environmental Science and Technology 34:3885–3889

CDC (2014) About the National Health and Nutrition Examination Survey. National Center for Health Statistics https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed 07.17 2017

CDC (2017) National Health and Nutrition Examination Survey. 2013–2014 Overview. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2013. Accessed 07.20 2017

Cequier E, Marce RM, Becher G, Thomsen C (2014) A high-throughput method for determination of metabolites of organophosphate flame retardants in urine by ultra performance liquid chromatography-high resolution mass spectrometry. Analytica chimica acta 845:98–104. doi: 10.1016/j.aca.2014.06.026 [PubMed: 25201278]

Cequier E, Sakhi AK, Marce RM, Becher G, Thomsen C (2015) Human exposure pathways to organophosphate triesters - a biomonitoring study of mother-child pairs. Environment international 75:159–165. doi:10.1016/j.envint.2014.11.009 [PubMed: 25461425]

Cooper EM, Covaci A, van Nuijs AL, Webster TF, Stapleton HM (2011) Analysis of the flame retardant metabolites bis(1,3-dichloro-2-propyl) phosphate (BDCPP) and diphenyl phosphate (DPP) in urine using liquid chromatography-tandem mass spectrometry. Analytical and bioanalytical chemistry 401 (7):2123–2132. doi:10.1007/s00216-011-5294-7 [PubMed: 21830137]

Cooper EM, Kroeger G, Davis K, Clark CR, Ferguson PL, Stapleton HM (2016) Results from Screening Polyurethane Foam Based Consumer Products for Flame Retardant Chemicals: Assessing Impacts on the Change in the Furniture Flammability Standards. Environmental science & technology 50 (19):10653–10660. doi:10.1021/acs.est.6b01602 [PubMed: 27552529]

Covaci A, Harrad S, Abdallah MA, Ali N, Law RJ, Herzke D, de Wit CA (2011) Novel brominated flame retardants: a review of their analysis, environmental fate and behaviour. Environment international 37 (2):532–556. doi:10.1016/j.envint.2010.11.007 [PubMed: 21168217]

de Wit CA (2002) An overview of brominated flame retardants in the environment. Chemosphere 46 (5):583–624. doi:http://dx.doi.org/10.1016/S0045-6535(01)00225-9 [PubMed: 11999784]

Dishaw LV, Macaulay LJ, Roberts SC, Stapleton HM (2014) Exposures, mechanisms, and impacts of endocrine-active flame retardants. Current opinion in pharmacology 19:125–133. doi:10.1016/j.coph.2014.09.018 [PubMed: 25306433]

Dishaw LV, Powers CM, Ryde IT, Roberts SC, Seidler FJ, Slotkin TA, Stapleton HM (2011) Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. Toxicology and applied pharmacology 256 (3):281–289. doi: 10.1016/j.taap.2011.01.005 [PubMed: 21255595]

Dodson RE, Perovich LJ, Covaci A, Van den Eede N, Ionas AC, Dirtu AC, Brody JG, Rudel RA (2012) After the PBDE phase-out: a broad suite of flame retardants in repeat house dust samples

from California. Environmental science & technology 46 (24):13056–13066. doi:10.1021/es303879n [PubMed: 23185960]

Dodson RE, Van den Eede N, Covaci A, Perovich LJ, Brody JG, Rudel RA (2014) Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. Environmental science & technology 48 (23):13625–13633. doi:10.1021/es503445c [PubMed: 25388620]

ECHA (2017) Tris(2-chloroethyl) phosphate. European Chemicals Agency. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.003.744. Accessed 07.28 2017

EPA (2009) Polybrominated Diphenyl Ethers (PBDEs) Action Plan. . https://www.epa.gov/sites/production/files/2015-09/documents/pbdes_ap_2009_1230_final.pdf. Accessed 03.07 2017

EPA (2014) Technical Fact Sheet - Polybrominated Diphenyl Ethers (PBDEs) and Polybrominated Biphenyls (PBBs). https://www.epa.gov/sites/production/files/2014-03/documents/ffrrofactsheet_contaminant_perchlorate_january2014_final_0.pdf.

EPA (2015) Flame Retardants used in Flexible Polyurethane Foam: An Alternatives Assessment Update. 744-R-15–02. https://www.epa.gov/sites/production/files/2015-08/documents/ffr_final.pdf. Accessed 02.08 2017

García M, Rodríguez I, Cela R (2007) Microwave-assisted extraction of organophosphate flame retardants and plasticizers from indoor dust samples. Journal of Chromatography A 1152 (1):280–286. doi:https://doi.org/10.1016/j.chroma.2006.11.046 [PubMed: 17140588]

Greaves AK, Letcher RJ (2017) A Review of Organophosphate Esters in the Environment from Biological Effects to Distribution and Fate. Bulletin of environmental contamination and toxicology 98 (1):2–7. doi:10.1007/s00128-016-1898-0 [PubMed: 27510993]

Greaves AK, Su G, Letcher RJ (2016) Environmentally relevant organophosphate triesters in herring gulls: In vitro biotransformation and kinetics and diester metabolite formation using a hepatic microsomal assay. Toxicology and applied pharmacology 308:59–65. doi:10.1016/j.taap.2016.08.007 [PubMed: 27523639]

Heitkamp MA, Freeman JP, McMillan DC, Cerniglia CE (1985) Fungal metabolism of tert-butylphenyl diphenyl phosphate. Applied and environmental microbiology 50 (2):265–273 [PubMed: 4051482]

Hoffman K, Butt CM, Chen A, Limkakeng AT, Stapleton HM, Jr. (2015a) High Exposure to Organophosphate Flame Retardants in Infants: Associations with Baby Products. Environmental science & technology 49 (24):14554–14559. doi:10.1021/acs.est.5b03577 [PubMed: 26551726]

Hoffman K, Butt CM, Webster TF, Preston EV, Hammel SC, Makey C, Lorenzo AM, Cooper EM, Carignan C, Meeker JD, Hauser R, Soubry A, Murphy SK, Price TM, Hoyo C, Mendelsohn E, Congleton J, Daniels JL, Stapleton HM (2017a) Temporal Trends in Exposure to Organophosphate Flame Retardants in the United States. Environmental science & technology letters 4 (3):112–118. doi:10.1021/acs.estlett.6b00475 [PubMed: 28317001]

Hoffman K, Daniels JL, Stapleton HM (2014) Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. Environment international 63:169–172. doi:10.1016/j.envint.2013.11.013 [PubMed: 24316320]

Hoffman K, Garantziotis S, Birnbaum LS, Stapleton HM (2015b) Monitoring indoor exposure to organophosphate flame retardants: hand wipes and house dust. Environmental health perspectives 123 (2):160–165. doi:10.1289/ehp.1408669 [PubMed: 25343780]

Hoffman K, Lorenzo A, Butt CM, Adair L, Herring AH, Stapleton HM, Daniels JL (2017b) Predictors of urinary flame retardant concentration among pregnant women. Environment international 98:96–101. doi:10.1016/j.envint.2016.10.007 [PubMed: 27745946]

Hoffman K, Sosa JA, Stapleton HM (2017c) Do flame retardant chemicals increase the risk for thyroid dysregulation and cancer? Current opinion in oncology 29 (1):7–13. doi:10.1097/cco.0000000000000335 [PubMed: 27755165]

Hornung RW, Reed LD (1990) Estimation of Average Concentration in the Presence of Nondetectable Values. Applied Occupational and Environmental Hygiene 5 (1):46–51. doi:10.1080/1047322X.1990.10389587

Hou R, Xu Y, Wang Z (2016) Review of OPFRs in animals and humans: Absorption, bioaccumulation, metabolism, and internal exposure research. Chemosphere 153:78–90. doi:http://dx.doi.org/10.1016/j.chemosphere.2016.03.003 [PubMed: 27010170]

Jayatilaka NK, Restrepo P, Williams L, Ospina M, Valentin-Blasini L, Calafat AM (2017) Quantification of three chlorinated dialkyl phosphates, diphenyl phosphate, 2,3,4,5-tetrabromobenzoic acid, and four other organophosphates in human urine by solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Analytical and bioanalytical chemistry 409 (5):1323–1332. doi:10.1007/s00216-016-0061-4 [PubMed: 27838756]

Kile ML, Scott RP, O'Connell SG, Lipscomb S, MacDonald M, McClelland M, Anderson KA (2016) Using silicone wristbands to evaluate preschool children's exposure to flame retardants. Environmental research 147:365–372. doi:10.1016/j.envres.2016.02.034 [PubMed: 26945619]

Lipscomb ST, McClelland MM, MacDonald M, Cardenas A, Anderson KA, Kile ML (2017) Cross-sectional study of social behaviors in preschool children and exposure to flame retardants. Environmental health : a global access science source 16 (1):23. doi:10.1186/s12940-017-0224-6 [PubMed: 28274271]

Luongo G, Ostman C (2016) Organophosphate and phthalate esters in settled dust from apartment buildings in Stockholm. Indoor air 26 (3):414–425. doi:10.1111/ina.12217 [PubMed: 25929991]

Makiguchi K, Ogasawara Y, Kikuchi S, Satoh T, Kakuchi T (2013) Diphenyl Phosphate as an Efficient Acidic Organocatalyst for Controlled/Living Ring-Opening Polymerization of Trimethylene Carbonates Leading to Block, End-Functionalized, and Macrocyclic Polycarbonates. Macromolecules 46 (5):1772–1782. doi:10.1021/ma4000495

Makiguchi K, Satoh T, Kakuchi T (2011) Diphenyl Phosphate as an Efficient Cationic Organocatalyst for Controlled/Living Ring-Opening Polymerization of δ-Valerolactone and ε-Caprolactone. Macromolecules 44 (7):1999–2005. doi:10.1021/ma200043x

Marklund A, Andersson B, Haglund P (2005) Organophosphorus flame retardants and plasticizers in air from various indoor environments. Journal of environmental monitoring : JEM 7 (8):814–819. doi:10.1039/b505587c [PubMed: 16049584]

Meeker JD, Cooper EM, Stapleton HM, Hauser R (2013a) Exploratory analysis of urinary metabolites of phosphorus-containing flame retardants in relation to markers of male reproductive health. Endocrine disruptors (Austin, Tex) 1 (1):e26306. doi:10.4161/endo.26306

Meeker JD, Cooper EM, Stapleton HM, Hauser R (2013b) Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environmental health perspectives 121 (5):580–585. doi:10.1289/ehp.1205907 [PubMed: 23461877]

Mendelsohn E, Hagopian A, Hoffman K, Butt CM, Lorenzo A, Congleton J, Webster TF, Stapleton HM (2016) Nail polish as a source of exposure to triphenyl phosphate. Environment international 86:45–51. doi:10.1016/j.envint.2015.10.005 [PubMed: 26485058]

Mizouchi S, Ichiba M, Takigami H, Kajiwara N, Takamuku T, Miyajima T, Kodama H, Someya T, Ueno D (2015) Exposure assessment of organophosphorus and organobromine flame retardants via indoor dust from elementary schools and domestic houses. Chemosphere 123:17–25. doi:10.1016/j.chemosphere.2014.11.028 [PubMed: 25532762]

Nishimaki-Mogami T, Minegishi K, Tanaka A, Sato M (1988) Isolation and identification of metabolites of 2-ethylhexyl diphenyl phosphate in rats. Archives of toxicology 61 (4):259–264 [PubMed: 3377680]

OEHHA (2016a) Current Proposition 65 List. California Office of Environmental Health Hazard Assessment https://oehha.ca.gov/proposition-65/proposition-65-list. Accessed 03.07 2017

OEHHA (2016b) Fact Sheet-Chlorinated Tris. https://www.p65warnings.ca.gov/sites/default/files/downloads/factsheets/chlorinated_tris_fact_sheet.pdf. Accessed 08.04 2017

Oliveri AN, Bailey JM, Levin ED (2015) Developmental exposure to organophosphate flame retardants causes behavioral effects in larval and adult zebrafish. Neurotoxicology and teratology 52 (Pt B):220–227. doi:10.1016/j.ntt.2015.08.008 [PubMed: 26344674]

Ouyang X, Weiss JM, de Boer J, Lamoree MH, Leonards PEG (2017) Non-target analysis of household dust and laundry dryer lint using comprehensive two-dimensional liquid

chromatography coupled with time-of-flight mass spectrometry. Chemosphere 166 (Supplement C):431–437. doi:https://doi.org/10.1016/j.chemosphere.2016.09.107 [PubMed: 27705830]

Preston EV, McClean MD, Claus Henn B, Stapleton HM, Braverman LE, Pearce EN, Makey CM, Webster TF (2017) Associations between urinary diphenyl phosphate and thyroid function. Environment international 101:158–164. doi:10.1016/j.envint.2017.01.020 [PubMed: 28162782]

Roberts SC, Macaulay LJ, Stapleton HM (2012) In vitro metabolism of the brominated flame retardants 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (TBB) and bis(2-ethylhexyl) 2,3,4,5-tetrabromophthalate (TBPH) in human and rat tissues. Chemical research in toxicology 25 (7): 1435–1441. doi:10.1021/tx300086x [PubMed: 22575079]

Sasaki K, Suzuki T, Takeda M, Uchiyama M (1984) Metabolism of phosphoric acid triesters by rat liver homogenate. Bulletin of environmental contamination and toxicology 33 (3):281–288 [PubMed: 6478075]

Schreder ED, La Guardia MJ (2014) Flame retardant transfers from U.S. households (dust and laundry wastewater) to the aquatic environment. Environmental science & technology 48 (19):11575–11583. doi:10.1021/es502227h [PubMed: 25288150]

Schreder ED, Uding N, La Guardia MJ (2016) Inhalation a significant exposure route for chlorinated organophosphate flame retardants. Chemosphere 150:499–504. doi:10.1016/j.chemosphere.2015.11.084 [PubMed: 26775187]

Solbu K, Thorud S, Hersson M, Ovrebo S, Ellingsen DG, Lundanes E, Molander P (2007) Determination of airborne trialkyl and triaryl organophosphates originating from hydraulic fluids by gas chromatography-mass spectrometry. Development of methodology for combined aerosol and vapor sampling. Journal of chromatography A 1161 (1–2):275–283. doi:10.1016/j.chroma.2007.05.087 [PubMed: 17574560]

Stapleton HM, Allen JG, Kelly SM, Konstantinov A, Klosterhaus S, Watkins D, McClean MD, Webster TF (2008) Alternate and new brominated flame retardants detected in U.S. house dust. Environmental science & technology 42 (18):6910–6916 [PubMed: 18853808]

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, Webster TF (2009) Detection of organophosphate flame retardants in furniture foam and U.S. house dust. Environmental science & technology 43 (19):7490–7495 [PubMed: 19848166]

Stapleton HM, Klosterhaus S, Keller A, Ferguson PL, van Bergen S, Cooper E, Webster TF, Blum A (2011) Identification of flame retardants in polyurethane foam collected from baby products. Environmental science & technology 45 (12):5323–5331. doi:10.1021/es2007462 [PubMed: 21591615]

Stapleton HM, Misenheimer J, Hoffman K, Webster TF (2014) Flame retardant associations between children's handwipes and house dust. Chemosphere 116:54–60. doi:10.1016/j.chemosphere.2013.12.100 [PubMed: 24485814]

Stapleton HM, Sharma S, Getzinger G, Ferguson PL, Gabriel M, Webster TF, Blum A (2012) Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out. Environmental science & technology 46 (24):13432–13439. doi:10.1021/es303471d [PubMed: 23186002]

Su G, Crump D, Letcher RJ, Kennedy SW (2014) Rapid in vitro metabolism of the flame retardant triphenyl phosphate and effects on cytotoxicity and mRNA expression in chicken embryonic hepatocytes. Environmental science & technology 48 (22):13511–13519. doi:10.1021/es5039547 [PubMed: 25350880]

Ta N, Li C, Fang Y, Liu H, Lin B, Jin H, Tian L, Zhang H, Zhang W, Xi Z (2014) Toxicity of TDCPP and TCEP on PC12 cell: changes in CAMKII, GAP43, tubulin and NF-H gene and protein levels. Toxicology letters 227 (3):164–171. doi:10.1016/j.toxlet.2014.03.023 [PubMed: 24717766]

Tullo A (2003) Great Lakes To Phase Out Flame Retardants. Chemical & Engineering News Archive 81 (45):13. doi:10.1021/cen-v081n045.p013a

Van den Eede N, Heffernan AL, Aylward LL, Hobson P, Neels H, Mueller JF, Covaci A (2015) Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. Environment international 74:1–8. doi:10.1016/j.envint.2014.09.005 [PubMed: 25277340]

Van den Eede N, Maho W, Erratico C, Neels H, Covaci A (2013) First insights in the metabolism of phosphate flame retardants and plasticizers using human liver fractions. Toxicology letters 223 (1): 9–15. doi:10.1016/j.toxlet.2013.08.012 [PubMed: 23994729]

Van den Eede N, Tomy G, Tao F, Halldorson T, Harrad S, Neels H, Covaci A (2016) Kinetics of tris (1-chloro-2-propyl) phosphate (TCIPP) metabolism in human liver microsomes and serum. Chemosphere 144:1299–1305. doi:10.1016/j.chemosphere.2015.09.049 [PubMed: 26473552]

van der Veen I, de Boer J (2012) Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88 (10):1119–1153. doi:10.1016/j.chemosphere.2012.03.067 [PubMed: 22537891]

Table 1.

Geometric mean and selected percentiles of bis(13-dichloro-2-propyl) phosphate (BDCIPP) concentrations in urine (in μg/L first row and in μg/g creatinine second row) for the U.S. population six years of age and older. Data from the National Health and Nutrition Examination Survey 2013-2014.

	Geometric mean (95% CI)	Selected percentile (95% CI)				N
		50th	75th	90th	95th	
Total	**.856** (.750-.976)	**.880** (.790-.970)	**2.21** (1.90-2.57)	**4.77** (3.88-5.77)	**7.23** (6.07-8.60)	2666
	.913 (.795-1.05)	**.874** (.746-1.03)	**1.90** (1.58-2.22)	**3.72** (2.88-4.97)	**6.30** (4.77-7.93)	2666
Age group						
6-11 years	**2.25** (1.82-2.77)	**2.31** (1.62-2.86)	**5.40** (3.69-7.33)	**11.3** (7.39-14.9)	**14.9** (10.8-25.4)	421
	2.89 (2.38-3.51)	**2.81** (2.28-3.66)	**6.10** (4.42-7.98)	**11.0** (8.41-14.3)	**14.8** (11.2-21.1)	421
12-19 years	**1.34** (1.13-1.59)	**1.43** (1.23-1.74)	**3.08** (2.39-3.99)	**5.58** (4.02-8.18)	**8.61** (5.58-9.87)	427
	1.14 (.931-1.40)	**1.10** (.887-1.45)	**2.20** (1.75-2.57)	**4.26** (2.75-6.46)	**6.82** (3.43-10.5)	427
20-59 years	**.818** (.747-.895)	**.850** (.760-.940)	**1.99** (1.76-2.25)	**4.03** (3.54-4.80)	**6.44** (5.09-7.23)	1266
	.850 (.756-.956)	**.824** (.696-.964)	**1.63** (1.40-1.90)	**2.93** (2.45-3.76)	**4.33** (3.29-5.91)	1266
60 years and older	**.497** (.379-.651)	**.430** (.290-.640)	**1.21** (.820-1.93)	**3.21** (2.04-4.83)	**5.20** (3.38-10.8)	552
	.599 (.475-.757)	**.542** (.407-.652)	**1.21** (.872-1.81)	**2.64** (1.82-3.75)	**4.03** (2.49-9.11)	552
Gender						
Males	**.914** (.802-1.04)	**.940** (.830-1.06)	**2.20** (1.87-2.59)	**4.49** (3.47-5.75)	**7.15** (5.18-9.41)	1344
	.837 (.723-.968)	**.825** (.696-.964)	**1.69** (1.41-2.05)	**3.07** (2.53-4.30)	**4.97** (3.71-6.96)	1344
Females	**.803** (.679-.949)	**.820** (.690-.960)	**2.25** (1.81-2.60)	**5.09** (3.98-6.30)	**7.48** (6.17-8.83)	1322
	.993 (.853-1.16)	**.917** (.750-1.15)	**2.07** (1.74-2.48)	**4.26** (3.18-5.63)	**7.02** (5.23-8.90)	1322
Race/ethnicity						
All Hispanic	**.977** (.840-1.14)	**1.02** (.850-1.22)	**2.20** (1.76-2.61)	**4.39** (3.30-5.43)	**7.39** (4.83-9.07)	671
	1.01 (.862-1.19)	**.977** (.833-1.19)	**1.92** (1.62-2.23)	**3.97** (2.87-4.69)	**5.80** (4.19-7.84)	671
Non-Hispanic Blacks	**.975** (.873-1.09)	**.960** (.860-1.12)	**2.16** (1.86-2.54)	**4.23** (3.43-4.94)	**6.18** (5.08-7.02)	587
	.750 (.674-.834)	**.731** (.630-.842)	**1.44** (1.29-1.60)	**2.81** (2.21-3.54)	**4.27** (3.38-5.80)	587
Non-Hispanic Whites	**.833** (.708-.980)	**.850** (.710-.990)	**2.26** (1.93-2.66)	**4.93** (3.98-6.44)	**7.42** (6.76-8.83)	1015
	.943 (.806-1.10)	**.896** (.708-1.09)	**2.00** (1.68-2.43)	**3.94** (3.00-5.11)	**6.77** (5.00-9.20)	1015
Others	**.666** (.495-.898)	**.660** (.430-.880)	**1.78** (1.17-3.17)	**4.34** (2.91-6.71)	**7.02** (4.23-13.0)	393
	.774 (.603-.992)	**.675** (.536-.895)	**1.63** (1.22-2.26)	**3.51** (2.47-6.53)	**6.91** (3.47-12.6)	393

CI, confidence interval; N, sample size; %, detection frequency

Table 2.

Geometric mean and selected percentiles of diphenyl phosphate (DPHP) concentrations in urine (in μg/L first row and in μg/g creatinine second row) for the U.S. population six years of age and older. Data from the National Health and Nutrition Examination Survey 2013-2014.

	Geometric mean (95% CI)	Selected percentile (95% CI)				N
		50th	75th	90th	95th	
Total	**.845** (.772-.925)	**.820** (.750-.920)	**1.77** (1.58-1.91)	**3.71** (3.14-4.63)	**6.23** (5.16-7.90)	2666
	.904 (.846-.966)	**.794** (.762-.850)	**1.60** (1.40-1.81)	**3.34** (2.84-4.10)	**5.51** (4.72-6.36)	2666
Age group						
6-11 years	**1.69** (1.37-2.10)	**1.70** (1.24-2.02)	**3.47** (2.71-4.35)	**8.17** (5.70-10.0)	**13.0** (8.17-17.8)	421
	2.18 (1.89-2.51)	**1.95** (1.66-2.26)	**3.70** (3.05-4.56)	**7.17** (5.72-8.69)	**9.66** (7.06-17.8)	421
12-19 years	**1.41** (1.19-1.67)	**1.44** (1.24-1.79)	**2.99** (2.20-3.57)	**5.31** (4.42-6.99)	**7.96** (6.28-13.0)	427
	1.21 (1.07-1.37)	**1.12** (.940-1.32)	**2.21** (1.62-2.79)	**3.77** (3.00-5.46)	**6.59** (4.02-8.47)	427
20-59 years	**.760** (.695-.832)	**.730** (.650-.830)	**1.51** (1.40-1.65)	**3.13** (2.59-3.78)	**5.50** (3.81-7.08)	1266
	.793 (.738-.853)	**.701** (.636-.771)	**1.31** (1.13-1.49)	**2.55** (2.20-3.17)	**4.70** (3.27-5.77)	1266
60 years and older	**.640** (.527-.777)	**.650** (.490-.760)	**1.24** (1.02-1.57)	**2.97** (1.83-3.81)	**5.05** (3.19-6.61)	552
	.767 (.645-.912)	**.688** (.584-.820)	**1.28** (1.06-1.63)	**3.11** (2.16-4.18)	**4.89** (4.18-5.52)	552
Gender						
Males	**.778** (.695-.871)	**.800** (.690-.910)	**1.56** (1.38-1.73)	**3.00** (2.44-3.71)	**4.91** (3.68-6.23)	1344
	.715 (.671-.761)	**.653** (.605-.715)	**1.14** (1.08-1.28)	**2.26** (1.96-2.67)	**3.91** (2.69-4.90)	1344
Females	**.915** (.826-1.01)	**.890** (.760-1.00)	**2.02** (1.81-2.25)	**4.81** (3.56-5.81)	**8.17** (5.69-11.3)	1322
	1.13 (1.05-1.23)	**1.00** (.910-1.11)	**2.02** (1.80-2.36)	**4.65** (3.60-5.46)	**6.84** (5.77-8.47)	1322
Race/ethnicity						
All Hispanic	**.880** (.775-1.00)	**.830** (.740-1.02)	**1.79** (1.48-2.29)	**3.71** (2.97-4.51)	**5.51** (4.43-6.40)	671
	.913 (.807-1.03)	**.800** (.669-.944)	**1.56** (1.32-1.95)	**3.24** (2.69-4.04)	**5.18** (3.89-6.50)	671
Non-Hispanic Blacks	**1.09** (.944-1.27)	**1.05** (.920-1.16)	**2.16** (1.81-2.65)	**5.06** (3.33-8.22)	**8.69** (5.85-13.5)	587
	.842 (.701-1.01)	**.701** (.627-.789)	**1.57** (1.19-2.06)	**3.53** (2.37-5.46)	**6.26** (4.01-9.66)	587
Non-Hispanic Whites	**.819** (.726-.923)	**.800** (.680-.930)	**1.71** (1.49-1.87)	**3.54** (2.98-4.91)	**6.23** (5.11-8.17)	1015
	.930 (.855-1.01)	**.824** (.757-.931)	**1.64** (1.43-1.85)	**3.55** (2.79-4.54)	**5.52** (4.56-6.84)	1015
Others	**.681** (.567-.817)	**.750** (.540-.960)	**1.56** (1.27-1.91)	**2.96** (2.40-3.85)	**4.80** (3.21-7.07)	393
	.789 (.704-.885)	**.752** (.633-.843)	**1.40** (1.03-1.75)	**2.58** (1.97-3.36)	**3.77** (2.83-5.04)	393

CI, confidence interval; N, sample size; %, detection frequency

Table 3.

Geometric mean and selected percentiles of bis(2-chloroethyl) phosphate (BCEP) concentrations in urine (in μg/L first row and in μg/g creatinine second row) for the U.S. population six years of age and older. Data from the National Health and Nutrition Examination Survey 2013-2014.

	Geometric mean (95% CI)	Selected percentile (95% CI)				N
		50th	75th	90th	95th	
Total	**.419** (.376-.466)	**.390** (.350-.420)	**.950** (.840-1.12)	**2.31** (1.90-2.82)	**3.94** (3.08-5.17)	2666
	.447 (.396-.505)	**.388** (.337-.444)	**.856** (.743-.981)	**2.03** (1.72-2.38)	**3.94** (2.74-5.13)	2666
Age group						
6-11 years	**.662** (.545-.804)	**.660** (.500-.850)	**1.50** (1.05-1.77)	**2.91** (1.77-5.63)	**5.63** (2.99-7.34)	421
	.855 (.720-1.02)	**.833** (.676-.981)	**1.60** (1.18-2.12)	**4.25** (3.39-5.43)	**6.83** (4.97-8.99)	421
12-19 years	**.602** (.508-.713)	**.570** (.450-.730)	**1.47** (.950-2.21)	**3.18** (2.57-3.80)	**4.24** (3.76-6.40)	427
	.516 (.429-.620)	**.442** (.350-.568)	**1.06** (.768-1.38)	**2.33** (1.70-3.03)	**4.48** (2.42-6.77)	427
20-59 years	**.394** (.352-.440)	**.370** (.310-.410)	**.880** (.720-1.09)	**2.12** (1.82-2.64)	**3.55** (2.77-4.67)	1266
	.410 (.357-.471)	**.333** (.297-.397)	**.754** (.635-.886)	**1.89** (1.41-2.37)	**3.32** (2.44-4.86)	1266
60 years and older	**.336** (.278-.405)	**.300** (.230-.380)	**.810** (.590-.900)	**1.75** (1.09-2.96)	**3.22** (2.13-7.38)	552
	.403 (.348-.467)	**.367** (.316-.438)	**.722** (.559-.909)	**1.68** (1.06-2.53)	**2.61** (1.68-7.51)	552
Gender						
Males	**.458** (.401-.523)	**.420** (.390-.470)	**1.03** (.890-1.28)	**2.46** (1.85-3.07)	**4.00** (3.00-6.92)	1344
	.420 (.370-.476)	**.373** (.322-.406)	**.826** (.725-.954)	**2.01** (1.50-2.43)	**3.70** (2.44-5.50)	1344
Females	**.384** (.335-.439)	**.350** (.310-.390)	**.850** (.740-1.03)	**2.28** (1.90-2.75)	**3.90** (2.98-4.64)	1322
	.476 (.417-.543)	**.407** (.350-.467)	**.909** (.742-1.04)	**2.06** (1.75-2.41)	**3.99** (2.61-5.26)	1322
Race/ethnicity						
All Hispanic	**.478** (.398-.575)	**.470** (.390-.570)	**1.06** (.770-1.52)	**2.38** (1.71-3.50)	**4.00** (3.01-5.35)	671
	.495 (.406-.604)	**.472** (.371-.585)	**.980** (.736-1.36)	**2.27** (1.69-2.75)	**3.14** (2.53-3.94)	671
Non-Hispanic Blacks	**.483** (.431-.541)	**.400** (.380-.480)	**1.03** (.820-1.26)	**2.41** (1.95-2.88)	**4.26** (2.84-5.60)	587
	.374 (.321-.435)	**.328** (.267-.450)	**.732** (.630-.867)	**1.56** (1.18-1.80)	**2.41** (1.86-3.17)	587
Non-Hispanic Whites	**.394** (.352-.441)	**.360** (.310-.400)	**.910** (.820-1.09)	**2.28** (1.85-2.75)	**3.73** (2.82-5.41)	1015
	.446 (.393-.506)	**.379** (.333-.437)	**.857** (.731-1.00)	**2.03** (1.64-2.44)	**4.68** (2.51-5.58)	1015
Others	**.414** (.328-.522)	**.390** (.290-.490)	**.850** (.690-1.03)	**2.86** (1.42-4.04)	**5.23** (3.55-6.93)	393
	.480 (.401-.573)	**.420** (.333-.506)	**.836** (.630-1.22)	**2.31** (1.62-3.23)	**4.09** (2.74-9.58)	393

CI, confidence interval; N, sample size; %, detection frequency

Table 4.

Geometric mean and selected percentiles of dibutyl phosphate (DNBP) concentrations in urine (in μg/L first row and in μg/g creatinine second row) for the U.S. population six years of age and older. Data from the National Health and Nutrition Examination Survey 2013-2014.

	Geometric mean (95% CI)	Selected percentile (95% CI)				N
		50th	75th	90th	95th	
Total	**.188** (.162-.217)	**.250** (.220-.280)	**.370** (.350-.400)	**.520** (.490-.570)	**.670** (.610-.750)	2666
	.200 (.171-.234)	**.215** (.186-.246)	**.357** (.321-.393)	**.545** (.500-.583)	**.719** (.612-.813)	2666
Age group						
6-11 years	**.272** (.203-.365)	**.340** (.270-.390)	**.490** (.450-.590)	**.790** (.660-.980)	**1.10** (.740-5.23)	421
	.350 (.266-.461)	**.373** (.304-.435)	**.543** (.484-.660)	**.909** (.682-1.47)	**1.47** (.875-4.17)	421
12-19 years	**.207** (.175-.244)	**.270** (.240-.320)	**.390** (.340-.440)	**.570** (.450-.750)	**.790** (.600-1.19)	427
	.177 (.152-.205)	**.191** (.157-.223)	**.286** (.256-.325)	**.440** (.373-.548)	**.566** (.481-.619)	427
20-59 years	**.169** (.142-.200)	**.220** (.170-.260)	**.340** (.320-.380)	**.490** (.430-.520)	**.590** (.520-.660)	1266
	.175 (.145-.212)	**.190** (.152-.231)	**.318** (.270-.366)	**.500** (.417-.548)	**.606** (.541-.758)	1266
60 years and older	**.205** (.177-.238)	**.280** (.230-.310)	**.380** (.350-.450)	**.530** (.470-.620)	**.710** (.550-1.00)	552
	.246 (.215-.281)	**.261** (.233-.304)	**.395** (.347-.473)	**.577** (.488-.704)	**.761** (.596-1.10)	552
Gender						
Males	**.191** (.166-.221)	**.260** (.220-.290)	**.380** (.350-.410)	**.530** (.500-.570)	**.670** (.590-.850)	1344
	.175 (.151-.204)	**.192** (.159-.227)	**.308** (.278-.342)	**.479** (.415-.515)	**.582** (.543-.619)	1344
Females	**.184** (.157-.216)	**.240** (.210-.270)	**.360** (.330-.400)	**.510** (.460-.580)	**.670** (.590-.790)	1322
	.227 (.191-.271)	**.238** (.205-.286)	**.407** (.361-.444)	**.585** (.542-.704)	**.763** (.696-.892)	1322
Race/ethnicity						
All Hispanic	**.185** (.151-.228)	**.230** (.190-.280)	**.360** (.330-.420)	**.510** (.450-.590)	**.700** (.570-.870)	671
	.191 (.158-.231)	**.200** (.174-.246)	**.323** (.281-.370)	**.518** (.441-.571)	**.651** (.554-.864)	671
Non-Hispanic Blacks	**.235** (.206-.268)	**.300** (.280-.320)	**.420** (.370-.460)	**.610** (.520-.740)	**.810** (.690-.980)	587
	.181 (.157-.208)	**.194** (.167-.217)	**.323** (.269-.375)	**.473** (.424-.519)	**.609** (.519-.734)	587
Non-Hispanic Whites	**.189** (.161-.222)	**.250** (.210-.280)	**.370** (.340-.400)	**.510** (.480-.570)	**.640** (.590-.740)	1015
	.214 (.179-.257)	**.234** (.196-.265)	**.378** (.333-.417)	**.561** (.521-.617)	**.762** (.617-.893)	1015
Others	**.131** (.106-.162)	**.130** (.070-.210)	**.310** (.260-.380)	**.480** (.370-.610)	**.660** (.470-.810)	393
	.152 (.127-.181)	**.154** (.127-.195)	**.302** (.241-.342)	**.487** (.375-.595)	**.640** (.505-.708)	393

CI, confidence interval; N, sample size; %, detection frequency

Table 5.

Geometric mean and selected percentiles of bis(1-chloro-2-propyl) phosphate (BCIPP) concentrations in urine (in μg/L first row and in μg/g creatinine second row) for the U.S. population six years of age and older. Data from the National Health and Nutrition Examination Survey 2013-2014.

	Geometric mean (95% CI)	Selected percentile (95% CI)				N
		50th	75th	90th	95th	
Total	**.188** (.174-.202)	**.160** (.140-.180)	**.380** (.330-.410)	**.790** (.690-.880)	**1.25** (1.07-1.48)	2666
	.200 (.184-.218)	**.187** (.173-.201)	**.347** (.313-.375)	**.701** (.619-.787)	**1.21** (1.03-1.49)	2666
Age group						
6-11 years	**.267** (.227-.314)	**.250** (.200-.300)	**.490** (.400-.590)	**1.08** (.630-1.98)	**2.12** (1.28-4.21)	421
	.344 (.296-.399)	**.349** (.292-.381)	**.568** (.500-.701)	**1.37** (.953-2.13)	**2.41** (1.26-3.30)	421
12-19 years	**.190** (.164-.220)	**.160** (.130-.220)	**.410** (.290-.520)	**.670** (.600-.790)	**1.04** (.700-1.31)	427
	.162 (.135-.194)	**.159** (.130-.191)	**.314** (.226-.384)	**.500** (.416-.667)	**.753** (.500-1.26)	427
20-59 years	**.188** (.172-.206)	**.160** (.130-.180)	**.360** (.320-.420)	**.800** (.700-.960)	**1.30** (1.07-1.73)	1266
	.196 (.175-.219)	**.179** (.165-.198)	**.328** (.281-.375)	**.729** (.550-.921)	**1.27** (.940-1.73)	1266
60 years and older	*	**.130** (<LOD-.160)	**.330** (.250-.360)	**.630** (.490-.840)	**1.02** (.830-1.25)	552
	*	**.189** (<LOD-.217)	**.304** (.280-.333)	**.587** (.467-.665)	**.840** (.665-1.23)	552
Gender						
Males	**.199** (.183-.217)	**.170** (.140-.200)	**.420** (.360-.480)	**.880** (.760-.980)	**1.34** (1.17-1.67)	1344
	.182 (.165-.201)	**.167** (.152-.179)	**.333** (.284-.382)	**.722** (.610-.842)	**1.21** (1.00-1.56)	1344
Females	*	**.150** (.130-.180)	**.340** (.280-.390)	**.700** (.560-.830)	**1.11** (.870-1.52)	1322
	*	**.210** (.187-.233)	**.352** (.316-.390)	**.688** (.560-.847)	**1.26** (.921-1.53)	1322
Race/ethnicity						
All Hispanic	*	**.150** (.110-.180)	**.320** (.310-.360)	**.660** (.550-.780)	**1.11** (.860-1.50)	671
	*	**.171** (.153-.189)	**.333** (.305-.350)	**.556** (.470-.735)	**.977** (.638-1.23)	671
Non-Hispanic Blacks	**.190** (.171-.212)	**.170** (.150-.200)	**.340** (.310-.390)	**.690** (.580-.820)	**1.01** (.820-1.23)	587
	.146 (.124-.172)	**.144** (.116-.163)	**.250** (.229-.292)	**.459** (.391-.550)	**.727** (.574-.890)	587
Non-Hispanic Whites	**.189** (.172-.208)	**.150** (.130-.180)	**.380** (.330-.450)	**.820** (.700-.990)	**1.31** (1.07-1.73)	1015
	.214 (.195-.235)	**.198** (.179-.219)	**.358** (.318-.389)	**.777** (.644-.965)	**1.49** (1.04-1.80)	1015
Others	**.203** (.165-.250)	**.180** (.130-.240)	**.410** (.330-.530)	**.770** (.650-1.00)	**1.28** (.890-2.26)	393
	.235 (.197-.281)	**.216** (.189-.259)	**.421** (.351-.541)	**.787** (.621-1.00)	**1.30** (.865-1.66)	393

CI, confidence interval; N, sample size; %, detection frequency

< LOD means less than the limit of detection (LOD= 0.1 μg/L).

* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

Table 6.

Weighted Pearson's correlation coefficients describing bivariate associations among OPFR urinary metabolites[a].

Variable	log_DPHP	log_BDCIPP	log_DNBP	log_BCEP	log_BCIPP
log_DPHP	1 (2447)				
log_BDCIPP	0.45 (2,319)	1 (2,461)			
log_DNBP	0.29 (2,045)	0.29 (2,026)	1 (2,151)		
log_BCEP	0.36 (2,257)	0.41 (2,256)	0.20 (1,979)	1 (2,375)	
log_BCIPP	0.19 (1,580)	0.28 (1,587)	0.12 (1,433)	0.29 (1,563)	1 (1,632)

[a]All correlations were statistically significant ($p < 0.0001$). Number of samples with detectable concentrations are in parentheses. Concentrations were not corrected for creatinine.

Table 7.

Adjusted geometric mean urinary concentrations (95% confidence interval, CI) in μg/L of OPFR biomarkers in various demographic groups.[a]

VARIABLE	BIOMARKER				
	BDCIPP	DPHP	BCEP	DNBP	BCIPP
Male	0.76 (0.67-0.87)			0.17 (0.15-0.20)	
Female	0.96 (0.84-1.09)			0.21 (0.17-0.25)	
6-11 years				0.32 (0.24-0.43)	0.31 (0.27-0.36)
12-19 years				0.18 (0.15-0.21)	0.17 (0.14-0.19)
20-59 years				0.17 (0.14-0.20)	0.19 (0.17-0.21)
≥60 years				0.22 (0.19-0.25)	0.17 (0.15-0.18)
Hispanic				0.18 (0.15-0.22)	0.17 (0.15-0.18)
non-Hispanic white				0.20 (0.16-0.24)	0.20 (0.18-0.22)
non-Hispanic black				0.18 (0.16-0.21)	0.15 (0.13-0.17)
Other race/ethnicity				0.14 (0.12-0.17)	0.21 (0.18-0.25)
Male: 6-11 years		1.91 (1.60-2.28)	0.76 (0.62-0.92)		
Female: 6-11 years		2.25 (1.90-2.66)	0.87 (0.67-1.13)		
Male: 12-19 years		0.91 (0.75-1.11)	0.52 (0.43-0.63)		
Female: 12-19 years		1.49 (1.30-1.70)	0.45 (0.36-0.56)		
Male: 20-59 years		0.58 (0.52-0.64)	0.35 (0.29-0.41)		
Female: 20-59 years		0.95 (0.86-1.05)	0.42 (0.37-0.49)		
Male: ≥60 years		0.52 (0.44-0.62)	0.37 (0.30-0.45)		
Female: ≥60 years		0.91 (0.76-1.07)	0.39 (0.33-0.46)		
Male, Hispanic		0.60 (0.53-0.66)			
Female, Hispanic		1.07 (0.94-1.22)			
Male, non-Hispanic white		0.71 (0.64-0.78)			
Female, non-Hispanic white		1.12 (1.02-1.23)			
Male, non-Hispanic black		0.57 (0.52-0.62)			
Female, non-Hispanic black		0.98 (0.79-1.23)			
Male, Other race/ethnicity		0.61 (0.54-0.69)			
Female, Other race/ethnicity		0.83 (0.74-0.94)			
6-11 years, Hispanic	2.36 (1.79-3.11)		0.83 (0.59-1.18)		

VARIABLE	BIOMARKER				
	BDCIPP	DPHP	BCEP	DNBP	BCIPP
6-11 years, non-Hispanic white	3.48 (2.83-4.27)		0.88 (0.68-1.13)		
6-11 years, non-Hispanic black	1.82 (1.47-2.25)		0.54 (0.43-0.67)		
6-11 years, Other race/ethnicity	2.30 (1.33-3.99)		0.78 (0.54-1.12)		
12-19 years, Hispanic	0.90 (0.75-1.09)		0.54 (0.40-0.73)		
12-19 years, non-Hispanic white	1.21 (0.92-1.59)		0.48 (0.36-0.63)		
12-19 years, non-Hispanic black	0.79 (0.63-0.99)		0.38 (0.28-0.50)		
12-19 years, Other race/ethnicity	1.10 (0.75-1.62)		0.55 (0.40-0.74)		
20-59 years, Hispanic	0.86 (0.72-1.02)		0.40 (0.32-0.50)		
20-59 years, non-Hispanic white	0.85 (0.74-0.97)		0.40 (0.34-0.46)		
20-59 years, non-Hispanic black	0.62 (0.55-0.71)		0.32 (0.27-0.37)		
20-59 years, Other race/ethnicity	0.60 (0.49-0.74)		0.37 (0.30-0.45)		
≥60 years, Hispanic	0.58 (0.46-0.73)		0.42 (0.32-0.54)		
≥60 years, non-Hispanic white	0.59 (0.45-0.75)		0.36 (0.31-0.42)		
≥60 years, non-Hispanic black	0.43 (0.35-0.54)		0.36 (0.28-0.46)		
≥60 years, Other race/ethnicity	0.50 (0.32-0.78)		0.53 (0.32-0.88)		

[a]The final multivariate regression models included: sex, age, race, sex*age, and sex*race (DPHP); race, sex, age, age*race (BDCIPP); race, sex, age, sex*age, and age*race (BCEP); race, age, and sex (DNBP); and age and race (BCIPP).