# Evaluating Exposures to Semi-Volatile Organic Compounds in Indoor Environments

# Using Silicone Wristbands

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy in Environment in the Graduate School
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ABSTRACT

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## Abstract

Semi-volatile organic compounds (SVOCs) are used in consumer products in a wide variety of applications such as flame retardants, plasticizers, pesticides, preservatives, and fragrances. Due to their extensive use in everyday products, SVOCs are widely detected in indoor environments, and human exposure is common and often chronic. As the wealth of toxicological data examining the negative health impacts of these compounds grows, the need for reliable tools to accurately measure human exposure becomes increasingly more crucial. In the past few decades, external exposure to these compounds have been evaluated through measurements in indoor air, house dust, and hand wipes, all of which have been shown to be associated with internal dose (e.g., concentrations in urine or blood). However, there are significant limitations to using each of these approaches to characterizing exposure. In recent years, silicone wristbands have been used as personal passive samplers for evaluating ambient exposure to a wide array of consumer product and industrial compounds. While over a thousand chemicals have been reported to be detected on the wristbands, very few studies have measured the concentrations on wristbands and determined how well they correlate to established biomarkers of exposure. This dissertation research sought to evaluate the use of silicone wristbands for measuring personal exposure to three classes of SVOCs- organophosphate esters (OPEs), brominated flame retardants (BFRs), and

phthalates. The central hypothesis is that wristbands are an effective tool for evaluating personal exposure to SVOCs and provide more accurate measures of exposure compared to tools currently in use.

Within the first aim of this dissertation research, paired samples of polyurethane foam (collected from sofas), house dust, and serum were analyzed for flame retardants (FRs) chemicals and associations were evaluated. The detection of two FR mixtures, PentaBDE and FM 550, in foam was significantly associated with 4 to 6.5 times as high concentrations of their primary components in house dust ($p<0.01$). These relationships were modified by the size of the sofa footprint within the room and dust-loading rates. PentaBDE in foam was also associated with higher levels of individual PBDE congeners in serum, particularly two of the primary congeners BDE-47 and -153. Participants who lived in a home with a sofa containing PentaBDE had serum BDE-47 levels that were 2.5 times as high as participants whose sofa did not contain PentaBDE ($p<0.01$). This study was the first to relate a specific FR application in a consumer product with house dust and a known biomarker of exposure.

For the second aim of this research, adult exposure to OPEs and BFRs were evaluated using silicone wristbands. OPEs quantified on the wristbands were significantly associated with metabolites from pooled urine samples, and polybrominated diphenyl ethers (PBDEs) on the wristbands were similarly correlated to PBDE levels in serum ($r_s$=0.4-0.6, $p<0.05$). Several novel BFR compounds which lack

verified biomarkers of exposure were also measured on the wristbands and reported for the first time. These two studies were the first to evaluate FR concentrations on wristbands with known biomarkers and represent two of now four published manuscripts providing evidence that measurements on wristbands are predictive of internal dose.

In the third aim of this research, children's exposure to OPEs, phthalates, and BFRs were examined using silicone wristbands. The ability of the wristband measurements to predict urinary metabolite levels of OPEs and phthalates was compared to that of hand wipes and house dust. Across the three classes, the children's wristband concentrations were positively and significantly associated with a number of their corresponding biomarkers in both urine and serum, similar to observations in our adult cohort. For OPEs, phthalates, and PBDEs, the wristbands were found to have similar or an improved utility, compared to hand wipes and dust, for evaluating children's exposures to these compounds. For instance, one of the OPEs, 4-tertbutylphenyl diphenyl phosphate (4tBPDPP), on wristbands was more strongly correlated to its urinary metabolite, tert-butyl phenyl phenyl phosphate (tb-PPP), compared to that on hand wipes and dust ($r_s$=0.35, $p<0.01$, compared to $r_s$=0.16 and 0.05 for hand wipes and dust, respectively). For the phthalate benzyl butyl phthalate (BBP), wristbands and hand wipes were similarly associated with the urinary metabolite, mono benzyl phthalate (MBzP), but both were stronger than the dust correlation ($r_s$=0.56 for

wristbands and hand wipes, $p<0.001$; $r_s=0.23$ for dust, $p<0.05$). Similar results were observed among the PBDEs on the three exposure media and their serum biomarkers, although the magnitudes of correlation with serum were more similar for wristbands and dust.

Taken together this dissertation research provides some of the first insights on the evaluation of personal exposures to SVOCs using silicone wristbands. It includes six distinct studies evaluating human exposure to sixty-five chemicals from three classes of compounds. Further, this research offers novel contributions to the field of exposure science, evaluating the relationship between wristbands and established biomarkers of exposure and comparing them to the existing tools used in standard exposure assessments. Wristbands have the potential to serve as an inexpensive and non-invasive medium for evaluating human exposure to chemical mixtures. This work provides support for their use in large-scale research efforts to characterize SVOC exposures. Additional research should continue to assess wristbands for their ability to measure meaningful exposures for additional classes of chemicals, and importantly, identify the pathways of exposure (e.g., dermal absorption, inhalation, etc.) that are captured by the wristbands.

## Dedication

To Iris, for never leaving my side.

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# List of Abbreviations

**Chemical Classes and Compounds**

| | |
|---|---|
| BFR (*Class*) | Brominated Flame Retardant |
| EH-TBB | 2,3,4,5-tetrabromoethylhexylbenzoate |
| BEH-TEBP | Bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate |
| OBIND | Octabromotrimethylphenylindane |
| DBDPE | Decabromodiphenyl ethane |
| TBBPA-DBPE | Tetrabromobisphenol A bis(2,3-dibromopropyl ether) |
| TTBP-TAZ | 2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine |
| PBDE | Polybrominated Diphenyl Ether |
| BDE-47 | 2,2′,4,4′-tetrabromodiphenyl ether |
| BDE-99 | 2,2′,4,4′,5-pentabromodiphenyl ether |
| BDE-100 | 2,2′,4,4′,6-pentabromodiphenyl ether |
| BDE-153 | 2,2′,4,4′,5,5′-hexabromodiphenyl ether |
| BDE-154 | 2,2′4,4′,5,6′-hexabromodiphenyl ether |
| BDE-209 | Decabromodiphenyl ether |
| PentaBDE | Commercial PentaBDE mixture |
| DecaBDE | Commercial DecaBDE mixture |
| OPE (*Class*) | Organophosphate Ester |
| TCEP | Tris(2-chloroethyl) phosphate |

| | |
|---|---|
| TCIPP | Tris(1-chloroisopropyl) phosphate |
| TDCIPP | Tris(1,3-dichloroisopropyl) phosphate |
| TBOEP | Tris(2-butoxyethyl) phosphate |
| EHDPHP | 2-ethylhexyldiphenyl phosphate |
| TPHP | Triphenyl phosphate |
| ITP | Isopropylated triaryl phosphate |
| 2IPPDPP | 2-isopropylphenyl diphenyl phosphate |
| 3IPPDPP | 3-isopropylphenyl diphenyl phosphate |
| 4IPPDPP | 4-isopropylphenyl diphenyl phosphate |
| 24DIPPDPP | 2,4-diisopropylphenyl diphenyl phosphate |
| B2IPPPP | Bis(2-isopropylphenyl) phenyl phosphate |
| B3IPPPP | Bis(3-isopropylphenyl) phenyl phosphate |
| B4IPPPP | Bis(4-isopropylphenyl) phenyl phosphate |
| B24IPPPP | Bis(2,4-diisopropylphenyl) phenyl phosphate |
| MPP | Methyl phenyl phosphate |
| TBPP | Tert-Butylated triaryl phosphate |
| 2tBPDPP | 2-tert-butylphenyl diphenyl phosphate |
| 4tBPDPP | 4-tert-butylphenyl diphenyl phosphate |
| B2tBPPP | Bis(2-tertbutylphenyl) phenyl phosphate |
| B4tBPPP | Bis(4-tert-butylphenyl) phenyl phosphate |

| | |
|---|---|
| T4tBPP | Tris(4-tertbutylphenyl) phosphate |
| Phthalate/Non-phthalate Plasticizers (*Class*) | |
| DMP | Dimethyl phthalate |
| DEP | Diethyl phthalate |
| DiBP | Di-isobutyl phthalate |
| DBP | Dibutyl phthalate |
| BBP | Benzylbutyl phthalate |
| DEHP | Bis(2-ethylhexyl) phthalate |
| DiNP | Di-isononyl phthalate |
| DEHTP | Bis(2-ethylhexyl) terephthalate |
| DEHA | Bis(2-ethylhexyl) adipate |
| TOTM | Tris(2-ethylhexyl) trimellitate |
| DINCH | 1,2-cyclohexane dicarboxylic acid, diisononyl ester |
| PAH | Polycyclic aromatic hydrocarbon |
| PFAS | Per- and polyfluoroalkyl substance |
| PFR | Organophosphate flame retardant |
| Urinary Metabolites (OPEs) | |
| BCIPP | Bis(2-chloroisopropyl) phosphate |
| BCIPHIPP | Bis(1-chloroisopropyl) 1-hydroxyisopropyl phopshate |
| BDCIPP | Bis(1,3-dichloroisopropyl) phosphate |

| | |
|---|---|
| DPHP | Diphenyl phosphate |
| ip-PPP | Isopropyl phenyl phenyl phosphate |
| tb-PPP | Tert-butyl phenyl phenyl phosphate |

Urinary Metabolites (Phthalates)

| | |
|---|---|
| MEP | Monoethyl phthalate |
| MHiBP | Mono-2-hydroxy-isobutyl phthalate |
| MiBP | Mono-isobutyl phthalate |
| MHBP | Mono-3-hydroxybutyl phthalate |
| MCPP | Mono-3-carboxypropyl phthalate |
| MBzP | Monobenzyl phthalate |
| MEHP | Mono-2-ethylheyxl phthalate |
| MEOHP | Mono-2-ethyl-5-oxohexyl phthalate |
| MEHHP | Mono-2-ethyl-5-hydroxyhexyl phthalate |
| MECPP | Mono-2-ethyl-5-carboxypentyl phthalate |
| MCOP | Mono-carboxyisooctyl phthalate |
| MONP | Mono-oxo-isononyl phthalate |
| MCNP | Mono-carboxyisononyl phthalate |
| MNP | Mono-isononyl phthalate |
| MECPTP | Mono-2-ethyl-5-carboxypentyl terephthalate |
| MEHHTP | Mono-2-ethyl-5-hydroxyhexyl terephthalate |

| | |
|---|---|
| MHINCH | Cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester |
| MCOCH | Cyclohexane-1,2-dicarboxylic acid monocarboxyisooctyl ester |

**Reagents and Materials**

| | |
|---|---|
| CDE-141 | 2,2′,3,4,5,5′-hexachlorodiphenyl ether |
| DCM | Dichloromethane |
| FBDE-69 | 4′-fluoro-2,3′,4,6-tetrabromodiphenyl ether |
| FBDE-208 | 4′-fluoro-2,2′,3,3′,4,5,5′,6,6′-nonabromodiphenyl ether |
| HCl | Hydrochloric acid |
| KCl | Potassium chloride |
| MTBE | Methyl tert-butyl ether |
| PTFE | Polytetrafluoroethylene |

**Other Terms**

| | |
|---|---|
| CDC | Centers of Disease Control & Prevention |
| CPSC | Consumer Product Safety Commission |
| ECNI | Electron capture negative ionization |
| EI | Electron ionization |
| FM 550 | Commercial Firemaster® 550 mixture |
| FM 600 | Commercial Firemaster® 600 mixture |

| | |
|---|---|
| FR | Flame retardant |
| GC/MS | Gas chromatography/mass spectrometry |
| GC/MS/MS | Gas chromatography tandem mass spectrometry |
| $K_{oa}$ | Octanol-air partitioning coefficient |
| $K_{ow}$ | Octanol-water partitioning coefficient |
| $K_P$ | Particle-gas partitioning coefficient |
| LC/MS/MS | Liquid chromatography tandem mass spectrometry |
| MDL | Method detection limit |
| NHANES | National Health and Nutrition Examination Survey |
| NIST | National Institute of Standards and Technology |
| NOAEL | No-observed-adverse-effect level |
| PUF | Polyurethane foam |
| QA/QC | Quality assurance/quality control |
| RfD | Reference dose |
| SG | Specific gravity |
| SPE | Solid-phase extraction |
| SRM | Standard reference material |
| SVOC | Semi-volatile organic compound |
| T3 | 3,3′,5-triiodothyronine |
| TB 117 | Technical Bulletin 117 |

| | |
|---|---|
| TB 117-2013 | Technical Bulletin 117-2013 |
| TSH | Thyroid stimulating hormone |
| VOC | Volatile organic compound |
| XRF | X-ray fluorescence |

# Acknowledgements

First, I would like to thank my advisor, Dr. Heather Stapleton, for her mentorship. I cannot thank you enough for the kindness, support, and guidance that you have offered me over the last five years. You are someone I respect immensely, and I feel incredibly lucky to have had the opportunity to work with you. I would also like to thank Dr. Kate Hoffman, who in many ways has served as a second, unofficial advisor to me. Kate- thank you for your advice, for your mentorship, and for always challenging me to think more clearly and deeply about my research. Additionally, I would like to thank my committee, Dr. Lee Ferguson, Dr. Tom Webster, and Dr. Jim Zhang, for guiding me through my dissertation research.

I have been extremely fortunate to have found friends in my colleagues and lab mates. A huge thank you to all of my lab mates, past and present, who have offered so much support, perspective, and good humor through all of the best and more challenging times. I'm especially indebted to my office mates, Chris Leonetti, Alli Phillips, Matt Ruis, Jess Levasseur, and my pseudo-office mate Emina Hodzic- I could not have completed this dissertation without you.

To my former research mentors, Dr. AJ Shaka and Dr. Dele Ogunseitan- thank you for believing in me and instilling in me a love for research and a curiosity for knowledge.

The last five years have included a lot of challenging times and moments of personal growth, and I've been incredibly lucky to have close friendships that have spanned multiple time zones and thousands of miles. To Janelle Miyashiro, Amy Kasahara, Catherine Donnelly, and Tracey Baldemor- thank you for always having my back, for picking up the phone when I needed someone, for meeting up all over the continent for a weekend away, and for always (always) knowing the right words to say. I would not be here today without you.

Last but certainly not least, I would like to thank my family. To Mom, Dad, and Jonathan- thank you for always supporting me regardless of the path I choose and for showing me unconditional love. To Patrick and Iris- thank you for teaching me the value in watching the sun rise, for creating a beautiful and safe space to call home, and for showing me what happiness can look like.

# 1. Introduction

Semi-volatile organic compounds (SVOCs) are ubiquitous in our environment due to their prevalence of use in the manufacture of consumer products. By the World Health Organization definition, SVOCs have boiling points ranging from 240-260 to 380-400°C and vapor pressures around $10^{-9}$ to 10 Pa at room temperature, which indicates that they partition between the gas and condensed phases at room temperature.[1] SVOCs are typically man-made chemicals, many of which are used as pesticides, plasticizers, flame retardants, and stain repellents, among other usages, and are found in a wide array of products. Many SVOCs are additive rather than chemically bound, leading to leaching into their surroundings over time. As such, human exposure to SVOCs and their consequent health impacts have been points of interest and concern over the last several decades. This dissertation research focuses on sixty-five different SVOCs across three chemical classes which are primarily used as flame retardants and plasticizers and for which concern has been mounting due to their potential health impacts.

## *1.1 Flame retardants*

Flame retardants (FRs) are chemicals applied to polymers and textiles (e.g., upholstered furniture, insulation, electronics) to reduce their flammability and slow or prevent combustion. In particular, they are applied to polyurethane foam (PUF) in upholstered furniture to comply with rigorous flammability standards in various regions of the world. Widespread application of chemical flame retardants to PUF in the

U.S. have long been attributed to the State of California's Technical Bulletin 117 (TB 117), which was implemented in 1975 and mandated that the cushions and filling material in upholstered furniture pass a 12-second open flame test.[2] Implementation of TB 117 led to increasing volumes of FR chemicals in many products containing PUF, including furniture and some baby products. Polybrominated diphenyl ethers (PBDEs) were among the first class of compounds used as additive FRs, and the commercial mixture PentaBDE was the predominant FR added to PUF in furniture. Due to concerns about persistence, bioaccumulation, and toxicity, the PentaBDE mixture was phased out globally in the mid-2000s. As a result, organophosphate esters (OPEs), individually [e.g., tris(1,3-dichloroisopropyl)phosphate (TDCIPP), tris(1-chloroisopropyl)phosphate (TCIPP)] and in mixtures [e.g., Firemaster® 550 (FM 550), isopropylated triaryl phosphate (ITP) mix] were increasingly applied as replacements.[3,4] In 2013, California revised TB 117 (TB 117-2013) and replaced the open flame test with a 12-second smolder test and exempted several juvenile products (e.g., strollers, baby car seats, nursing pillows) from FR applications.[5] Several other states (e.g., Maine, Washington, New York, Maryland) have also banned the use of specific flame retardants in children's products and/or upholstered furniture.[6] This has led to a push to stop the addition of flame retardants in baby products and reduce their applications to foam in upholstered furniture. In 2013, DecaBDE became the last PBDE mixture to be phased-out, leading to an increase in demand for replacements in electronics. This has led to the increase in

uses of alternative brominated flame retardant (BFRs) replacements [e.g., decabromodiphenyl ethane (DBDPE), 2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine (TTBP-TAZ)]. Further, a recent U.S. Consumer Product Safety Commission (CPSC) ruling initiated rulemaking under the Federal Hazardous Substances Act and further investigate the use of organohalogen FRs across multiple product categories.[7] While these recent regulatory changes suggest some reduction of FR uses, particularly halogenated chemicals, application of non-halogenated FR chemicals may increasingly be used in products, especially where OPEs have additional roles as plasticizers. FRs, including components of PentaBDE and DecaBDE, are still detected in home environments, likely due to slow product turnover, recycling of older products, and continued use of FR-treated foam.[8]

Exposure and toxicity to FRs have been studied and characterized over the last few decades. PBDE toxicity has been assessed extensively, both using *in vivo* and *in vitro* models, following detections in the environment starting in the late 1980s.[9] BDE congeners have been associated with a variety of negative health outcomes such as thyroid hormone disruption and neurodevelopmental deficits in both human and animal studies.[10–12] They have also been measured in various compartments of the environment, in wildlife, and in human tissues (e.g., breast milk, serum).[13–17] Historically, PBDEs in serum have been utilized as a gold standard for human exposure;

however, as the levels have decreased with their global phase-out, the levels have been more difficult to detect.[18] External exposure measures have largely relied on indoor dust.

In general, less is known about other FRs, the OPEs and alternative BFRs, although data on both of these classes has been growing steadily over the last few years. Among the OPEs, research from the late 1970s first suggested that TDCIPP is mutagenic, while more recent studies suggest that it is possibly neurotoxic.[19–22] In 2011, TDCIPP was added to California's Proposition 65 List of Possible Carcinogens to require the labeling of products containing the chemical FR and has since been regulated in consumer products in California under their Safer Consumer Product Regulations and in other states. In human and animal studies, both chlorinated and aryl OPEs have been shown to adversely impact regulation of endocrine systems, reproductive endpoints, and neurological, cardiological, and developmental outcomes.[23–30] OPEs have been widely detected in air and dust from various indoor environments, oftentimes at an order of magnitude higher than PBDEs.[31–36] In terms of internal dose measurements, OPE urinary metabolites have been frequently measured at varying levels in humans, especially among the U.S. population where the metabolites are largely ubiquitous, and these measurements have been indicators of internal dose.[37] External exposure measures have largely been inconclusive for associations with urinary metabolites, but a few studies have suggested weak associations with indoor dust.

Much less is known about the alternative BFRs and their toxicity and presence in the environment. Components of the FM 550 mixture, which includes both brominated and organophosphate compounds, have been associated with metabolic and endocrine disruption and activation of nuclear receptors regulating adipogenic pathways in *in vitro* studies.[38–41] The brominated components have been measured in furniture foam and house dust, and urinary metabolites have been frequently detected in humans.[3,4,42,43] For one of the brominated components of FM 550, 2,3,4,5-tetrabromoethylhexylbenzoate (EH-TBB), a urinary metabolite has been identified and frequently detected in both adults and children.[37,44,45] The DecaBDE replacements have little information on toxicity but have been measured in the environment, indoor dust, product wipes, and electronic plastics.[46–50] However, for most of the other alternative BFR compounds, there is a lack of known biomarkers of exposure, and thus, external exposure measures, particularly measurements in dust, have been used to evaluate personal exposures. Overall, FRs, both those which have been regulated and those that are currently in use, are detected frequently in our daily environments, providing evidence for chronic exposure and concern about potential adverse health impacts.

## *1.2 Plasticizers*

Phthalate esters are used as plasticizers in a wide variety of personal care and industrial products as well as building materials.[51] Due to their prevalence of use in consumer products and high application rates (~10-30% by mass), phthalates are some of

the most abundant compounds measured in the indoor environment, and are the most abundant class of compound measured in U.S. indoor dust.[52,53] As such, human exposure is extremely common, and exposure biomarkers have been measured in urine samples in populations around the world.[54–56] In both animal and human studies, phthalate esters have been shown to have developmental and reproductive effects, disrupt endocrine systems, and spur the development of cancer.[57] This is of particular concern for children since phthalate esters are common plasticizers in children's products such as toys, and several phthalates have been shown to adversely impact child development.[58] As a result, the last decade has seen the introduction of several bans regarding the use of phthalates in products. In the Consumer Product Safety Improvement Act of 2008 (later updated in 2017), the U.S. CPSC mandated the removal of five different phthalate esters [diisobuyl phthalate (DiBP), di-n-butyl phthalate (DBP), benzyl butyl phthalate (BBP), bis(2-ethylhexyl) phthalate (DEHP), and di-isononyl phthalate (DiNP)] from use in children's toys and child care products.[59] The European Union banned 4 of the same phthalates and prohibited their use in any product throughout the continent.[60] Like the FRs, their extensive use in products over several decades has ensured that many of these compounds persist in the environment through recycled products, in spite of their bans in new products. In response to the global outcry and phase-outs, several phthalate and non-phthalate plasticizers have been introduced as replacements (e.g., bis(2-ethylhexyl) terephthalate (DEHTP), bis(2-

ethylhexyl) adipate (DEHA)). Although their toxicity appear to be less than their predecessors, their already extensive use in products suggests that they will be detected at equivalent levels and with equal prevalence in the environment as the chemicals they may have replaced.

## *1.3 Evaluation of existing exposure assessment tools*

Even with all of the technological advancements of the current age, we are still unable to determine where chemical contaminants found in our bodies originate (i.e., what products they come from). Therefore, we rely upon a variety of exposure assessment tools to evaluate potential pathways of exposure and provide insight into possible sources of exposure. While many of these tools may be helpful in improving our overall understanding of human exposure, we are consistently limited by the assumptions we make in using each method (e.g., homogenous application of chemical in a product, using cross-sectional measures as representations of exposure, assuming similar metabolism in a population in measuring biomarkers) and thus must use each metric as a small piece in attempting to solve a much larger puzzle.

### 1.3.1 Product testing

Direct testing of consumer products allows us to determine what chemicals are applied to the product itself and at what levels. Previous work in our laboratory has analyzed polyurethane foam collected from residential sofas and other foam-containing products to identify the specific FR applications, and this was further evaluated in

Chapter 2.[8,61,62] Intentional FR applications in foam, particularly in upholstered furniture, are generally within a limited range, between 2-7% by weight.[62] Identifying specific products that are primary sources of exposure provides information that could be helpful in designing intervention studies, where samples could be removed or replaced to determine their overall impact on exposure. This was done in a recent study at childcare centers with children's nap mats, where the authors found that the exchange of flame-retarded mats for FR-free mats led to significant decreases in FR dust concentrations within the center after a three-month period.[63] A similar analysis was performed for PBDEs where older furniture and carpets were removed from homes and a reduction in dust concentrations by approximately one-half was observed between 2006 and 2011, although the sources of the PBDEs were not evaluated.[64] In the case of polyurethane foam, whether from upholstered furniture or baby products, sampling of the foam is fairly simple and can be non-destructive if some of the foam is exposed or zippers allow for easy access to remove a small piece for analysis.[4,61] With electronic products such as televisions or cell phones, direct tests of the material or plastic casing are much more difficult. Product wipes have been used to evaluate FR applications and to examine associations with dust levels; however, these wipes likely also capture settled dust (in the case of larger products) or reflect hand contacts (in the case of cell phones) thereby making it difficult to quantify the FR concentration in the product itself.[47,65] In a recent collaboration, we analyzed plastic casings from twelve newly-purchased

televisions and reported on the FR applications in the TVs, quantifying several BFR and OPE compounds in the plastic samples.[46] While we were able to quantify the exact FR concentrations in the TV housings, this required destructive sampling of twelve brand-new TVs, which were expensive to acquire and were unable to be used after sampling was completed.

In terms of product testing, destructive sampling is oftentimes not a feasible approach, since products like electronics are expensive to acquire and people are not often willing to donate objects for research purposes. Further, testing every product in a household or even a single room of a home would be costly, and samples may be especially difficult to acquire due to their location despite being possible sources of exposure (e.g., insulation, carpet padding). And although many of these chemicals are additive and not chemically-bound, identifying the chemical applications does not provide insights into how much of the compound leaches into the surrounding environment nor how the chemical partitions out of the product and into the air or dust. The pathways of exposure can be hypothesized based on the type of product, but it is still uncertain how much each pathway contributes to an individual's total exposure. For instance, if a person sits on a couch that contains foam with a FR, would this person experience the majority of their exposure to that FR via dermal contact or inhalation? We can posit that dermal contact would be largely responsible; however, this proportion of exposure could change based on the volatility of the FR chemical itself, the density of the

foam, the type of upholstery, and the compression of the material. Recent work with BFRs in furniture fabrics seems to suggest that dermal exposure could be a dominant pathway; however, this is only one study which needs further validation and follow-up.[66] Additionally, the lack of knowledge regarding behavioral and activity patterns are also limitations for evaluating exposure based on product testing, since this provides very little information about how much time a person spends using a product.

### 1.3.2 Hand wipes

Hand wipes are also used to evaluate individual exposure to FRs and plasticizers among both children and adults, as presented here in Chapters 3, 5, 6, and 7 and elsewhere.[43,67–69] When the entire surface area of the hands are sampled, hand wipes are hypothesized to capture hand-to-mouth behaviors and dermal contact and absorption. These pathways, particularly hand-to-mouth contact, are especially important among children who tend to touch their hands to their mouths with much higher frequency than adults and may come in contact with a different set of products than adults. As such, hand wipes may be especially insightful for evaluating children's exposure to FRs and plasticizers.

In terms of sample collection, hand wipes are fairly simple and inexpensive to collect, typically requiring only a pre-cleaned wipe and isopropanol. They are also useful for the purpose of sampling exposures in the most recent microenvironments occupied by the participant. If sampling occurs in the home, then this could reflect a

large portion of an individual's exposure. The wipes additionally sample two important pathways of exposure that are difficult to capture using other methods of exposure assessment. These include hand-to-mouth contact and dermal absorption, which could include any compounds sorbed to the skin. Because they have been shown to be significantly associated with biomarkers of exposure in several studies across multiple classes of compounds (i.e., OPEs, phthalates, PBDEs), hand wipes clearly serve as an important and reliable tool for examining individual exposure to consumer product chemicals. However, a major limitation in using hand wipes as an exposure tool is that hand washing behaviors may modify the relationship between the wipes and biomarkers of exposure.[70] It is difficult to control for how recently an individual washed their hands prior to the wipe being collected. Additionally, for the purpose of consistency and among children, they often require research personnel to wipe the individual's hands and the technique used for wiping the skin surface could vary from person to person. Hand wipes are also limited in their ability to capture the totality of an individual's exposure, as they may only capture exposure from the person's most recent environment and not every microenvironment a person may occupy throughout the day. Although they have been shown to be significantly associated with both spot and pooled urine, hand wipes may not reflect average exposure over long time periods, since they are considered to be cross-sectional samples. Few studies have examined the intra-individual variability over time for chemicals measured on hand wipes.

### 1.3.3 House dust

Indoor dust has been used to evaluate individual exposures to environmental chemicals over the last several decades. More recent studies have quantified flame retardants, plasticizers, and other consumer product chemicals in house dust, suggesting links with human exposure via inhalation of dust particles, inadvertent dust ingestion, or dermal contact with dust.[3,71–74] Dust may be an especially important source of exposure for young children who spend more time closer to the ground and touching their hands to their mouths. House dust has been positively associated with human serum for compounds such as PBDEs.[75] Positive associations between OPEs in dust and urinary metabolites have been observed as well, but the relationships have generally been weaker or not statistically significant.[68,76]

House dust collection is fairly simple and is often performed using a vacuum, whether sampling occurs by collection dust out of individual homes' vacuum cleaner containers or research personnel visit homes to vacuum the homes in a standardized procedure. Dust is also a fairly convenient matrix since there is typically a large enough amount available for multiple analyses to be conducted (i.e., measuring multiple chemical classes using either targeted or non-targeted analyses). In addition, the National Institute of Standards and Technology (NIST) has several indoor dust Standard Reference Materials (SRMs) available and certified for several classes of compounds to support QA/QC needs. However, when trying to link house dust to human exposure,

we are confronted with a series of limitations. Oftentimes, a single room of the home is sampled out of convenience, such as the main living area, which limits our ability to comment on the totality of human exposure from dust in the home. Differences may occur by particle size for evaluating concentrations of specific analytes and location of sampling within a single room or home, which could lead to difficulties in comparing dust across studies.[77–79] For compound classes other than PBDEs, house dust has not conclusively been observed to be significantly associated with exposure biomarkers. Although typically people spend more time in the home than other microenvironments, house dust is limited to evaluating a single microenvironment, and occasionally a single area of that microenvironment. Thus, the extrapolation of a chemical concentration in house dust to total human exposure could be less insightful than other measures presented here. Nonetheless, house dust represents a long-term repository of chemicals in the home, which could serve as an important baseline for determining what is in the home environment, and thus potential exposure for residents via dust ingestion or inhalation, which in some cases can be fairly minimal compared to other pathways.

### 1.3.4 Biomarkers

Biological samples such as urine and serum have been used extensively for evaluating exposures to SVOCs, with biomarkers oftentimes cited as the gold standard for individual exposures. These exposure biomarkers are useful for evaluating internal dose of a compound and verifying that an external exposure resulted in the compound

entering the human body. Biomarkers allow for population-wide examinations (e.g., National Health and Nutrition Examination Survey, or NHANES) of chemical concentrations and trends over time. They also serve as an integrative measure for all pathways of exposure by which individuals may encounter an environmental chemical. However, identifying exposure biomarkers with adequate sensitivity and specificity for effective epidemiological studies can be difficult.[80] Further, evaluating differences in biomarkers based on factors contributing to inter- and intra-individual variability (e.g., metabolism rates, chemical toxicokinectics, timing of exposure, timing of sample, body mass index) can lead to limitations in how these levels can be interpreted across populations. Variation in persistence of chemicals in the body can lead to exposure misclassification, particularly for compounds with short half-lives and when spot samples are used to indicate individual exposure. While biomarkers indicate the presence of a chemical in the body and may be correlated with external exposure measures, they may not represent a mass balance for total exposure (e.g., currently measured metabolites of DEHTP only account for 16% of total ingested dose).[81]

Collection of biological samples can also be invasive (e.g., blood sampling), thereby making biospecimen collection challenging, especially among children. Once collected, the biospecimens themselves typically need to be frozen or kept on ice to maintain the integrity of the sample and biomarkers, whether parent compounds or metabolites, as they tend to be sensitive to temperature changes. Sample volumes also

tend to be small and sample analyses expensive, leading to limited numbers of targeted analytes available for evaluation. In addition, this limitation reduces the ability for researchers to evaluate exposure to mixtures across classes of compounds, which may be important for evaluating health outcomes.

## *1.4 Silicone wristbands*

Silicone wristbands were first introduced as personal passive samplers in 2014 by O'Connell et al.[82] The wristbands have often been worn as fashion statements or accessories and are fairly common. In their first publication, O'Connell et al. demonstrated that the wristbands could also be used to measure adult ambient exposures to a wide array of chemicals including polycyclic aromatic hydrocarbons (PAHs), pesticides, phthalates, and flame retardants (FRs). They are posited to primarily capture gas-phase chemicals and thus represent an integrated measure of dermal absorption and inhalation exposure due to the proximity to the skin and binding capacity of the silicone material. Further, the presence of particles on the wristbands following wear suggests that the bands could also capture exposure via ingestion or inhalation of aerosols. The wristbands have been assessed for acceptability among community members as a tool for exposure monitoring, in which environmental justice communities were the primary focus.[83] They have also been worn in high compliance and acceptability among children, particularly because they are non-invasive.[84,85] As an

inexpensive medium, the wristbands have the potential to serve as an integrated measure encompassing multiple pathways of exposure.

## *1.5 Dissertation research aims*

The overall objective of this dissertation research is to evaluate the utility of silicone wristbands as personal passive samplers for assessing exposure to SVOCs in the context of existing quantitative assessment tools currently in use. With the prevalence of SVOCs in our everyday environment, a greater knowledge of the exposure sources and body burdens is essential to better characterize health risks. Other measures of exposure such as hand wipes, dust collection, and biological sampling are limited by the cost of resources, sampling of single microenvironments, examinations of singular exposure pathways, and handwashing behaviors. As such, silicone wristbands may hold a strong potential for characterizing personal exposures in an inexpensive, non-invasive manner across multiple microenvironments and over a given period of time.

This dissertation research sough to improve our understanding of exposure by examining links between consumer products and exposure and by investigating the use of a new personal sampler, the silicone wristband. A central hypothesis of this research is that silicone wristbands serve as effective and improved measure of SVOC exposure compared to contemporary assessment tools when evaluated in the context of human biomarkers of exposure. This hypothesis was tested through the following specific aims:

**Aim 1. Examine how specific FR applications in furniture foam impacts human exposure (Chapter 2).** Paired samples of furniture foam, house dust, and serum were collected from a cohort in North Carolina, USA and analyzed for FRs typically applied to foam. The presence of PentaBDE and FM 550 mixtures in foam was associated with higher levels of their primary components in house dust, and PentaBDE in foam was significantly associated with higher levels of BDE congeners in serum. The footprint of the sofa and dust-loading rates were observed to modify these associations. This was the first study to compare levels of specific FRs in products to a known biomarker of exposure and to house dust.

**Aim 2. Evaluate the use of silicone wristbands for measuring adult personal exposures with known biomarkers (Chapters 3 and 4).** In Chapter 3, OPEs were measured on the wristbands, and urinary metabolites quantified in pooled urine samples from the sampling period. In Chapter 4, BFRs were analyzed on the wristbands and PBDEs measured in paired serum. Significant associations were observed between OPEs and PBDEs on the wristbands and their urinary metabolites and serum biomarkers, respectively. Together, these studies were among the first studies to link wristband concentrations and internal dose measurements, providing evidence for their appropriate use in exposure assessment.

**Aim 3. Determine the utility of silicone wristbands compared to hand wipes and house dust for evaluating children's SVOC exposures (Chapters 5, 6, and 7).**

Paired wristband, hand wipe, dust, pooled urine, and serum samples were collected from children within a North Carolina pregnancy cohort. In Chapter 5, OPEs on hand wipes and in house dust were evaluated for associations with urinary metabolites; hand wipes were found to be better than dust for predicting children's exposure to OPEs. In Chapter 6, phthalates on hand wipes and in house dust were related to corresponding urinary metabolites, with the evaluation of housing characteristics; both hand wipes and dust provided some helpful insights for children's exposures to phthalates, and the presence of vinyl flooring in the home may contribute to greater phthalate exposures. In Chapter 7, OPEs, phthalates, and BFRs on wristbands were evaluated for associations with the appropriate biomarkers of exposure and compared to hand wipes and dust. In general, many of the compounds across the three classes were significantly associated with their biomarkers in urine or serum. Wristbands were observed to have similar or improved utility compared to hand wipes for OPEs and hand wipes and dust for phthalates.

**Chapter 8** summarizes the major conclusions from this dissertation research and discusses the advantages and disadvantages of the silicone wristband in characterizing SVOC exposures. Additional discussion focuses on the challenges faced in accurately measuring personal exposures to SVOCs.

Determining how both adults and children are exposed to SVOCs is an integral step in improving exposure estimates to reduce exposure misclassification in risk

assessment and epidemiological studies and determine if these chronic daily exposures pose a true health hazard. Continued work in understanding and validating use of the wristbands as personal samplers may then improve our ability to collect reliable exposure data using a non-invasive method of evaluating individual exposures.

# 2. Associations between flame retardant applications in furniture foam, house dust levels, and residents' serum levels

This chapter is adapted with permission from Hammel, S. C.; Hoffman, K.; Lorenzo, A. M.; Chen, A.; Phillips, A. L.; Butt, C. M.; Sosa, J. A.; Webster, T. F.; Stapleton, H. M. Associations between flame retardant applications in furniture foam, house dust levels, and residents' serum levels. *Environ. Int.* 2017, *107*, 181–189 (Publisher: Elsevier). The accompanying supporting information is included in Appendix A.

## *2.1 Introduction*

Flame retardants (FRs) are applied to polyurethane foam (PUF) in upholstered furniture to reduce its flammability. Implemented in 1975, the State of California's Technical Bulletin 117 (TB 117) mandated that all upholstered furniture pass a 12-second open flame test.[2] To pass these flammability tests, FR chemicals have been added to the PUF, and sometimes other components of furniture such as textile coverings. The polybrominated diphenyl ether (PBDE) commercial mixture known as PentaBDE was a common FR used in furniture foam; however, it was phased out in the mid-2000s. In response, organophosphate FRs such as tris(1,3-dichloroisopropyl)phosphate (TDCIPP), tris(1-chloro-2-propyl)phosphate (TCIPP), and the commercial FR mixture Firemaster® 550 (FM550), which contains triphenyl phosphate (TPHP), isopropylated triaryl phosphates (ITPs), 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)-tetrabromophthalate (BEH-TEBP), were increasingly applied as

replacements.[67] In a recent study analyzing over one thousand foam samples collected between 2014 and 2016, TDCIPP was found to be the most common FR detected in furniture foam.[8] Despite the phase-out of PentaBDE and the recent amendment to TB 117 in 2013, which replaced the open flame test with a smolder test, flame retardants, including PentaBDE, are still detected in home furnishings and other foam-containing consumer products. This is due, in part, to slow product turnover and recycling of products themselves as well as the use of PUF in applications.[5,8]

PBDE exposure and toxicity have been studied and characterized over the last few decades. The PBDE congeners associated with the PentaBDE mixture have been measured extensively in the environment and in human tissues, and exposure has been associated with negative impacts on thyroid hormone regulation and neurodevelopment, both in human and animal studies.[10,11,15,68–70] Although less is known about other FRs, research conducted in the late 1970s suggested that TDCIPP is mutagenic, and more recently, that it may also be neurotoxic.[19–21,71,72] Additionally, TDCIPP was added to California's Proposition 65 List of Possible Carcinogens in 2011. In contrast to PBDEs, TDCIPP is rapidly metabolized and excreted. The metabolite, bis(1,3-dichloroisopropyl)phosphate (BDCIPP), has been measured ubiquitously in urine samples, suggesting widespread human exposure to TDCIPP in North America, Australia, and Europe; however, TDCIPP exposure appears to be higher in the U.S. population compared to other countries.[34–36,73,74] Comparatively less is known about the

toxicity of TCIPP, although it has been associated with endocrine disruption and limited neurodevelopmental changes in a few animal studies. [75,76] Like TDCIPP, exposure to TCIPP is also widespread. The hydroxylated metabolite of TCIPP has been ubiquitously detected in humans in several recent studies.[35,77,78] Components of FM550 have been associated with endocrine and metabolic disruption in exposed rodents, and they have been shown to bind and activate nuclear receptors that regulate adipogenic pathways in *in vitro* models.[39,40,79,80] Metabolites of both the organophosphate and brominated components of FM550, identified through dosed rodent studies and *in vitro* studies, are now frequently detected in human urine.[42,43,81–83] Notably, all of the aforementioned FR compounds have been widely detected in indoor house dust, which may serve as an important exposure pathway via hand-to-mouth activity.[3,84–86] In fact, several studies have found significant positive associations between PBDE levels in house dust and serum or breast milk in the US, reinforcing house dust as a primary exposure pathway.[87–90] More recent studies have suggested that diet may play a larger role than dust for exposure to PBDEs, especially in European populations where PentaBDE was not used as pervasively in furniture as in North America. One recent study found no association between PBDEs in dust and serum but did find significant associations with various dietary items.[91]

Despite these studies, research linking specific FR applications in products to house dust or biomarker levels is limited. Previously, portable x-ray fluorescence (XRF)

measurements of bromine in products found in the home were shown to be highly correlated with Penta-BDE levels in paired house dust and serum samples.[92,93] However, these portable XRF instruments are only sensitive to specific elements, such as bromine, and are not capable of differentiating between PBDEs or FM550, for example. Furthermore, XRF appears to have limited utility for chlorinated FRs.[61] The presence of foam-containing napping equipment in early childhood education facilities also was associated with higher levels of tris(2-chloroethyl) phosphate (TCEP) and TDCIPP in dust.[94] A significant reduction in dust PBDE levels were observed with the removal of older furniture and carpets between sampling in 2006 and 2011; however, furniture was not verified to contain any specific FR chemicals, and the source of the reduction (e.g., furniture, dust-loading, or FRs in carpet padding) was not evaluated.[64] FR levels found on product surface wipes have been associated with dust levels; however, only prominent electronic products found in the home were evaluated, and most of the relationships were observed among these products and plastic casings, such as televisions and computers.[47] In one study, counts of baby products used in the home were correlated with urinary BDCIPP levels in infants, highlighting a possible link between product use and exposure.[95]

In the present study, we sought to further examine specific relationships between FR application in furniture foam and human exposure. Our goal was to identify and quantify specific FR applications in PUF from study participants' sofas in the main

living area and determine how the presence or absence of a specific FR related to levels measured in house dust and residents' serum levels. Further, we sought to determine whether characteristics of the furniture or living space modified this relationship. To our knowledge, this is the first study to compare levels of specific FRs in a consumer product, particularly levels in upholstered furniture, to a known biomarker and to house dust.

## *2.2 Materials and methods*

### 2.2.1 Study design

Participants were recruited as a part of a case-control thyroid cancer study between April 2014 and January 2016. Papillary thyroid cancer patients treated at the Duke Cancer Institute and Duke University Medical Center were invited to participate in the study by their physicians, and willing participants were contacted by our study team for enrollment (n=72). Control participants (n=81) were recruited via flyers in the Duke University Medical Center facilities or randomly selected as other Duke patients undergoing routine wellness care or care for unrelated illnesses. We assume that case status does not affect concentrations of flame retardants in furniture, dust or serum; hence, we included both cases and controls in the current study. The study population is described in greater detail in Hoffmann et al. 2017.[96] Once enrolled, study personnel visited each participant's home to conduct questionnaires and collect environmental samples and biospecimens. The participants in the study all lived within 50 miles of

Duke University and had lived in their homes for at least two years, ensuring that their current homes reflected several years of past exposure. On average, participants in this study lived in their homes approximately 11 years. All study protocols and related materials were approved by the Duke Medicine Institutional Review Board for Clinical Investigations, and all participants gave informed consent before providing any information or samples.

### 2.2.2 Sample collection

All participants were instructed not to vacuum their homes in the two days before the visit. During each visit, the entire floor surface of main living area in the participant's home was vacuumed using a Eureka Mighty Mite vacuum fitted with a cellulose thimble in the hose attachment for dust collection.[88] The thimbles containing the dust were wrapped in aluminum foil and immediately frozen at -20°C. One small piece of foam (approximately 1-3 $cm^3$) was removed from the sofa located in the main living area, wrapped in foil, and immediately frozen. Almost all homes contained one sofa, but if other upholstered furniture (e.g., loveseats, chairs, ottomans, etc.) were present in the room, they were noted in the study log. Only PUF from the sofa, and not textile or fabric samples, were analyzed as part of this study. All participants provided non-fasting blood samples in serum-separator tubes which were centrifuged and frozen for analysis of PBDEs. Urine was not collected as part of this protocol, and thus no biomarkers of organophosphate flame retardants were measured. Although all

participants were asked to provide all samples, under some circumstances a particular sample could not be collected. For example, samples could not be collected from sofas that did not have accessible foam (e.g., leather sofas with no zippers to the cushion compartment). As such, there was not complete overlap in the number of participants with each sample type. Additional information on the sample sizes is included in the supplementary material (Figure A1).

### 2.2.3 Dust extraction

Dust samples were extracted and analyzed similar to the methods developed by Van den Eede et al. 2012.[85] In brief, dust samples (about 100 mg) were spiked with the following internal standards: $d_{15}$-tris(1,3-dichloro-2-propyl)phosphate ($d_{15}$-TDCIPP; 154.8 ng), $^{13}$C-triphenyl phosphate ($^{13}$C-TPHP; 100.0 ng), $^{13}$C-2-ethylhexyl-2,3,4,5-tetrabromobenzoate ($^{13}$C-EH-TBB; 100.0 ng), $^{13}$C-bis(2-ethylhexyl)-tetrabromophthalate ($^{13}$C-BEH-TEBP; 100.0 ng), 4-fluoro-2,3,4,6-tetrabromodiphenylether (FBDE-69; 30.0 ng), and $^{13}$C-decabromodiphenyl ether (13C-BDE-209; 67.0 ng). The dust was extracted with 1:1 dichloromethane/hexane (v/v) via sonication extraction then concentrated to 1.0 mL using a nitrogen evaporator system. These extracts were purified using Florisil® solid-phase extraction cartridges (Supelclean ENVI-Florisil, 6 mL, 500 mg bed weight; Supelco), eluting the F1 fraction with 6 mL hexane (brominated compounds) and the F2 fraction with 10 mL ethyl acetate (PFRs). Each fraction was concentrated to 1 mL and then transferred to an autosampler vial for analysis by GC/MS. Recovery of the internal

standards was assessed using $^{13}C$ labeled 2,2′,3,4,5,5′-hexachlorodiphenyl ether ($^{13}C$-CDE-141; 50 ng) for FBDE-69, $d_9$-tris(2-chloroethyl) phosphate ($d_9$-TCEP; 227 ng) for $d_{15}$-TDCIPP, and $d_{15}$-triphenyl phosphate ($d_{15}$-TPHP; 128 ng) for $^{13}C$-TPHP. Recoveries of FBDE-69, $^{13}C$-BDE-209, $d_{15}$-TDCIPP, and $^{13}C$-TPHP were on average 109 ± 4%, 109 ± 7%, 90.6 ± 2%, and 79.6 ± 2%, respectively. Laboratory blanks and house dust standard reference materials (SRM 2585; National Institute of Standards and Technology, Gaithersburg, MD) were analyzed in each batch for quality assurance and quality control. Dust samples were analyzed in three separate batches, and MDLs were consistent across matches. Detection frequencies were determined based on the corresponding batch's MDL, and samples were blank-corrected by batch as well. Measurements of PBDEs in SRM 2585 were very similar to their certified levels, and ranged from 73 to 111% relative to the certified values. Levels of the FM550 components (TPHP, EH-TBB, BEH-TEBP) in SRM 2585 were 60-98% of the values reported in published literature.[85,97,98]

### 2.2.4 Foam extraction

Foam samples were extracted and analyzed as in previously described methods.[67] Briefly, ~50 mg of foam was accurately weighed and extracted via sonication with dichloromethane (DCM) and then filtered with a 25 mm syringe filter with a 0.2 μm PTFE membrane. A 100 μL aliquot of each extract was removed and diluted to 1 mL for an initial screening of flame retardant additives by gas chromatography/mass

spectrometry (GC/MS) in full scan using both electron ionization and electron capture negative chemical ionization (Tables A1, A2). Three laboratory blanks (DCM with no foam) were analyzed with each batch of samples. Significant peaks in the total ion chromatogram were compared against a custom spectral library of known FRs.[8] Based on the FRs identified in the scans, $d_{15}$-TDCIPP, $^{13}$C-TPHP, $^{13}$C-EH-TBB, $^{13}$C-BEH-TEBP, and FBDE-69 were spiked into sample extracts for quantification by GC/MS. Due to the lack of standards at the time of analysis, the isopropylated triaryl phosphate (ITP) compounds were not quantified, but retention times and *m*/*z* ions were verified based on similarity with the FM550 mixture.[99] The TBPP mixture (containing TPHP and mono-, di- and tri-tert-butylated phenyl phosphate esters) and MPP mixture (containing methyl phenyl phosphate esters) were similarly matched to a custom spectral library of FRs from previous characterization.[8,67] It should be noted that FM550 was classified in this study by detection of EH-TBB and BEH-TEBP. Although typically associated with the ITP compounds, EH-TBB and BEH-TEBP were also observed in combination with the TBPP mixture.[8] Similar to dust, foam samples were analyzed in three separate batches, and detection frequencies were determined by each batch's MDL. MDLs were consistent across batches and therefore an average MDL was reported.

### 2.2.5 Serum analysis

Serum was analyzed for PBDEs and extracted according to methods described in Butt et al. 2016.[100] Briefly, the samples were spiked with 2.5 ng of FBDE-69 and $^{13}$C-BDE-

209. The samples were sonicated with 2.0 mL 0.1 M formic acid and 6.0 mL water to denature the serum proteins. Following column conditioning with 5.0 mL DCM, methanol, and water, the samples were loaded on a Waters Oasis® HLB column (500 mg bed weight, 6 mL) and washed with 5.0 mL water. PBDE analytes were eluted with 10.0 mL of 1:1 DCM/ethyl acetate (v/v), then concentrated to near dryness using a nitrogen evaporator and reconstituted in 1.0 mL hexane. These samples were further cleaned using a silica column cartridge (1 g, Waters, Sep-Pak), eluting the F1 fraction with 10.0 mL hexane for the PBDEs. The F1 fraction was concentrated to approximately 100 μL and spiked with 5.0 ng $^{13}$C-CDE-141 to assess recovery of FBDE-69. This fraction was analyzed using GC/MS in electron capture negative chemical ionization mode for 27 PBDEs. Average recovery of FBDE-69 in the samples was 65 ± 2%. PBDE masses in serum were normalized to mass serum extracted as well as total lipid content. Serum triglycerides (TG) and total cholesterol (CHOL) were measured via enzymatic techniques (LabCorps, Burlington, NC). Total lipid content (TL) in serum was estimated using the equation reported by Covaci et al. 2006.[101] Lab blanks and serum SRM 1957 (National Institute of Standards and Technology, Gaithersburg, MD) were extracted alongside the samples for quality assurance and quality control. The serum samples were analyzed in two separate batches, and detection frequencies as well as blank-correction was performed within each batch of samples. Measurements in SRM 1957

relative to the certified values were 129% for BDE-47 and 75% for BDE-153, and the range for all PBDEs measured in the SRM relative to certified values was 71 to 141%.

### 2.2.6 Product and living space characteristics

To examine how product characteristics impacted analyzed relationships in this study, sofa footprint and dust-loading were defined based on measurements taken during home visits. The sofa footprint represents the sofa size relative to the size of a room, which allowed us to account for the amount of foam present in a main living space. This was calculated by dividing the two-dimensional surface area of the sofa (length x width) by the surface area of the vacuumed main living space. Dichotomized at the median footprint, a small footprint represented sofas that took up <17.5% of the room, whereas a large footprint was indicative of a couch that took up >17.5% of the room. Dust-loading was determined by dividing the total mass of dust collected while vacuuming the main living space by the surface area of that room. Again, dichotomized at the median of 1.66 μg dust/in$^2$, low dust-loading is representative of lower dust masses collected from the surface area of the room, whereas high dust represented large masses of dust per area vacuumed.

### 2.2.7 Statistical analyses

All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC). Analyses were performed for analytes detected in >70% of samples. Method detection limits (MDLs) were calculated by the standard deviation of

the blanks multiplied by three and divided by the average mass of sample extracted. For all concentrations below the MDL, the concentration was replaced by MDL/2.[102,103] The FR concentrations in dust, foam, and serum were all log-normally distributed. For analyses, FR detections in foam were assessed as a dichotomized variable (FR present or absent in foam) due to the smaller sample sizes associated with each FR application. Positive identification of a FR in foam was determined as a concentration of at least 1 mg FR/g foam.

Linear regression models were performed to determine if FR presence in PUF and other variables were associated with dust or serum FR concentrations ($log_{10}$-transformed analyte concentrations used as outcomes). Beta coefficients were exponentiated to assist with interpreting the results and are representative of multiplicative change in the outcome relative to the reference category. Through all analyses, statistical results were assessed at a level of $\alpha$=0.05 for significance.

## *2.3 Results and discussion*

### 2.3.1 Study population

Overall, 153 participants were recruited for this study, and 115 provided a foam sample. Most of the study participants were female, and the mean age was 48 years. Further details about this cohort can be found in Hoffman et al. 2017.[96] In brief, the cases and controls were similar in race and ethnicity, household income, and health history as

well as average time reported living in the address at which the home visit was conducted (mean of 11 years).

## 2.3.2 FRs in individual matrices

### 2.3.2.1 Polyurethane foam

Of the 115 foam samples collected, about two-thirds contained at least one flame retardant. The ITP mixture, which is associated with FM550 but also may be applied in other mixtures, was the most frequently detected flame retardant application (29% of total foam samples), followed by TDCIPP and then the brominated components (EH-TBB and BEH-TEBP) in FM550 (Table 1). Although it was the most frequently detected chemical in the foam samples (44%), TPHP is not typically applied on its own as a flame retardant. To our knowledge, TPHP is always co-applied with another flame retardant mixture, such as with PentaBDE, or found with a mixture of phosphates as in the ITP mixture and the TBPP mixture. Therefore, while it is commonly detected, it is not the most frequently detected flame retardant application. The average FR levels in this study are similar to previously reported measurements in foam.[67] Penta-BDEs were still detected in over 15% of foam samples collected despite their voluntary phase-out in upholstered furniture occurring over a decade ago. While most of these particular sofas were reported as purchased prior to 2005, others were purchased second-hand or handed down; therefore, the original manufacturer and purchase date is unknown. Concentrations of FRs in foam reported in Table 1 are for individual FRs; however,

many of these FRs are applied as mixtures. Generally, the total concentration of all FRs applied to the foam were >1% of the product by weight.

**Table 1: Detections, geometric means, and ranges (mg/g foam) for flame retardants in polyurethane foam samples (n = 115).**

| Compound | Number of Detects | % Detect of Total Samples | Average MDL | Geometric Mean | Minimum | Maximum |
|---|---|---|---|---|---|---|
| **EH-TBB** | 20 | 17.4 | 0.227 | 8.79 | 1.97 | 15.9 |
| **BEH-TEBP** | 20 | 17.4 | 0.341 | 3.91 | 0.514 | 7.54 |
| **ΣPentaBDE*** | 18 | 15.6 | 0.055 | 3.74 | 0.941 | 35.0 |
| **TCIPP** | 7 | 6.08 | 0.261 | 6.32 | 0.768 | 46.0 |
| **TDCIPP** | 22 | 19.1 | 0.236 | 19.9 | 0.534 | 88.1 |
| **TPHP** | 51 | 44.3 | 0.124 | 0.983 | 0.0013 | 15.0 |
| **ITP Compounds**[#] | 33 | 28.7 | n.a. | n.a. | n.a. | n.a. |
| **TBPP Compounds**[%] | 14 | 12.2 | n.a. | n.a. | n.a. | n.a. |
| **MPP Mixture**[&] | 4 | 3.47 | n.a. | n.a. | n.a. | n.a. |
| **No FR** | 37 | 32.2 | n.a. | n.a. | n.a. | n.a. |

*ΣPenta-BDEs includes BDE-17, 28, 47, 49, 66, 85, 99, 100, 153, 154, and 155.
[#]ITP compounds refer to a mixture of isopropylated triaryl phosphate esters.
[%]TBPP compounds refer to a mixture of tert-butylated phenyl phosphate esters.
[&]MPP Mixture refers to a mix of methyl phenyl phosphate esters.

#### 2.3.2.2 Serum

Serum samples were analyzed for a suite of PBDE compounds but only BDE-47 and BDE-153 were detected in >70% of the samples and are the only congeners analyzed in this study for associations with FR applications in foam (other congeners were detected in under 50% of samples) (Table 2). More information on the serum PBDE measurements can be found in Hoffman et al. 2017.[96] In general, the levels of these two compounds were lower than previously reported among U.S. adults, which likely reflects a decline in overall exposure to Penta-BDEs following their phase-out.[18,104] While

such a decrease is expected with a now decade-old global phase-out of Penta-BDEs, detection of these two BDEs in serum suggests continued exposure to these compounds.

#### 2.3.2.3 House dust

Of the FRs quantified in foam, all were detected in 70% or more of the dust samples (Table 2). Overall, the geometric means of organophosphate FRs in dust were at least an order of magnitude greater than the brominated compounds, which suggests greater exposure potential for organophosphate compounds via dust ingestion. The most abundant organophosphate FR in dust was TCIPP, which follows a trend observed in the U.S. and parts of Europe and Asia.[36,105–108] Although PBDEs have been largely phased out, detections and concentrations of the more widely used PBDEs (BDE-47 and BDE-99 in PentaBDE and BDE-209 of the DecaBDE mixture) in dust were similar to the levels of the other brominated compounds, EH-TBB and BEH-TEBP. This suggests that despite decreased use, house dust serves as a continued repository for PBDEs, and sources of PBDEs may still be present in homes.

**Table 2: Geometric means and selected percentiles for FRs in serum (n = 135) and house dust (n = 137).**

| Matrix and Compound | Percent Detect | Average MDL | Geometric Mean | Percentile | | | |
|---|---|---|---|---|---|---|---|
| | | | | 25th | 50th | 75th | Maximum |
| **Serum (ng/g lipid)** | | | | | | | |
| **BDE-47** | 77.8 | 1.321 | 7.855 | 3.852 | 8.891 | 16.01 | 144.2 |
| **BDE-153** | 94.8 | 0.5490 | 4.541 | 2.386 | 4.371 | 8.576 | 143.2 |
| **Dust (ng/g dust)** | | | | | | | |
| **EH-TBB** | 94.2 | 3.833 | 239.4 | 82.86 | 188.4 | 754.4 | 16,320 |
| **BEH-TEBP** | 81.8 | 15.60 | 117.1 | 44.67 | 160.4 | 420.6 | 11,190 |
| **TCIPP** | 94.2 | 90.90 | 2,141 | 823.5 | 2,118 | 6,350 | 66,210 |
| **TDCIPP** | 92.0 | 56.97 | 1,384 | 640.7 | 1,220 | 3,269 | 59,490 |
| **TPHP** | 95.6 | 5.000 | 1,409 | 475.5 | 1,345 | 4,049 | 111,300 |
| **PBDEs** | | | | | | | |
| **BDE-47** | 92.0 | 78.50 | 222.2 | 71.65 | 202.2 | 518.5 | 17,010 |
| **BDE-99** | 96.4 | 74.30 | 346.1 | 100.3 | 310.4 | 789.7 | 32,820 |
| **BDE-100** | 70.1 | 20.70 | 62.51 | 18.35 | 44.38 | 155.0 | 6,396 |
| **BDE-153** | 87.6 | 10.37 | 43.99 | 11.90 | 34.49 | 124.5 | 4,488 |
| **BDE-154** | 81.8 | 8.100 | 31.88 | 9.067 | 27.27 | 77.79 | 3,657 |
| **BDE-209** | 93.4 | 20.13 | 524.1 | 184.2 | 536.9 | 1198 | 28,490 |

### 2.3.3 Comparing PBDEs in foam and serum

Levels of serum BDE-47 and BDE-153 were greater in participants who lived in a home with a sofa containing Penta-BDEs (Figure 1). Serum BDE-47 levels were 2.5 times as high in these participants compared to those whose sofa did not contain Penta-BDE (95% CI: 1.4, 4.5; $p<0.01$). Although not statistically significant, a similar pattern was observed for serum BDE-153 levels, with BDE-153 in serum being about 1.7 times as high if the participants had a Penta-BDE-containing sofa (95% CI: 0.84, 3.3; $p=0.14$). The lack of a significant association between BDE-153 in serum and Penta-BDE in foam may be due to a difference in the half-lives of BDE-153 compared to BDE-47, or differences in exposure. Additionally, diet may be a greater source of exposure for BDE-153 in the present day than it did prior to the global phase-out due to its persistence in the environment. BDE-47 has been estimated to have a half-life of 1.8 years, while BDE-153's half-life has been estimated to be 6.5 years.[109] Therefore, BDE-153 measured in serum would likely reflect longer-term average exposures from either past furniture containing Penta-BDE or other sources present in the last several years of the participants' exposure, which could include diet or other microenvironments.[89] Additionally, the relationship between Penta-BDE in sofa foam and BDE-47 in serum was slightly stronger if individuals spent an average of 13 hours or more in their homes per day ($10^{\beta}=2.8$, $p=0.01$) compared to people who did not have Penta-BDE in their sofas. Furthermore, BDE-47 in dust was significantly correlated with paired BDE-47 serum levels in this

cohort ($r_s$=0.35, p=0.004) but a similar relationship between dust and serum was not observed for BDE-153.[96] Past studies have shown significant associations between serum and house dust for certain PBDEs ($r_s$=0.8 for BDE-47 in adults, r=0.3 for a summed BDE-47, -99, and -100 in toddlers; p<0.01), but not for BDE-153.[87,88] To our knowledge, serum PBDE levels have not been previously linked to a specific application in a product. The significant association between foam Penta-BDE and serum BDE-47 suggests that these pieces of upholstered furniture serve as major sources of BDE-47 in humans. Because there are no other reliable serum biomarkers for the additional FRs investigated here, only relationships with PentaBDE were investigated with serum.

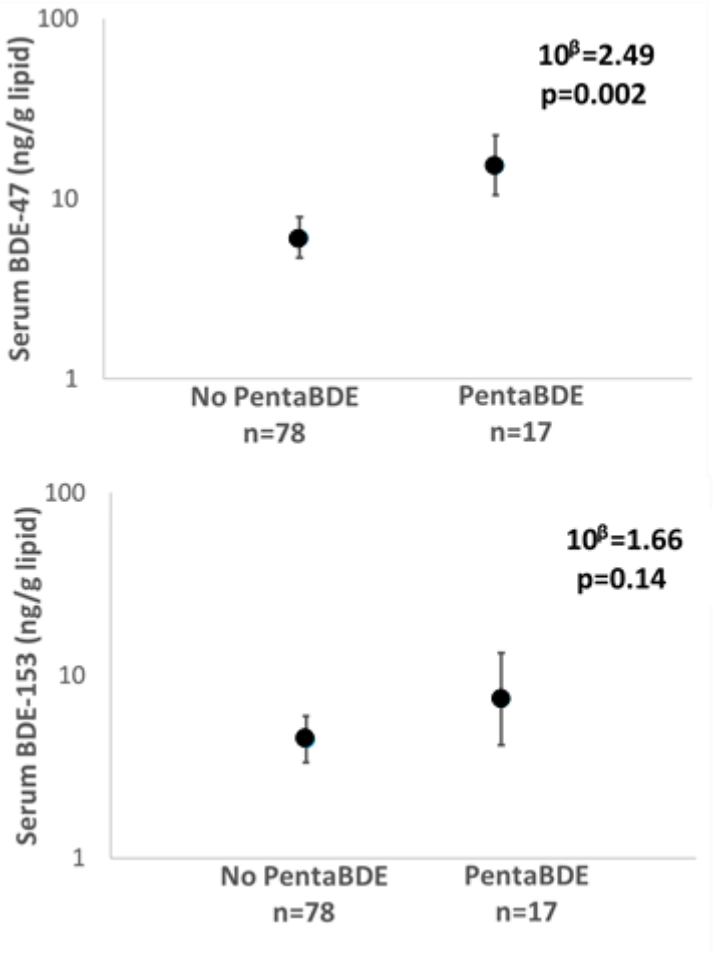



**Figure 1: Geometric means and 95% confidence intervals of serum PBDE levels based on presence or absence of PentaBDE in paired foam. Absence of PentaBDE in foam was the reference category for determining the magnitude of effect on serum BDE-47 and BDE-153, which was determined by linear regression.**

### 2.3.4 FRs in foam and dust

The presence of FM550 and PentaBDE in the sofa foam were significantly associated with higher levels of EH-TBB and BDE-47 in dust, respectively (Figure 2). The EH-TBB and BDE-47 dust levels were between 4 to 6.5 times as high when a sofa containing that specific FR was in the same living area (FM550 95% CI: 1.7, 9.8;

PentaBDE 95% CI: 2.8, 14.3; $p<0.01$). While sofas may not be the sole source of FRs, associations indicate that foam-containing furniture contributes heavily to house dust and serves as a major source of brominated FRs in house dust. This implies that having a sofa that does not contain either of these brominated FR mixtures could potentially decrease a person's exposure to these compounds via decreases in FR levels in dust. The magnitude of effect between Penta-BDE detection in foam and BDE-47 dust levels was much greater than the effect with BDE-47 in serum (6.5 times in dust compared to 2.5 in serum), which suggests that the relationship observed between foam and serum is attenuated, perhaps by the time spent in other micro-environments (e.g. home, work), handwashing, and/or dietary sources, even if the sofa may serve as a major source of exposure.[89] Relationships between dust levels of other PBDEs (BDE-99, -100, -153, -154) were evaluated with Penta-BDE in foam and were found to be significantly associated ($10^{\beta}$=3.2-3.9, $p<0.01$) with one exception being BDE-153 ($10^{\beta}$=2.2; $p=0.07$). Dust levels of BEH-TEBP were also assessed with FM550 presence in foam and were found to be statistically significant ($10^{\beta}$=3.8, 95% CI: 1.3, 11.2, $p<0.01$). Because BDE-47 and EH-TBB showed the strongest relationship with their respective applications in foam, and BEH-TEBP may be applied in other commercial mixtures in the home, the results with BDE-47 and EH-TBB are presented in the figures and further evaluated with other characteristics.

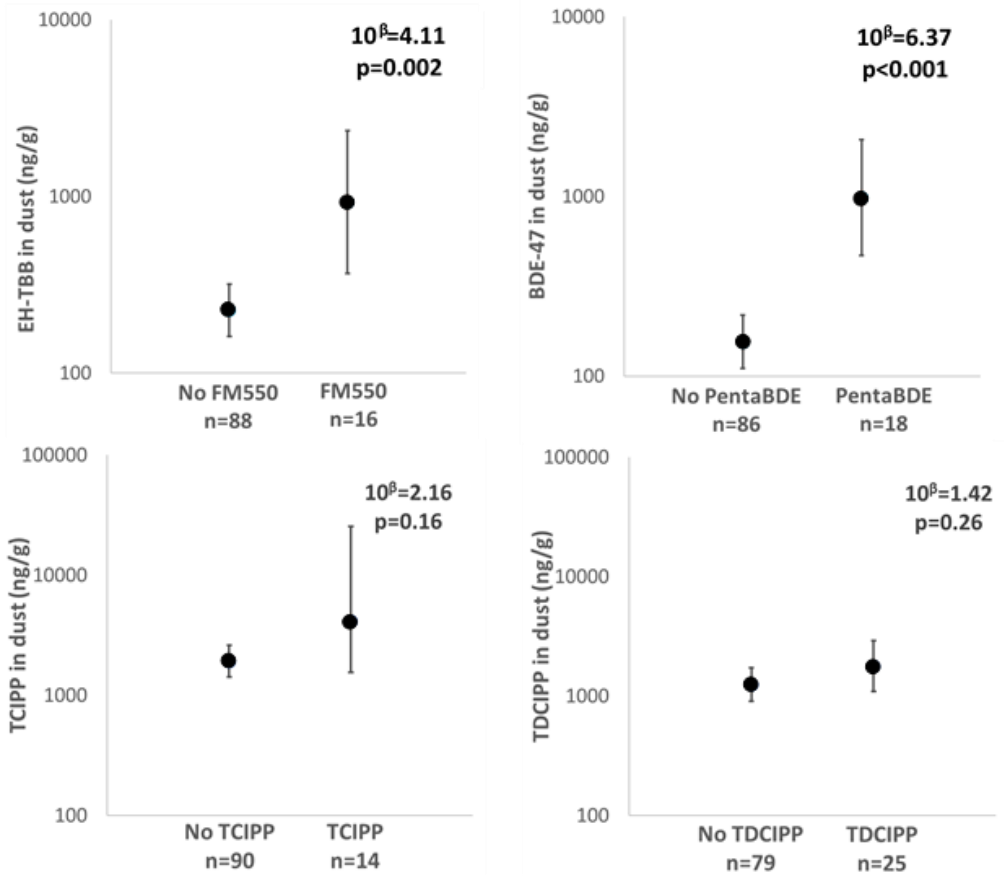



**Figure 2: Geometric means and 95% confidence intervals of dust concentrations based on the corresponding FR's presence or absence in paired foam. The magnitude of increase in outcome and associated p-value with the FR foam presence compared to absence (reference category) are displayed in the top right of each panel, which was assessed by linear regression.**

The relationships between foam and dust were investigated further based on various product characteristics and living space traits. When the Penta-BDE relationship between foam and dust was assessed based on the sofa footprint, levels of BDE-47 in dust were found to be 9.7 times as high when the sofa had a large footprint compared to only 4.3 times as high with a small footprint (large footprint 95% CI: 3.0, 31.8; small footprint 95% CI: 1.6, 11.3; $p<0.01$; Figure 3), relative to dust levels in homes without a Penta-BDE sofa. A similar trend was observed with FM550 and EH-TBB in dust (large footprint $10^{\beta}=4.5$, 95% CI: 1.5, 13.3; small footprint $10^{\beta}=7.6$, 95% CI: 1.5, 39.8; $p<0.05$), although the sample sizes for each category were small, resulting in overlapping confidence intervals in the small and large footprint categories. Overall, the trend suggests that sofas that take up more of the surface area of the room contribute to higher levels of these brominated FRs in dust.

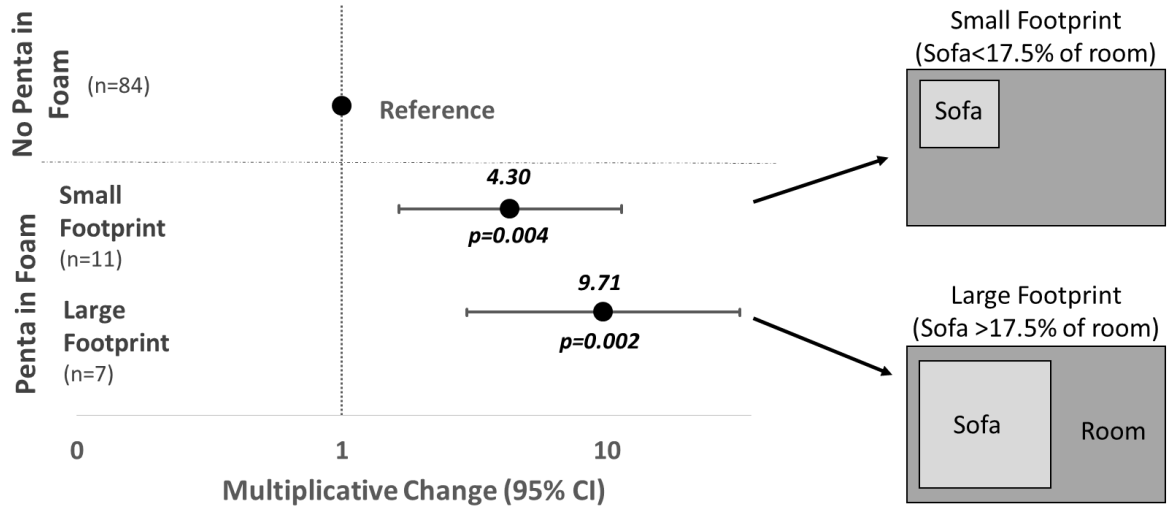



**Figure 3: Multiplicative change and 95% confidence intervals of BDE-47 in dust depending on the presence of PentaBDE in paired foam and the size of the sofa relative to the vacuumed room, designated as a footprint. The sofa footprint was dichotomized at the median percent of the room covered by the sofa (17.5%).**

Dust-loading of the vacuumed room was also examined as a potential modifying factor in the foam-dust relationship. When compared to the reference category (low dust mass loadings and no Penta-BDE in foam), a significant relationship between Penta-BDE in foam and BDE-47 levels in dust was observed with low dust-loading ($10^{\beta}$=10.4; 95% CI: 3.5, 31.1; $p<0.0001$; Figure 4). A significant relationship was not observed with high dust-loading levels, although the results were suggestive of a trend ($10^{\beta}$=2.8; 95% CI: 0.9, 8.2; p=0.07). Again, the same trend was observed with FM550 in foam and EH-TBB in dust (low dust $10^{\beta}$=6.5; 95% CI: 1.8, 22.8; high dust $10^{\beta}$=4.3; 95% CI: 1.2, 15.1; $p<0.05$), but sample sizes were not sufficiently large, resulting in overlapping confidence intervals. This finding may suggest that a dilution effect is occurring, whereby the brominated compounds are diluted in a room that accumulates more soil or dust particles (leading to higher dust mass in a room). Therefore, dust-loading may be an important variable to consider when assessing relationships between product use and house dust levels, as it could modify the observed relationships and lead to incorrect estimates.

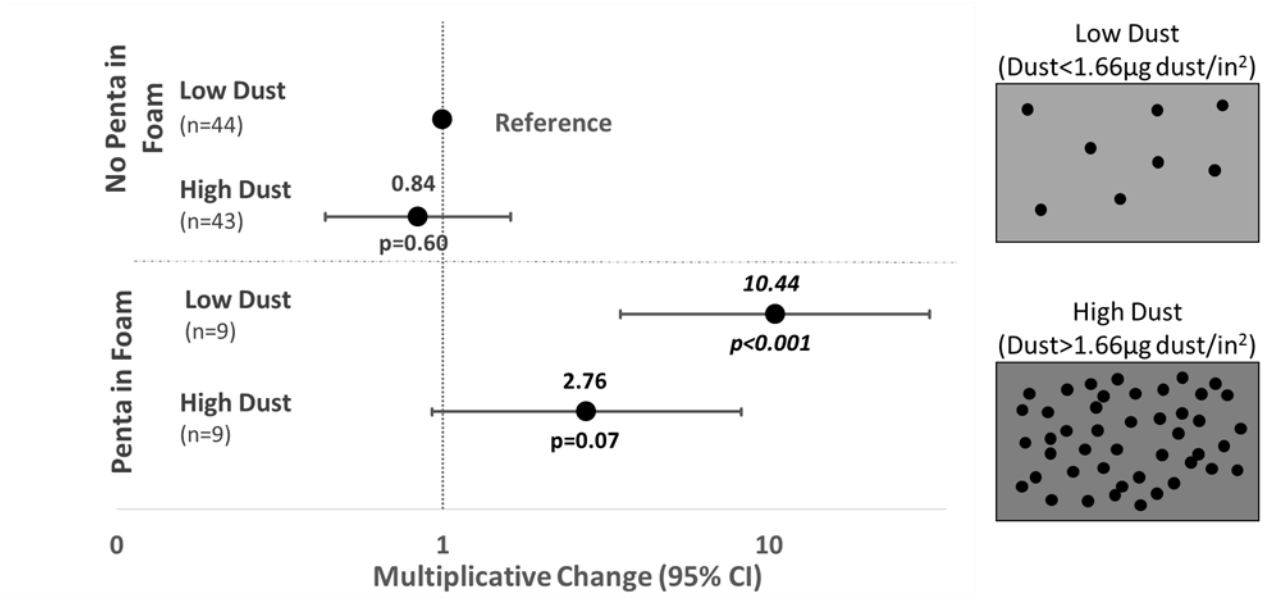



**Figure 4: Multiplicative change and 95% confidence intervals of BDE-47 in dust depending on the presence of PentaBDE in paired foam and dust-loading of the vacuumed room. Dust-loading was dichotomized at the median dust mass per area vacuumed, which was 1.66 µg/in².**

As for the organophosphate FRs, higher levels of TCIPP and TDCIPP in dust were observed when detected in the sofa foam; however, the relationships were not statistically significant ($10^{\beta}$=1.6-2.5, p>0.1; Figure 2). Interestingly, when TCIPP and TDCIPP were not detected in the sofa foam, the GM dust levels of these two organophosphate compounds were an order of magnitude greater than EH-TBB and BDE-47. This suggests that product sources other than sofas in the main living area may be contributing to the dust concentrations of these two organophosphate FRs, or TCIPP and TDCIPP may have different migration behaviors than the brominated compounds from foam to dust due to physicochemical properties. However, the upholstered furniture seems to be a major source of FM550 and Penta-BDE in the home. TDCIPP and TCIPP relationships between foam and dust were assessed based on footprint and dust-loading but no associations were observed, further suggesting that sofa foam assessed in this study may not be the main source of these organophosphates in dust. For instance, TCIPP is frequently used in thermal insulation, and both of these organophosphates could be used in a variety of applications in textiles.[33,110,111]

### 2.3.5 Limitations

Although participants in this study were recruited for the purpose of a case-control study to examine thyroid cancer, this should not bear any effects on this particular study since case status should not impact foam, dust, or serum levels of FRs. As shown in Hoffman et al. 2017, there was no significant difference in serum BDE-47 or

BDE-153 levels by case status.[96] Still, our results should be interpreted in the context of a few limitations. First, one foam sample was assessed per household for associations with house dust; this does not account for the possible contribution of other upholstered furniture in the room or adjacent rooms. Due to different applications of FRs in foam, the sample sizes of foam samples containing a specific FR were relatively small compared to those that did not. As a result, relationships between foam and dust were assessed based on detection (>1 mg/g foam) rather than on a continuous basis. Detailed behavioral information such as how much time an individual spent in the main living area or on the sampled sofa and frequency of handwashing could provide additional insights, as these factors could modify the relationship between foam and human exposure. Future studies including analyses with urine measurements from participants may also be helpful to determine how organophosphates assessed in foam relate to biomarkers for exposure.

## *2.4 Conclusion*

Our results indicate that foam in sofas serves as an important source of flame retardants for exposure in humans, suggesting that removal of FRs from the foam or furniture pieces in the home could indeed reduce human exposure to these compounds. FR compounds were measured in foam samples and evaluated for their associations with paired serum and house dust samples. Significantly higher levels of serum BDE-47 were observed when the participant had a sofa containing Penta-BDE in the main living

area with a similar but non-significant relationship observed with serum BDE-153. Detections of FM550 and Penta-BDE in foam were also indicative of significantly greater levels of EH-TBB and BDE-47 in dust, suggesting that foam in upholstered furniture containing these brominated mixtures serves as a major source of these compounds in the home environment. These relationships were strengthened with larger furniture pieces per area vacuumed (sofa footprint) and with lower dust-loading. Foam-dust relationships were not significant for TDCIPP or TCIPP, suggesting that other sources of these two compounds may be contributing to the levels measured in house dust or the compounds migrate from foam to dust in a manner different from the brominated compounds.

# 3. Measuring personal exposure to organophosphate flame retardants using silicone wristbands and hand wipes

This chapter is reprinted with permission from Hammel, S. C.; Hoffman, K.; Webster, T. F.; Anderson, K. A.; Stapleton, H. M. Measuring Personal Exposure to Organophosphate Flame Retardants Using Silicone Wristbands and Hand Wipes. *Environ. Sci. Technol.* 2016, *50* (8), 4483–4491.  This manuscript was published with a correction which is included in Appendix B, along with the accompanying supporting information.

## *3.1 Introduction*

Consumer products such as furniture, electronics, and building materials are typically treated with an array of chemicals to provide desired characteristics. In particular, flame retardants are applied to these products to reduce their flammability and adhere to national and state level fire safety standards. Polybrominated diphenyl ethers (PBDEs) were once among the most commonly applied flame retardants in consumer products; however, due to their persistence, bioaccumulation, and toxicity, the use of PBDEs has been largely phased out, leading to increased use of many alternative flame retardants.[67,70] Organophosphate flame retardants (PFRs) such as tris(1,3-dichloroisopropyl) phosphate (TDCIPP), tris(1-chloro-2-isopropyl) phosphate (TCIPP), and triphenyl phosphate (TPHP) are now among the most commonly used flame retardants in polyurethane foam (PUF) from upholstered furniture and have been

widely detected in both air and dust from indoor environments.[62,67,84,98,112] Components of Firemaster® 550 (FM550), another frequently detected commercial flame retardant mixture that is composed of approximately 60% organophosphate compounds [e.g., TPHP and mono-substituted isopropylated triaryl phosphate (mono-ITP)] and 40% brominated compounds, have also been quantified from a number of environmental samples such as PUF from furniture and indoor dust.[3,67,99]

Due to their prevalence in indoor environments, human exposure to PFRs is common and their metabolites are frequently detected in human urine (Figure 5). Bis(1,3-dichloroisopropyl) phosphate (BDCIPP) and diphenyl phosphate (DPHP), the respective metabolites of TDCIPP and TPHP, have been measured extensively in the general population.[42,61,86,113] A hydroxylated metabolite of TCIPP, bis(1-chloro-2-isopropyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP), was recently identified in urine and widely detected in a large population study in Australia.[35] While a specific biomarker for mono-ITP (present in FM550) has not been identified, isopropylphenyl phenyl phosphate (ip-PPP) has been suggested as a potential metabolite/biomarker.[42]

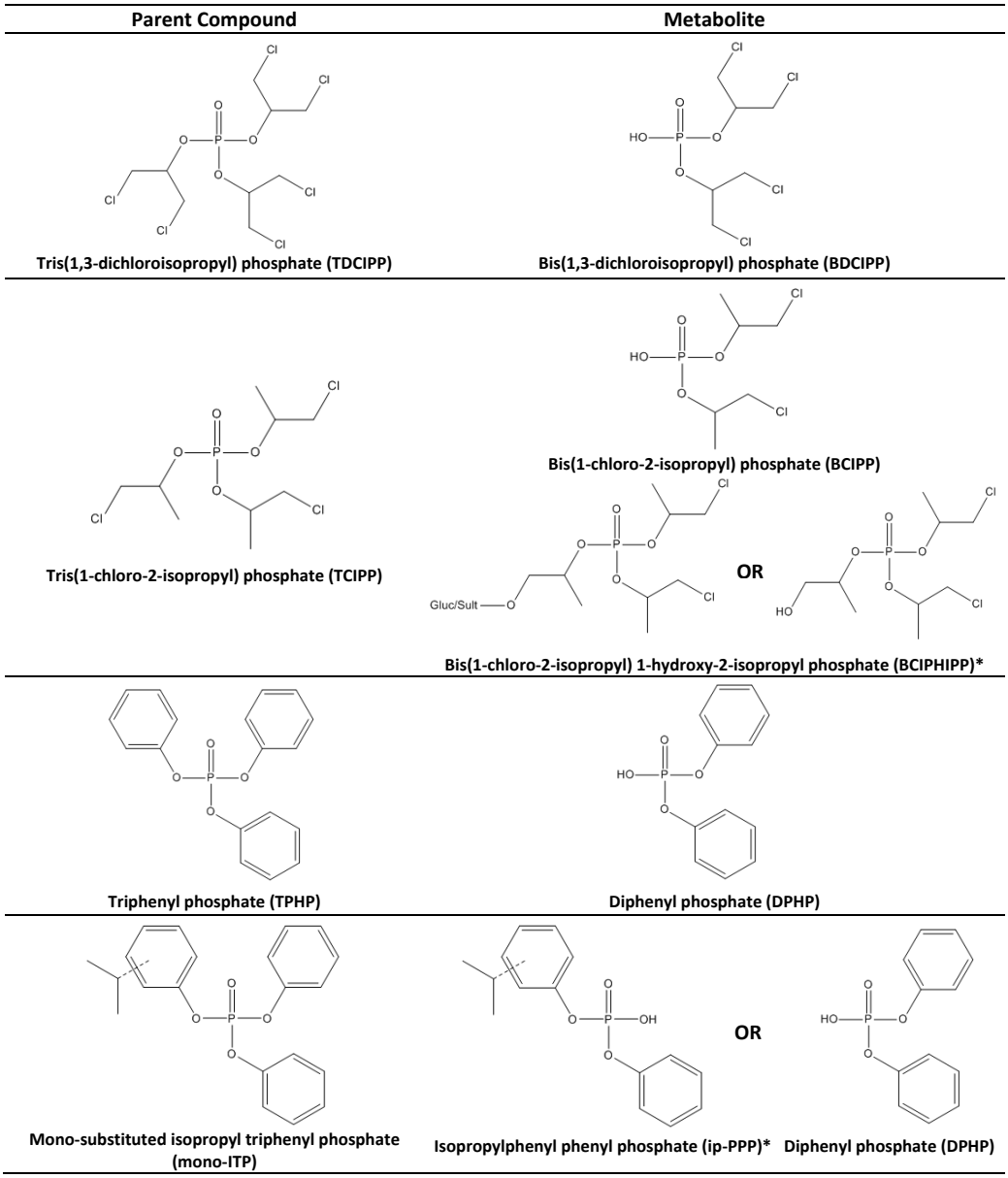



**Figure 5: Parent compound and urinary metabolites for common organophosphate flame retardants. Starred metabolites (*) are considered the primary metabolites for analysis.**

Toxicology studies in animals conducted with PFRs suggest that they may be associated with adverse health impacts such as carcinogenicity, cardiotoxicity, endocrine

disruption, and neurotoxicity; one epidemiological study in adult men found an association between increased PFR metabolites and reduced hormone levels, specifically BDCIPP and DPHP levels in urine with total T3 and BDCIPP concentrations with TSH levels.[20,24,25,38,40,114–116] Accurate means of assessing personal exposure are essential to characterizing human health risks related to these flame retardants. Indoor dust has been considered an important exposure pathway, with PBDE concentrations in serum significantly and positively correlated to dust concentrations.[87] However, this same relationship between indoor dust and PFR metabolites in urine has not been observed.[36] While hand wipes have been reliable in demonstrating exposure to PBDEs and PFRs and have been positively associated with spot urine samples, both of these samples are limited by measurement of exposure at a single time point.[86,105] Hand wipes are likely to primarily capture particle-bound contaminants, which poses additional limitations since many flame retardants are semi-volatile and are distributed between the particle-bound and vapor phases. Urinalysis of PFR metabolites can also be challenging due to the rapid metabolism of these compounds, with half-lives estimated around several hours using animal models.[117–119] To further characterize potential health outcomes, epidemiological studies require a reliable means of assessing longer-term exposures to these compounds compared to the short-term exposure measures provided by urinalysis.

Recently, silicone wristbands have been utilized as passive samplers in examining adult ambient and occupational exposures to a suite of compounds used in

personal care, industrial processes, and general consumer products.[120,121] These wristbands present a non-invasive and inexpensive method of quantifying personal exposures across multiple microenvironments and within a multi-day time period. However, the association between concentrations of compounds found on the wristbands and internal exposure has not been investigated. In the present study, we sought to determine the effectiveness of using silicone wristbands as an exposure tool in association with PFR metabolites in urine, and we further sought to compare wristbands to hand wipes as metrics of exposure. To our knowledge, this is the first study to validate the use of wristbands in capturing exposure to organophosphate flame retardant chemicals by measuring urinary metabolites.

## *3.2 Materials and methods*

### 3.2.1 Study design

Study participants were recruited from the Duke University community and general population around Durham County, North Carolina (n=40) by flyer and word of mouth in June through August of 2015. Eligible participants were at least eighteen years of age and were willing to wear wristbands for five days, to provide three urine and single hand wipe samples, and to complete questionnaires. All study protocols and related materials were approved by the Duke University Institutional Review Board, and all participants gave informed consent prior to providing any information or personal samples.

### 3.2.2 Wristband collection

Commercially available silicone wristbands were purchased in a single size (24hourwristbands.com, Houston, TX) and cleaned using two twelve-hour Soxhlet extractions with 1:1 ethyl acetate:hexane (v/v) followed by 1:1 ethyl acetate:methanol (v/v), a method adapted from O'Connell, et. al (2014).[120] After allowing the wristbands to passively dry in the fume hood, each one was wrapped in aluminum foil and placed in a labeled 40mL amber jar. Participants were asked to wear their wristbands continuously for a designated five-day period through sleeping, bathing, and any other daily activities, beginning on the morning of day 1 and removing the wristband at the same time of morning on day 6. Wearing the wristband while bathing may allow for compounds sorbed to the wristbands to be washed off in a similar manner as on the skin, as well as account for exposures occurring during bathing (e.g. application of soap). At this designated time, participants removed the wristband, which was then wrapped in a new sheet of clean foil and placed back in the amber jar. The wristbands were stored at -20°C until extraction. Four wristbands that were not deployed were wrapped in aluminum foil and stored at room temperature to serve as field blanks with the extraction.

### 3.2.3 Urine collection

Participants were asked to provide first morning void urine samples on three separate days during the five-day period in which they were wearing the wristbands

(day 2, day 4, and day 6). Urine samples were collected in standard polypropylene specimen containers and stored at -20°C until analysis. Just prior to analysis, equal volumes of the three individual urine samples were pooled to form a mixed/average sample.

### 3.2.4 Questionnaires

Study participants completed three short online questionnaires over the five days they wore the wristband (day 1, day 3, and day 5). Participants were asked to provide demographic information and to record the time spent in various microenvironments during that day (e.g. time spent in the home, work, and car). Mean fractions of days spent in these locations were calculated based on total hours in the day reported by the participant and averaged across the three questionnaires. For individuals who did not complete all three questionnaires, averages were performed based on those that were completed (85% completed all three questionnaires). Participants were also asked to report the average number of times that they washed their hands each day (never, 1-3, 4-6, 7-9, 10+ times per day) and the average number of times that they bathed each week (never, 1-2, 3-5, 6-8, 9-11, 12-14, 15+ times per week). The question regarding average number of times hands are washed a day was asked on two separate days, and the lower range reported was used in statistical analyses. For the purpose of later analysis, washing behaviors and time spent in the home, work, and car were dichotomized based on the median reported value (or category).

### 3.2.5 Hand wipe collection

Three inch square cotton twill wipes were pre-cleaned in a single twelve-hour Soxhlet extraction using 1:1 hexane:acetone (v/v) then dried in a fume hood and wrapped in aluminum foil. Hand wipe samples were collected from each participant on the morning of day 6 by gloved research personnel by soaking a pre-cleaned twill wipe with about 3 mL of isopropyl alcohol and wiping the entire surface area of both of the participant's hands from fingertips to wrist including between the fingers. This hand wipe collection protocol is similar to those described in previously published studies.[86,105,122] The hand wipe was then rewrapped in foil and stored at -20°C until analysis. Four twill wipes prepared as described above were stored wrapped in aluminum foil at room temperature to serve as field blanks.

### 3.2.6 Wristband and hand wipe sample extraction

Wristband and hand wipe samples were extracted and analyzed using previously published methods for each matrix for the aforementioned organophosphate flame retardants: TDCIPP, TCIPP, TPHP, and mono-ITP.[86,120] Each wristband, including the field blanks, was cut using solvent-rinsed scissors into two equal pieces to ensure that the wristbands would be submerged under the solvent within a Soxhlet apparatus used for extraction. Prior to beginning the extraction, the bands were spiked with $d_{15}$-TDCIPP (162 ng) and $^{13}$C-TPHP (100 ng) as internal standards. The wristbands were Soxhlet extracted with 1:1 hexane:acetone (v/v) for 12 hours, and the extracts were

concentrated using an automated nitrogen evaporation system (Turbo Vap II, Zymark Inc.). Extracts were filtered with a 25mm syringe filter with a 0.2 micrometer PTFE membrane to remove larger particles. This concentrated extract were later cleaned using a Florisil solid-phase extraction cartridge (Supelclean ENVI-Florisil, 6 mL, 500-mg bed weight; Supelco), eluting the F1 fraction with 10 mL hexane (brominated compounds) and the F2 fraction with 10 mL ethyl acetate (PFRs), which was adapted from the method developed by Van den Eede, et. al (2012).[85] Using a nitrogen evaporator system, each fraction was concentrated to about 1 mL then transferred to an autosampler vial for gas chromatography-mass spectrometry (GC/MS) analysis (Agilent Technologies, Models 6890N and 5975). The F1 concentrated fraction was stored at -20°C for future analysis. To measure recovery of the organophosphate internal standards in the wristbands, $d_9$-tris(2-chloroethyl) phosphate ($d_9$-TCEP; 227 ng) and $d_{15}$-TPHP (429 ng) were spiked into each sample to measure recovery of $d_{15}$-TDCIPP and $^{13}$C-TPHP, respectively. Recoveries of $d_{15}$-TDCIPP and $^{13}$C-TPHP averaged 33 ± 5% and 99 ± 6%, respectively, in all samples. Prior to the Florisil cleanup, recovery of the $d_{15}$-TDCIPP was 94 ± 5%, which suggests some of the compound was lost with additional processing. It is possible that short oligomers were extracted from the wristbands during the Soxhlet extraction which may have sorbed both labeled and unlabeled TDCIPP which were retained on the Florisil SPE column. However, due to the use of isotope-labeled standards, we still have confidence in the accuracy of our results following the cleanup

step. Four lab blanks were analyzed alongside the wristbands and field blanks for quality assurance and quality controls.

The whole hand wipe samples were each spiked with $d_{15}$-TDCIPP (180 ng) and $^{13}$C-TPHP (50 ng) as internal standards and extracted three times via sonication with 1:1 hexane: acetone (v/v). The combined extract of roughly 45 mL was concentrated to 1 mL using a nitrogen evaporator system, then transferred to an autosampler vial for GC/MS analysis. Recoveries of the internal standards in the hand wipes was measured by spiking all samples with $d_{15}$-TPHP (429 ng). Recoveries of $d_{15}$-TDCIPP and $^{13}$C-TPHP averaged 119 ± 14% and 97 ± 12%, respectively.

For both wristbands and hand wipes, mono-ITP was quantitated using a commercial mixture of FM550 and assuming the percent of mono-ITP in FM550 by mass is 32%.[99] All isomers at 368 m/z were integrated over a retention time of 15.90 minutes to comprise the mass of mono-ITP in each sample. PFR concentrations in wristbands and hand wipes were blank corrected based on the average concentrations measured in the field blanks (Table B1). Higher background levels were measured in the wristbands relative to the hand wipes for some chemicals. The Soxhlet extraction process may have contributed to the higher wristband field blank levels in wristbands; however, the wristband field blanks were still significantly lower than levels measured in the wristband samples. Method detection limits (MDLs) were calculated as three times the standard deviation of the levels in the field blanks. MDLs for the PFRs ranged from 5.7

ng for TPHP to 30.3 ng for TCIPP on wristbands and 0.19 ng for TPHP to 11.21 ng for TDCIPP on hand wipes.

### 3.2.7 Urine Sample Processing

Specific gravity was measured for each pooled urine sample using a digital handheld refractometer (Atago) prior to analysis. Urine samples were analyzed for BDCIPP, BCIPP, DPHP and ip-PPP following the methods described by Cooper et. al (2011) and Butt et. al (2014) and for BCIPHIPP using methods described by Van den Eede et. al (2015).[35,42,73] For each pooled sample, 5.0 mL of urine was spiked with internal standards $d_{10}$-BDCIPP (10 ng), $d_{10}$-DPHP (8.8 ng), and $d_9$-TCEP (25 ng) and placed with 1 M sodium acetate buffer (pH 5) and an enzyme solution (1000 units per mL β-glucoronidase and 33 units per mL sulfatase activity in 0.2 M sodium acetate buffer at pH 5) then incubated overnight at 37°C.[35] With the enzyme digestion step, the glucoronide and sulfate conjugates of BCIPHIPP cannot be differentiated from any of the free compound that may present in the urine. The five analytes (BDCIPP, BCIPP, DPHP, ip-PPP, and BCIPHIPP) were extracted via mixed-mode anion exchange solid-phase extraction and measured using atmospheric pressure chemical ionization liquid chromatography-tandem mass spectrometry (Agilent Technologies, Model 6410).[73] Recovery of the internal standards were evaluated using $^{13}C_2$-DPHP (25 ng) for $d_{10}$-BDCIPP and $d_{10}$-DPHP and $d_{15}$-TDCIPP (25 ng) for $d_9$-TCEP, both of which were spiked into all of the urine samples. Average recoveries for $d_{10}$-BDCIPP, $d_{10}$-DPHP, and $d_9$-

TCEP were 108 ± 77%, 111 ± 22%, and 52 ± 15%. The MDL was calculated using three times the standard deviation of the blanks normalized to the volume of urine extracted. Lab blanks and a urine Standard Reference Material (SRM 3673; National Institute of Standards and Technology, Gaithersburg, MD) were extracted alongside the samples for quality assurance and quality control. Specific gravity-normalized measurements in SRM 3673 were 1.49 ± 0.15 ng/mL, 0.32 ± 0.01 ng/mL, 0.29 ± 0.02 ng/mL, and 3.56 ± 0.06 ng/mL for BDCIPP, BCIPHIPP, DPHP, and ip-PPP, respectively. These values are similar to levels reported by A. Covaci's group during an interlab comparison exercise with this material (unpublished data).

### 3.2.8 Statistical analyses

All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC). Analyses were conducted for analytes in which the detection frequency was >70%. For concentrations below the MDL, the concentration was replaced by MDL divided by 2. Preliminary examination of the data indicated that the concentrations of PFRs and metabolites were log-normally distributed. Thus, Spearman correlation coefficients ($r_s$) were calculated to examine the associations between the wristbands, hand wipes, and urine.

To further explore associations, linear regression models were performed to determine if any of the measured or queried variables were associated with urinary metabolite concentrations ($log_{10}$-transformed concentrations of analytes were used in

regression analyses). Beta coefficients were exponentiated to facilitate interpretation and represented the multiplicative change in the outcome relative to the reference category or to a one-unit increase in continuous variables. PFR concentrations on wristbands and hand wipes were split into tertile categories to examine associations with the corresponding urine metabolites while reducing effects of outliers. Through all analyses, statistical results were assessed at a level of $\alpha$=0.05 for significance.

Specific gravity was measured in order to account for dilution of the urine samples (range of 1.0030 to 1.0254). Urine analyses of metabolites and associations with the corresponding PFRs on wristbands and hand wipes were assessed with raw metabolite concentrations and specific-gravity-corrected values. At least one pooled urine sample had extremely low specific gravity, which was unexpected for a mix of three first morning void samples. When analyses were run excluding this urine sample, the magnitude of the correlations remained unchanged. Analysis results using each set of urine concentrations were essentially not differentiable, and the specific-gravity adjusted associations and graphs are presented here.

## *3.3 Results and discussion*

All forty participants completed at least one of the three questionnaires with the majority (95%) completing two or more. Approximately two-thirds of the participants were female, and the average age of participants at the time of the survey as 29.8 years (range of 20 to 60 years) (Table 3).

**Table 3: Characteristics of PFR Wristband Cohort.**

| Variables | Number (Percent) |
|---|---|
| **Sex** | |
| **Male** | 15 (37.5) |
| **Female** | 25 (62.5) |
| **Age** | |
| **18-24** | 12 (30.0) |
| **25-28** | 11 (27.5) |
| **30-36** | 12 (30.0) |
| **40+** | 5 (12.5) |
| **Avg times hands washed/day** | |
| **Never** | 1 (2.50) |
| **1-3** | 5 (12.5) |
| **4-6** | 12 (30.0) |
| **7-9** | 10 (25.0) |
| **10+** | 12 (30.0) |
| **Avg number of baths or showers taken/week** | |
| **3-5** | 9 (23.7) |
| **6-8** | 20 (52.6) |
| **9-11** | 5 (13.2) |
| **12-14** | 4 (10.5) |
| **Avg hours of day spent in home** | |
| **<15** | 22 (55.0) |
| **≥15** | 18 (45.0) |
| **Avg hours of day spent at work/school** | |
| **<6** | 22 (55.0) |
| **≥6** | 18 (45.0) |
| **Avg hours of day spent in car** | |
| **<1** | 23 (58.0) |
| **≥1** | 17 (42.0) |

### 3.3.1 PFRs in individual matrices

#### 3.3.1.1 Wristbands

TDCIPP, TCIPP, TPHP, and mono-ITP were detected in all of the silicone wristbands (Table 4). The geometric means of TDCIPP and TCIPP were much higher than TPHP and mono-ITP on the bands. The ratio of geometric means of mono-ITP to TPHP (1.7:1) on the wristbands is similar to the relative percent compositions of these compounds in the FM550 mixture, suggesting that the TPHP concentrations on the wristbands may be at least partially attributed to exposure to FM550.[99] Mono-ITP has been measured in occupational air samples and non-targeted water analyses but to our knowledge has not been previously detected and quantified in hand wipes or wristbands.[123,124] A recently published study also measured PFR compounds on wristbands and verified the stability of these compounds on the wristbands through time in storage and temperature changes.[125] However, levels on the wristbands could not be compared between the two studies because of the units in which PFR concentrations were reported. While dust was not collected in this study, wristband PFR concentrations in this study reflected the trend of relative geometric means in indoor dust from recent studies in central North Carolina, with TCIPP present at higher levels than TDCIPP and TPHP.[36,85,86,105,126] Seeing as dust is an important exposure matrix and pathway, this could indicate similar sources reaching the wristbands and settling in the dust. Additionally, dust particles could be sorbing to the wristband through contact or settling on the band from the air, which could explain the similar observed trend.

**Table 4: Geometric means and selected percentiles for PFRs in wristbands and hand wipes and urinary metabolites.**

| | | | | | Percentile | | | |
|---|---|---|---|---|---|---|---|---|
| **Matrix and Compound** | *n* | Percent detects | MDLs | Geometric Mean | 25th | 50th | 75th | Maximum |
| **Wristbands (ng/band)** | | | | | | | | |
| **TDCIPP** | 40 | 100 | 6.562 | 1251 | 842.9 | 1155 | 1872 | 7737 |
| **TCIPP** | 40 | 100 | 30.34 | 1536 | 801.1 | 1018 | 3218 | 14030 |
| **TPHP** | 40 | 100 | 5.683 | 459.5 | 285.3 | 394.9 | 866.3 | 1841 |
| **Mono-ITP** | 40 | 100 | 23.71 | 783.1 | 460.9 | 845.9 | 1452 | 6283 |
| **Hand wipes (ng/wipe)** | | | | | | | | |
| **TDCIPP** | 38 | 95 | 11.21 | 108.3 | 48.02 | 99.52 | 213.8 | 535.0 |
| **TCIPP** | 38 | 100 | 1.421 | 45.42 | 30.48 | 54.03 | 77.36 | 255.0 |
| **TPHP** | 38 | 100 | 0.1871 | 22.41 | 11.49 | 18.75 | 39.29 | 416.7 |
| **Mono-ITP** | 38 | 100 | 1.002 | 120.2 | 57.22 | 107.0 | 198.7 | 1175 |
| **SG-corrected urine (ng/mL)** | | | | | | | | |
| **BDCIPP** | 40 | 100 | 0.3313 | 2.321 | 1.199 | 2.061 | 4.316 | 21.21 |
| **BCIPHIPP** | 40 | 100 | 0.02320 | 1.103 | 0.5135 | 1.119 | 2.467 | 16.99 |
| **BCIPP** | 40 | 18 | 1.054 | n.a. | n.a. | n.a. | n.a. | 0.57 |
| **DPHP** | 40 | 100 | 0.5316 | 1.137 | 0.5186 | 1.160 | 2.175 | 26.77 |
| **ip-PPP** | 40 | 100 | 0.07519 | 2.598 | 1.438 | 2.686 | 4.553 | 11.28 |

#### 3.3.1.2 Hand wipes

PFRs were detected in all of the hand wipes except for TDCIPP, which was detected in 95% of the samples (Table 4). Geometric mean amounts of mono-ITP and TDCIPP were two times higher on the hand wipes than the other two compounds, with mono-ITP being detected at levels nearly five times greater than TPHP. Although detection frequencies were slightly higher in our current cohort, concentrations of TDCIPP and TPHP on the hand wipes were similar to previously reported levels in a small cohort of adults recruited in 2012 from central North Carolina.[86] TDCIPP was present at higher levels on the hand wipes compared to TPHP and TCIPP which reflects the previously observed trend for hand wipes but is dissimilar to the pattern typically observed in U.S. indoor dust.[86,105]

#### 3.3.1.3 Specific gravity-corrected urine

The target PFR metabolites were detected in all of the urine samples except for BCIPP (18% detection) (Table 4). Therefore, total BCIPHIPP, including glucoronide and sulfate conjugates and the free compound, was used as the primary metabolite to examine associations with TCIPP. Geometric mean concentrations of BDCIPP and DPHP were 2.23 ng/mL and 1.14 ng/mL, respectively. Concentrations of DPHP were similar to previously reported levels but BDCIPP within this cohort seemed to be two to three times higher than other reported studies of U.S. adult cohorts,[73,86] with levels most comparable to adult women over age eighteen who were sampled in Butt et. al (2014).[42]

The difference in BDCIPP concentration observed in our cohort may reflect higher exposure to TDCIPP, timing and location of the urine sample, or other lifestyle or demographic differences within the cohort. As a hypothesized metabolite of mono-ITP, ip-PPP was measured at two times higher concentrations than previously detected in adults, which could suggest increased exposure to FM550 components.[42] Our work is the first to measure concentrations of BCIPHIPP in a U.S. population; however, concentrations were roughly similar to an Australian cohort in which it was first measured.[35]

### 3.3.2 Comparing wristbands and hand wipes to urine

The levels of TDCIPP and TCIPP on wristbands were significantly and positively correlated with their corresponding urinary metabolites, BDCIPP and BCIPHIPP [$r_s$=0.59, p<0.0001, and $r_s$=0.62, p<0.0001, respectively (Table 5, Figure 6)], suggesting that silicone wristbands worn over a five day period do capture personal exposures. TPHP and mono-ITP concentrations on wristbands were not correlated with DPHP. DPHP may be a urinary metabolite of these two parent compounds; however, other chemicals may also metabolize to form DPHP [e.g. 2-ethylhexyl diphenyl phosphate (EHDPHP), isodecyl diphenyl phosphate (id-DPP)] which may explain the lack of association.[127] Similarly, mono-ITP concentrations were not correlated with ip-PPP, as ip-PPP may not be the primary metabolite or may be one of several potential metabolites of mono-ITP. Exposures to TPHP could originate from diet or other sources such as nail polish and

plastic bottles, which were not expected to be captured by the wristbands but would still result in the presence of urinary DPHP.[128,129]

**Table 5: Spearman correlation coefficients for PFR and PFR metabolite levels measured in paired wristbands (*n* = 40), hand wipes (*n* = 38), and specific gravity-corrected urine (*n* = 40).**

| | | Wristbands | | | | Hand wipes | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | TDCIPP | TCIPP | TPHP | Mono-ITP | TDCIPP | TCIPP | TPHP | Mono-ITP |
| **Urine** | BDCIPP | 0.59† | -0.01 | 0.24 | 0.33* | 0.37* | 0.05 | 0.19 | 0.04 |
| | BCIPHIPP | -0.17 | 0.62† | -0.04 | -0.06 | -0.01 | 0.46# | 0.16 | 0.06 |
| | DPHP | -0.10 | 0.06 | 0.27 | 0.09 | 0.09 | -0.02 | 0.29 | 0.14 |
| | ip-PPP | 0.09 | -0.01 | -0.23 | -0.25 | 0.18 | 0.09 | -0.23 | -0.24 |
| **Hand wipes** | TDCIPP | 0.39* | 0.04 | -0.12 | -0.09 | | | | |
| | TCIPP | 0.10 | 0.69† | -0.15 | -0.20 | | | | |
| | TPHP | 0.13 | 0.09 | 0.23 | 0.23 | | | | |
| | Mono-ITP | 0.02 | 0.15 | 0.32* | 0.31 | | | | |

*p<0.05, #p<0.01, †p<0.0001

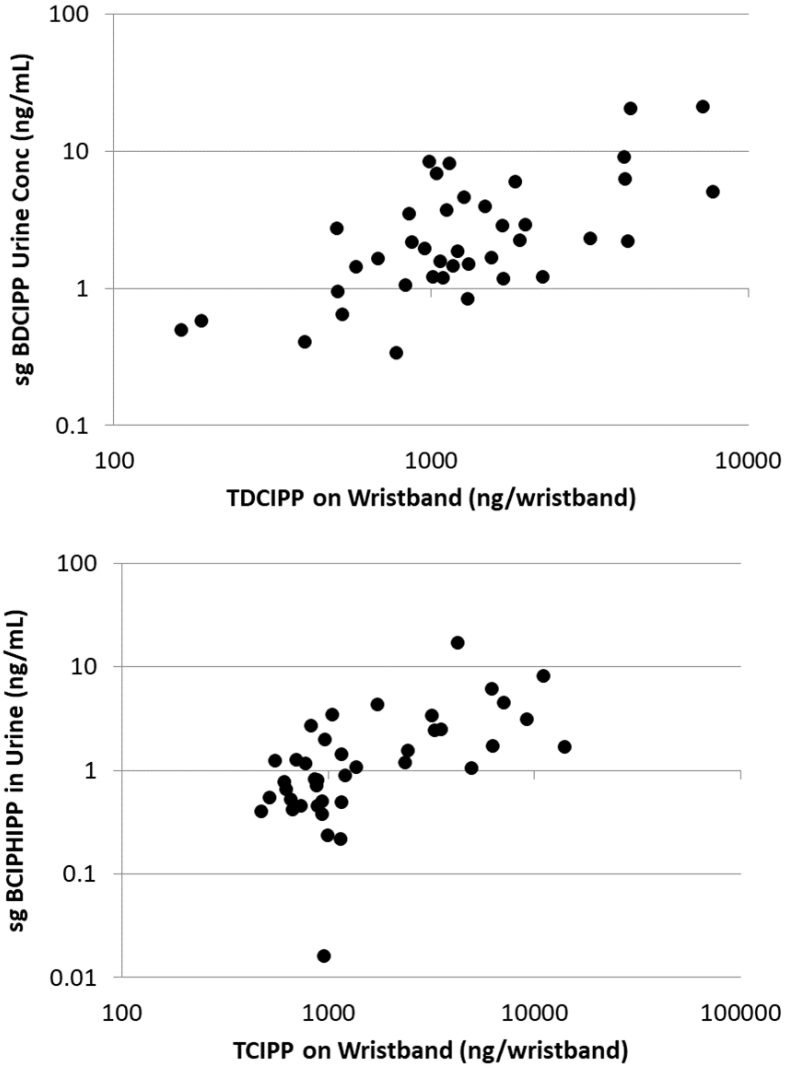



**Figure 6: Correlation of TDCIPP and TCIPP on wristbands with their urinary metabolites.**

Concentrations of TDCIPP and TCIPP on the hand wipes were also positively associated with urinary metabolites (i.e. BDCIPP and BCIPHIPP), although the correlations were smaller in magnitude than those for wristbands and urinary metabolites (Table 5). The correlation between hand wipe TDCIPP and BDCIPP in urine

was similar to a previous study with a North Carolina adult cohort, which is generally smaller in magnitude than the hand wipe to serum correlations for PBDEs observed in children.[86,88] This finding suggests that wristbands are likely better metrics of integrated exposure to these two compounds over five days compared to the use of hand wipes. DPHP levels in urine were not strongly correlated with TPHP and mono-ITP on hand wipes, again suggesting other potential sources of exposure to DPHP.[33,129] On the wristbands, mono-ITP was positively associated with urinary BDCIPP ($r_s$=0.33, p=0.04) which may reflect co-exposure with the parent compound, TDCIPP, particularly as the levels of mono-ITP and TDCIPP on the wristband were also weakly correlated ($r_s$=0.29, p=0.06) (Table 5, Table B2). Within each matrix (hand wipes or wristbands), mono-ITP and TPHP levels were highly correlated ($r_s$=0.71 and $r_s$=0.77, respectively, p<0.0001 for both), which could indicate that the two compounds were co-occurring and may share similar sources. PFRs in wristbands and hand wipes were significantly associated between matrices for TDCIPP and TCIPP ($r_s$=0.39 and $r_s$=0.69, respectively). Correlations for each PFR within a matrix (hand wipes or wristbands) can be found in Appendix B (Table B2).

While hand wipes are thought to capture information about multiple microenvironment in the short-term from recent exposures, wristbands may be capturing information from multiple microenvironments over the course of several days.[105,122] Different exposure pathways may be captured from the hand wipes compared

to the wristbands. Hand wipes are more likely to contain particle-bound compounds from contact with surfaces while wristbands may reflect more exposures from the gas phase and airborne particulates. Since hand wipes were collected either at home or when participants were coming from home, the hand wipes were more likely to reflect these short-term exposures in the home environment. To further investigate this possibility, we calculated correlations between PFRs and metabolites restricting to participants that spent more time at home (e.g. more time in a single microenvironment). TDCIPP and TCIPP on hand wipes and urinary metabolite concentrations were more strongly correlated when we restricted to participants who reported spending more time in their home ($n$=18; $r_s$=0.72 and $r_s$=0.67; $p<0.01$ for both; Table B3). Although the correlation between TDCIPP in wristbands was also slightly higher in participants who reported spending more time in their home environment ($r_s$=0.84), the correlation between TCIPP in wristbands and urinary BCIPHIPP was similar regardless of the percentage of time spend in different environments. This finding may indicate that wristbands perform better for these compounds because they integrate information over a longer time course and from more diverse microenvironments than hand wipes taken at a single point in time. However, hand wipes may be the better measure for examining exposures from surface contact or absorption through the dermal exposure pathway as described by Weschler and Nazaroff (2012) as well as from any hand-to-mouth activity.[130] The dermal absorption

pathway, particularly for PFRs, should be considered since models may be underestimating absorbed dosages, and handwashing may significantly alter absorption.[131]

Linear regression analyses were also conducted to examine exposure measures categorized by tertiles and personal characteristics as predictors of urinary metabolites. These analyses were conducted with and without outliers, particularly the one individual with notably low BCIPHIPP levels. Exclusion of the outliers did not change the interpretation of the results; therefore, we reported the outcomes including outliers. On average, concentrations of the three PFR metabolites were significantly higher in participants who had wristbands or hand wipes containing higher levels of TDCIPP, TCIPP, and TPHP (Table 6). For instance, participants with the highest levels of TDCIPP on their wristbands had urinary concentration of BDCIPP 3.34 times those with the lowest levels of TDCIPP ($10^{\beta}$=3.34; 95% Confidence Interval (CI): 1.70, 6.56; p=0.0009).

**Table 6: Results of regression analyses for associations with specific gravity (SG)-corrected urinary metabolites based on parent compounds on wristbands and hand wipes categorized as tertiles.**

| Levels of Parent Compound on Matrix | | SG-Corrected BDCIPP [$10^{\beta}$ (95% CI)- *p*-Value] | SG-Corrected BCIPHIPP [$10^{\beta}$ (95% CI)- *p*-Value] | SG-Corrected DPHP [$10^{\beta}$ (95% CI)- *p*-Value] |
|---|---|---|---|---|
| **Wristband** | Low | Reference ($p$=0.001 for trend) | Reference ($p$=0.002 for trend) | Reference ($p$=0.126 for trend) |
| | Medium | 1.85 (0.94, 3.64) – 0.07 | 0.85 (0.39, 1.86) – 0.68 | 0.83 (0.37, 1.90) – 0.66 |
| | High | 3.34 (1.70, 6.56) – 0.0009 | 4.00 (1.84, 8.70) – 0.0009 | 1.92 (0.85, 4.36) – 0.11 |
| **Hand wipe** | Low | Reference ($p$=0.032 for trend) | Reference ($p$=0.002 for trend) | Reference ($p$=0.274 for trend) |
| | Medium | 1.62 (0.75, 3.51) – 0.21 | 1.66 (0.75, 3.66) – 0.20 | 3.16 (1.41, 7.05) – 0.006 |
| | High | 2.34 (1.06, 5.14) – 0.04 | 3.81 (1.70, 8.55) – 0.002 | 1.58 (0.70, 3.59) – 0.26 |

With a few notable exceptions, behavior and activity patterns as well as age and sex were generally not associated with measured concentrations of PFRs on wristbands (Table 7). However, higher average time spent in a car, categorized dichotomously by the median (1 hour), was significantly associated with higher BDCIPP levels ($10^{\beta}$=2.33; 95% CI: 1.31, 4.17) (Table 7). More frequent washing behaviors such as more daily handwashing and weekly baths or showers, also categorized dichotomously by median, were associated with higher levels of BCIPHIPP in urine ($10^{\beta}$=2.61; 95% CI: 1.07, 6.31). BCIPHIPP was recently identified as a metabolite of TCIPP, and it is uncertain whether other sources related to washing may be contributing to BCIPHIPP levels in urine or other participant behaviors may be confounding this result.[78]

**Table 7: Results of regression analyses for predicting urinary concentrations of BDCIPP, BCIPHIPP, DPHP.**

| Predictor | SG-Corrected BDCIPP [$10^{\beta}$ (95% CI)- *p*-Value] | SG-Corrected BCIPHIPP [$10^{\beta}$ (95% CI)- *p*-Value] | SG-Corrected DPHP [$10^{\beta}$ (95% CI)- *p*-Value] |
|---|---|---|---|
| **Sex** | | | |
| **Female** | Reference | Reference | Reference |
| **Male** | 0.86 (0.45, 1.67) – 0.66 | 0.73 (0.33, 1.62) – 0.43 | 0.74 (0.36, 1.53) – 0.41 |
| **Age (years)** | 0.99 (0.96, 1.03) – 0.71 | 1.00 (0.95, 1.05) – 0.96 | 0.97 (0.93, 1.01) – 0.13 |
| **Avg times hands washed/day** | | | |
| **≤ 6 times/day** | Reference | Reference | Reference |
| **> 6 times/day** | 1.39 (0.74, 2.61) – 0.30 | 2.11 (1.01, 4.43) – 0.05 | 0.99 (0.49, 2.01) – 0.98 |
| **Avg times bath/shower taken/week** | | | |
| **≤ 8 times/week** | Reference | Reference | Reference |
| **> 8 times/week** | 1.58 (0.74, 3.36) – 0.23 | 2.61 (1.07, 6.31) – 0.04 | 1.21 (0.51, 2.88) – 0.65 |
| **Avg hours of day spent in home** | | | |
| **< 15** | Reference | Reference | Reference |
| **≥ 15** | 0.66 (0.35, 1.24) – 0.19 | 0.74 (0.34, 1.61) – 0.44 | 0.63 (0.32, 1.25) – 0.18 |
| **Avg hours of day spent at work/school** | | | |
| **< 6** | Reference | Reference | Reference |
| **≥ 6** | 0.78 (0.41, 1.48) – 0.44 | 1.15 (0.53, 2.22) – 0.71 | 1.34 (0.67, 2.70) – 0.40 |
| **Avg hours of day spent in car** | | | |
| **< 1** | Reference | Reference | Reference |
| **≥ 1** | 2.33 (1.31, 4.17) – 0.005 | 1.02 (0.46, 2.22) – 0.97 | 1.19 (0.58, 2.41) – 0.63 |

Our results should be interpreted in the context of several limitations. Only one paired wristband and hand wipe were collected per participant which does not account for individual variability. Further studies are needed to examine the utility of wristbands over designated periods of time (i.e. 1 day, 5 days, 10 days). In this study, we selected 5 days as the time period, but it is uncertain whether this is representative of average, longer-term exposures which could occur over the course of weeks, months, or even years. Wristband samples were collected over a short period of time (June to August) in central North Carolina so it is unclear how generalizable these results are to other seasons and climates. Our sample size of forty was relatively small which limited the number of variables that we could examine using multivariate regression analyses and may have restricted the power to detect other meaningful associations in the data. Additionally, first morning void urine samples were collected which should serve as a reliable average urine sample; however, collecting all urine samples throughout the five-day period would have served as improved measure for total exposure to the measured compounds. In our analyses, we assume urine PFR metabolites as the gold standard for exposure measurements for our comparisons with wristbands and hand wipes although there are still many data gaps in understanding PFR metabolism and excretion through urine. Lastly, our sample population included adults generally from the local community surrounding Duke University which led to a relatively homogenous cohort.

This may limit the generalizability of our results to the U.S. adult population but does not alter the internal validity of our study.

Overall, our results suggest that wristbands may serve as an additional and improved metric of exposure for organophosphate flame retardants compared to hand wipes. This is demonstrated by the greater magnitudes of correlations observed for TDCIPP and TCIPP with their urinary metabolites compared to those in hand wipes. These PFRs are classified as semi-volatile organic compounds, which suggests that they are likely partitioning between the gaseous and solid phases and specifically sorbing to multiple surfaces. The volatile fraction of compounds may also be a large source of exposure and uptake which may be underestimated with current exposure metrics. While hand wipes serve as more of a cross-sectional, single time point sample, wristbands may provide some insight into average exposures across a longer time period and capture some of the inhalation exposure that is currently lacking in measurements. Additionally, with the ability to capture exposures to multiple compounds simultaneously, silicone wristbands can improve how we examine exposures to mixtures in the environment. It is currently unclear whether the concentrations of these PFRs, particularly TDCIPP and TCIPP, are sorbing to the wristbands from the gaseous phase or from particles, which could be contributing to exposure via inhalation, ingestion of aerosolized small particles, or slow dermal absorption. Future studies should aim to elucidate the sources of TDCIPP and TCIPP on

the wristbands and thereby obtain a greater understanding of the primary pathway by which people are being exposed to these compounds.

# 4. Evaluating the use of silicone wristbands to measure personal exposure to brominated flame retardants

This chapter is reprinted with permission from Hammel, S.C.; Phillips, A.L.; Hoffman, K.; Stapleton, H.M. Evaluating the Use of Silicone Wristbands to Measure Personal Exposure to Brominated Flame Retardants. *Environ. Sci. Technol.* 2018, *52* (20), 11875-11885. Copyright 2018 American Chemical Society. The accompanying supporting information is included in Appendix C.

## *4.1 Introduction*

Consumer products have been frequently treated with additive flame retardants chemicals (FRs) as a manner of adhering to flammability standards worldwide. Polybrominated diphenyl ethers (PBDEs) were once the most commonly used class of flame retardant in a wide range of products such as furniture, electronics, and building materials.[70] However, due to extensive concerns about their persistence, bioaccumulative potential, and toxicity, PBDEs have been phased out globally over the last two decades, with the most recent being a U.S. voluntary phase out of DecaBDE in 2013.[132] Despite the phase-out, PBDEs are still found in products in many homes, likely due to low turnover rates and recycling of furniture, particularly the PentaBDE commercial mixture in furniture. For example, some televisions purchased in the U.S. as recently as 2017 were found to contain DecaBDE within the plastic casing.[8,46,133] As such, people are still being exposed to PBDEs, and serum biomarkers suggest exposure is widespread.[96,134]

A number of alternative brominated flame retardants (BFRs), some with similar structures to PBDEs, have been increasingly used as PBDE replacements. The PentaBDE commercial mixture, which was typically applied to furniture foam, has been replaced by other commercial mixtures such as Firemaster® 550 and 600 (FM550, FM600), which were recently characterized and shown to contain a variety of aryl phosphates and BFRs, including 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)-tetrabromophthalate (BEH-TEBP).[41,67] Octabromotrimethylphenylindane (OBIND), 2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine (TTBP-TAZ), decabromodiphenyl ethane (DBDPE), and tetrabromobisphenol A bis(2,3-dibromopropyl ether) (TBBPA-DBPE) have been used as replacements for DecaBDE, which was reported to be applied to plastic casings of electronics, among other products.[48,132,135]

Toxicity of PBDEs has been extensively assessed over the last few decades.[15,136] The individual BDE congeners associated with PBDE mixtures have been quantified in a number of environmental matrices such as air, sediment, dust, and human tissues, and negative health impacts such as thyroid hormone dysregulation and neurodevelopment deficits have been associated with exposure to these compounds in both human and animal studies.[10,11,68,69,137] In general, less is known about the alternative BFRs that are used as PBDE replacements. Components of FM550 have been associated with endocrine and metabolic disruption in exposed rodents and activation of nuclear receptors regulating adipogenic pathways in *in vitro* models.[40,79,138] They have also been

measured in different environmental matrices and in human biospecimens.[42,45,133] Very little is known about the toxicity potential of OBIND, DBDPE, TTBP-TAZ, and TBBPA-DBPE, although they have been detected in the environment, on product wipes, and in household dust.[48–50,135,139,140] With such structural similarity to BDE-209, DBDPE is often assumed to have similar toxicity and has been measured at similar detection frequencies and concentrations to BDE-209 on hand wipes and in dust.[85,141] In general, other than measurements in indoor air and house dust, little data is available on potential exposure to these alternative BFRs.

Historically, dust has been used as the primary external exposure measure for PBDEs in North America, as house dust has been shown to be significantly associated with serum PBDE measurements of residents.[87,89] In some cases, dust levels have been used as proxies for internal dose to quantitatively assess and monitor individual exposures. Similarly, hand wipes have been used to measure exposure as a method of estimating hand-to-mouth contact and exposure via dermal absorption and have been associated with both serum and urinary biomarkers for flame retardants.[86,88,142] To estimate inhalation exposure, both passive and active air samplers have been deployed in homes; however, personal air monitors have been shown to be generally more effective for sampling individual exposures across several micro-environments.[143–145] While all of these matrices serve as important measures for various exposure pathways, they only capture a single pathway or microenvironment (e.g., home environment), and

therefore necessitate the collection of numerous samples to capture an integrated picture of individual exposure. Biomarkers, which are typically used to determine internal doses, are invasive to collect (e.g., serum), analytically difficult to measure in biospecimen matrices, and expensive to analyze.

In recent years, silicone wristbands have been used as a method of assessing human exposure to various semi-volatile organic compounds in the environment such as FRs, plasticizers, industrial chemicals, and pesticides.[77,120,125,146–148] The wristbands provide the potential for a noninvasive and inexpensive tool for quantitative assessment of personal exposure. These are advantageous over other exposure measures such as dust and air samplers because they capture exposure from multiple microenvironments over a multiday time period. They may also capture individual exposures from multiple routes (i.e., inhalation, dermal absorption, and hand-to-mouth contact), whereas these other measures only often sample one exposure pathway. In this way, wristbands may represent a more sophisticated tool for assessing personal exposures than other methods that are more commonly in use. Previous work in our laboratory has shown that the wristbands serve as a reliable tool for quantifying personal exposure to organophosphate FRs (PFRs), as positive and significant correlations between the PFRs on the wristbands and corresponding metabolites in pooled urine samples were observed.[77] Since these compounds are rapidly metabolized ($t_{1/2}$= hours to days), this result suggested that the wristbands served as a good measurement of short-term

exposure. However, it is unclear how well the wristbands would reflect exposure for chemicals that have longer half-lives in the body, such as PBDEs ($t_{1/2}$= months to years).[149] Thus, we sought to examine if wristband levels would be associated with biomarkers for compounds that have longer half-lives in the body.

In the present study, our objective was to evaluate the relationship between PBDEs on silicone wristbands and serum biomarkers as well as analyze the wristbands for a variety of novel BFRs which may serve as replacements for the PBDE compounds. To our knowledge, this is the first study to examine the correlations between PBDEs on silicone wristbands with serum biomarkers, as well as the first to measure several DecaBDE replacements on the wristbands.

## *4.2 Materials and methods*

### 4.2.1 Study design

Study participants were recruited in August 2016 from the Duke University and Durham County communities in North Carolina, United States ($n$ = 30) by convenience sampling. Participants were eligible for the study if they were at least 18 years old, lived in their homes for at least one calendar year, and were willing to provide samples for the study (wear a wristband, give a serum sample, and complete questionnaires). All study protocols and materials related to the study were approved by the Duke University Institutional Review Board, and every participant provided informed consent prior to taking part in any aspect of the study.

### 4.2.2 Wristband collection

Commercially available wristbands were purchased in a single size and black color (24hourwristbands.com, Houston, TX) and cleaned as described in Hammel et al., with two 12-hour Soxhlet extractions with 1:1 ethyl acetate/hexane (v/v) and 1:1 ethyl acetate/methanol (v/v) and passive drying in a fume hood.[77] The wristbands were then wrapped in aluminum foil, which had been baked at 450°C, and placed in a labeled 40 mL amber jar. Participants were asked to wear the wristbands continuously for a 7-day period including during bathing, sleeping, or other daily activities. At the end of the study period, participants rewrapped the wristbands in clean aluminum foil and replaced it in the amber jar. Samples were stored at -20°C until extraction. Field blank wristbands ($n$ = 4) were not deployed and were stored at room temperature until extraction.

### 4.2.3 Serum collection

Each participant was asked to provide a blood sample on day 1 of the study period. A trained phlebotomist collected the samples using venipuncture to obtain 6-10 mL of blood in a serum separator tube. The blood was allowed to clot on ice for an hour then centrifuged at 3,000 rpm for 5 minutes to separate the red blood cells from the serum. These samples were stored at -20°C until extraction. Although the sample was taken at the time at which wristbands were deployed (day 1), serum PBDE levels have been shown to be stable over the course of a year (ICCs=0.87-0.99) in a sample size of 52

for the congeners for which we analyzed.[150] Therefore, we determined that the time of blood sample during the week-long sample period would not impact associations for exposure assessment.

### 4.2.4 Questionnaires

Study participants completed 3 short online surveys on alternating days within the 7 days during which they wore the wristbands. The surveys were similar to those distributed in Hammel et al., and results were handled in a similar fashion, with responses being dichotomized based on the median reported value (or category).[77] Briefly, participants were asked to provide information about demographics, time spent in various microenvironments, and a few daily activities such as handwashing frequency. Time spent in various microenvironments was averaged across each of the 3 surveys from the week. Handwashing frequency was queried on two separate days, and the lower reported range was used in analyses. Participants were additionally asked about the number of years they had lived in their current home (1-2, 3-4, 5-6, and 7+ years).

### 4.2.5 Wristband extraction

Wristband samples were extracted and analyzed for a suite of brominated flame retardants including 27 PBDEs, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB), bis(2-ethylhexyl)-tetrabromophthalate (BEH-TEBP), octabromotrimethylphenylindane (OBIND), decabromodiphenyl ethane (DBDPE), tetrabromobisphenol A bis(2,3-

dibromopropyl ether) (TBBPA-DBPE), and 2,4,6-tris(2,4,6-tribromophenoxy)-1,3,5-triazine (TTBP-TAZ) (Table C1, Figure C1). Using solvent-rinsed stainless steel scissors, each wristband and field blank was cut into 8 equal pieces to facilitate extraction then accurately weighed and placed into a labeled 50 mL glass centrifuge tube. The bands were spiked with $^{13}$C-EH-TBB (100 ng), $^{13}$C-BEH-TEBP (100 ng), 4'-fluoro-2,3',4,6-tetrabromodiphenylether (FBDE-69; 50 ng), and $^{13}$C-decabromodiphenyl ether ($^{13}$C-BDE-209; 100 ng) as internal standards. The samples were then extracted 3 times with 10 mL 1:1 hexane/acetone (v/v) via sonication extraction then concentrated to 1.0 mL using a Thermo Scientific SpeedVac Concentrator. These extracts were fractionated using Florisil® solid-phase extraction cartridges (Supelclean ENVI-Florisil, 6 mL, 500 mg bed weight; Supelco), eluting the first fraction (F1) with 8 mL hexane for brominated compounds and the second fraction (F2) with 10 mL ethyl acetate for organophosphate esters (data not included here). Each fraction was concentrated again to 1 mL using the SpeedVac Concentrator, with the F2 fractions transferred to autosampler vials and stored at -20 °C for future analysis. The F1 fractions were further purified by eluting through 12.0 g of deactivated silica gel (60-200 mesh), impregnated with 5% concentrated sulfuric acid by mass, using 1:1 hexane/dichloromethane (v/v) in 2 consecutive chromatography columns. Extracts were then concentrated to 1 mL using a nitrogen evaporator system and transferred to autosampler vials for analysis by gas chromatography/mass spectrometry (GC/MS) in electron capture negative chemical

ionization (ECNI) mode. Recovery of surrogate standards was evaluated using $^{13}$C-2,2′,3,4,5,5′-hexachlorodiphenyl ether ($^{13}$C-CDE141; 50 ng) for FBDE-69, $^{13}$C-EH-TBB, and $^{13}$C-BEH-TEBP and 4′-fluoro-2, 2′,3,3′,4,5,5′,6,6′-nonabromodiphenyl ether (FBDE-208; 100 ng) for $^{13}$C-BDE-209. Recoveries of FBDE-69, $^{13}$C-EH-TBB, $^{13}$C-BEH-TEBP, and $^{13}$C-BDE-209 were on average 105 ± 1%, 141 ± 8%, 51.2 ± 3%, and 61.1 ± 1%. Additionally, lab blanks ($n$ = 4) were analyzed alongside field blanks ($n$ = 4) and wristband samples for quality assurance and quality control.

TBBPA-DBPE was identified based on the presence of 79 and 81 m/z at a similar retention time as the authentic standard (Table C1, Figure C1). Quantification was performed using a standard from TCI (Tokyo, Japan).

### 4.2.6 Serum extraction

Serum was analyzed for PBDEs and extracted in a manner similar to Stapleton et al. and Hovander et al.[151,152] Briefly, serum samples were accurately weighed and spiked with FBDE-69 (5 ng) and $^{13}$C-BDE-209 (10 ng) as internal standards. Samples were vortexed following the addition of 1 mL 6.0 M HCl and 5 mL isopropyl alcohol. Then, 10 mL of 1:1 hexane/methyl-tert-butyl ether (MTBE) was added to the samples, which were vortexed again. Samples were allowed to stand for one hour then centrifuged at 2,500 RPM for 20 minutes. Organic layers were removed following centrifugation and extracted twice more with 10 mL hexane:MTBE. After, 5 mL of a 1% KCl solution and 5 mL hexane:MTBE were added to the organic fractions, vortexed, and centrifuged again

at 2500 RPM for 20 minutes. Again, the organic layers were removed following centrifugation and extracted twice more with 5 mL hexane:MTBE. Serum extracts were concentrated to 3 mL using a nitrogen evaporator then cleaned using solid-phase silica chromatography. The extracts were eluted through 10 g deactivated silica gel (60-200 mesh), impregnated with 40% sulfuric acid by mass, using 45 mL hexane. The eluent of each sample was again concentrated by nitrogen evaporator to 100 μL, transferred to autosampler vials, and spiked with 5.0 ng $^{13}$C-CDE-141 and 10 ng FBDE-208 to assess the recovery of FBDE-69 and $^{13}$C-BDE-209, respectively. The samples were analyzed using GC/ECNI-MS for 27 PBDEs. Average recovery of FBDE-69 and $^{13}$C-BDE-209 were 102 ± 30% and 69 ± 15%, respectively. Fetal bovine serum, which served as field blanks, and serum SRM 1958 (National Institute of Standards and Technology, Gaithersburg, MD) were extracted alongside the serum samples for quality assurance and quality control. One sample was lost during processing, leading to a sample size of 29. Measurements of SRM 1958 relative to the certified values were 82-123% for the PBDEs detected in serum samples within this study (BDE-28/33, -47, -99, -100, -153). PBDE masses in serum were normalized to total lipid content as well as to mass serum extracted. Total lipid (TL) content were calculated from serum triglycerides (TG) and total cholesterol (CHOL), which were measured via enzymatic techniques (Duke University Hospital Central Automated Laboratory, Durham, NC), using the equation TL=1.33*TG + 1.12*CHOL + 1.48 (g/L).[153]

### 4.2.7 Statistical analyses

Analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC). These were only conducted if analytes had >60% detection frequency. For samples with concentrations below the MDL, the concentrations were replaced by MDL divided by 2. All sample concentrations were blank-corrected based on the average field blank concentration. When the data were examined for normality, BFRs on wristbands and serum PBDEs were determined to be log-normally distributed. Therefore, Spearman correlation coefficients ($r_s$) were reported to assess the associations within wristbands and between wristbands and serum biomarkers. To account for the use of parametric and non-parametric statistical analyses, Pearson correlation coefficients using $log_{10}$-transformed concentrations were also reported in Appendix C (Table C4, C5).

Linear regression models were used to examine additional associations between data collected via the questionnaire and PBDE levels in the serum and BFRs on the wristbands. $Log_{10}$-transformed concentrations of analytes were used for the outcomes within the regression models; thus, beta coefficients were exponentiated and represent multiplicative change in the outcome variable relative to the reference category. PBDE concentrations on the wristbands were categorized into tertiles to examine relationships with serum levels, as a manner of reducing the potential bias from extreme observations

and allowing for a more flexible shape of the relationship between the wristbands and serum. Results were assessed at $\alpha = 0.05$ for significance in all analyses.

Analyses of serum biomarkers were performed with PBDE concentrations normalized to serum wet weight as well as total lipid content. Results between the two normalization methods were non-differentiable; therefore, the lipid-normalized serum concentrations and associations are presented here.

### 4.2.8 Evaluation of log $K_{OA}$

Data from this study and from Hammel et al. were used to examine associations between FR sorption to wristbands and their respective octanol-air partitioning coefficients (log $K_{OA}$).[77] Evaluating how FR sorption on wristbands relates to log $K_{OA}$ could provide additional insights for predicting which semi-volatile organic compounds (SVOCs), and possibly exposure pathways, are best captured by the wristbands. Wristband concentrations for FRs measured in our laboratory were normalized to mass per band per day. Compounds were included in the analysis if they were major components of FR application mixtures, defined as at least 1% by weight. Therefore, a subset of 6 PBDE congeners (BDE-47, -99, -100, -153, -154, and -209), all PFRs from Hammel et al., and novel BFRs detected here (EH-TBB, BEH-TEBP, DBDPE, TBBPA-DBPE, TTBP-TAZ) were included for a total of 15 compounds.[41,62,154] BDE-85 meets the criteria of being >1% in the PentaBDE mixture; however, BDE-85 and -155 co-elute in our GC/MS method so it was excluded from this analysis. Log $K_{OA}$ values were calculated

using the reported log $K_{OW}$ and Henry's Law constants reported on the EPA Chemistry Dashboard.[155] If experimental values were available, particular for the PBDEs, these were used instead of modeled data. Otherwise, the average predicted value given by the dashboard was used.

## *4.3 Results and discussion*

Of the 30 participants, approximately two-thirds were female, and the mean age was 34 years (range: 23-57 years; Table 8). Every participant completed the three questionnaires and provided all requested samples. The majority of participants (73%) had lived in their current home between 1-2 years.

**Table 8: Characteristics of BFR Wristband Cohort (n = 30).**

| Variables | Number (Percent) |
|---|---|
| **Sex** | |
| **Male** | 12 (40.0) |
| **Female** | 18 (60.0) |
| **Age (years)** | |
| **20-24** | 4 (13.3) |
| **25-29** | 9 (30.0) |
| **30-35** | 10 (33.3) |
| **36+** | 7 (23.3) |
| **Avg times hands washed/day** | |
| **1-3** | 4 (13.3) |
| **4-6** | 11 (36.7) |
| **7-9** | 9 (30.0) |
| **10+** | 6 (20.0) |
| **Avg hours of day spent in home** | |
| **≤ 15** | 15 (50.0) |
| **> 15** | 15 (50.0) |
| **Avg hours of day spent in work/school** | |
| **≤ 5.5** | 15 (50.0) |
| **> 5.5** | 15 (50.0) |
| **Avg hours of day spent in car** | |
| **≤ 1** | 18 (60.0) |
| **> 1** | 12 (40.0) |

## 4.3.1 BFRs in individual matrices

### 4.3.1.1 Wristbands

Our GC/ECNI-MS method sought to quantify 27 BDEs and 6 novel BFRs; however, only 26 of these BFRs were positively detected in the samples. Among these detected compounds, all BFRs were detected in >90% of samples with the exception of BDE-181, -190, -203, and -205 and OBIND (Table 9). BDE-47 was the most abundant

compound measured on the wristbands (GM = 55.9 ng/g band), closely followed by EH-TBB (GM = 43.0 ng/g band). This finding was similar to Kile et al. who analyzed wristbands worn by children and also observed BDE-47 to be most abundant of PBDEs on wristbands with similarly high detection frequency for BDE-47, -99, -100, -154, and -153.[125] Of the larger molecular weight compounds, BDE-209, DBDPE, and TBBPA-DBPE were each detected in every wristband at similar levels (GM=12.2, 12.2, and 14.2 ng/g band, respectively).

**Table 9: Geometric means and selected percentiles for BFRs in wristbands (*n* = 30) and PBDEs in serum (*n* = 29), with PBDEs reported >60% detection.**

| | | | | Percentile | | | |
|---|---|---|---|---|---|---|---|
| **Matrix and Compound** | Percent detect | MDL ($1x10^{-2}$) | Geometric Mean | 25th | 50th | 75th | Max |
| **Wristbands (ng/g band)** | | | | | | | |
| **PBDEs** | | | | | | | |
| **BDE-17** | 100 | 0.60 | 0.10 | 0.062 | 0.090 | 0.21 | 0.90 |
| **BDE-25** | 100 | 2.42 | 0.47 | 0.26 | 0.49 | 0.89 | 3.32 |
| **BDE-28,33** | 100 | 10.7 | 2.20 | 1.31 | 2.18 | 3.48 | 14.5 |
| **BDE-30** | 96.7 | 2.02 | 0.12 | 0.064 | 0.090 | 0.21 | 0.90 |
| **BDE-47** | 100 | 30.1 | 55.9 | 22.5 | 56.8 | 118 | 709 |
| **BDE-49** | 100 | 0.48 | 0.50 | 0.19 | 0.50 | 1.23 | 2.61 |
| **BDE-66** | 100 | 1.65 | 1.23 | 0.44 | 1.15 | 2.85 | 21.8 |
| **BDE-75** | 100 | 7.68 | 1.99 | 1.04 | 1.49 | 2.95 | 23.3 |
| **BDE-85,155** | 100 | 1.90 | 1.89 | 0.68 | 2.05 | 4.39 | 35.8 |
| **BDE-99** | 100 | 3.73 | 35.4 | 17.6 | 35.0 | 67.2 | 576 |
| **BDE-100** | 100 | 3.11 | 13.7 | 4.39 | 13.5 | 37.8 | 212 |
| **BDE-138** | 100 | 1.46 | 0.34 | 0.12 | 0.27 | 0.74 | 6.29 |
| **BDE-153** | 100 | 2.59 | 3.78 | 1.36 | 3.33 | 7.98 | 59.1 |
| **BDE-154** | 100 | 2.48 | 3.26 | 1.07 | 3.12 | 5.78 | 68.8 |
| **BDE-181** | 50 | 3.84 | 0.041 | 0.019 | 0.030 | 0.086 | 0.33 |
| **BDE-183** | 100 | 1.56 | 0.46 | 0.20 | 0.33 | 0.77 | 7.98 |
| **BDE-190** | 60 | 2.78 | 0.046 | 0.014 | 0.044 | 0.086 | 2.74 |
| **BDE-191** | 100 | 1.98 | 0.51 | 0.28 | 0.46 | 0.98 | 2.62 |
| **BDE-203,205** | 66.7 | 10.4 | 0.14 | 0.052 | 0.15 | 0.25 | 0.83 |
| **BDE-209** | 100 | 66.0 | 12.2 | 6.78 | 12.8 | 21.2 | 60.6 |
| **Novel BFRs** | | | | | | | |
| **EH-TBB** | 96.7 | 0.683 | 43.0 | 15.5 | 36.5 | 76.0 | 361 |
| **BEH-TEBP** | 90.0 | 4.40 | 32.6 | 26.3 | 50.6 | 146 | 1060 |
| **OBIND** | 40 | 5.88 | 0.098 | n.a. | n.a. | 0.083 | 2.46 |
| **DBDPE** | 100 | 56.7 | 12.2 | 5.43 | 7.83 | 31.3 | 222 |
| **TBBPA-DBPE** | 100 | 6.50 | 14.2 | 6.86 | 12.9 | 37.5 | 122 |
| **TTBP-TAZ** | 93.3 | 7.39 | 0.64 | 0.28 | 0.45 | 1.55 | 60.6 |
| **Serum (ng/g lipid)** | | | | | | | |
| **BDE-28,33** | 65.5 | 1.91* | 2.31 | 1.13 | 2.43 | 4.10 | 11.6 |
| **BDE-47** | 100 | 1.45* | 6.80 | 3.35 | 5.78 | 12.3 | 174 |
| **BDE-99** | 79.3 | 0.72* | 1.46 | 0.97 | 1.32 | 3.17 | 23.2 |
| **BDE-100** | 65.5 | 0.72* | 1.44 | 0.53 | 1.48 | 2.78 | 27.6 |
| **BDE-153** | 93.1 | 0.72* | 5.78 | 2.83 | 6.72 | 15.1 | 37.3 |
| **BDE-154** | 62.1 | 0.72* | 1.19 | 0.45 | 1.29 | 2.73 | 6.72 |
| **BDE-209** | 17.2 | 9.46* | - | - | - | - | - |

Correlations among BFRs detected within the wristbands were assessed for the most prominent PBDE congeners from Table 9 (Table 10). As expected, the PentaBDE components (BDE-28/33, -99, -100, -153, -154) were highly correlated on the wristbands ($r_s$=0.70-0.92, $p<0.01$). A similar trend for PentaBDEs has been observed in hand wipes and dust as well as serum.[105,122,134,156] BDE-209 was also significantly correlated with DBDPE ($r_s$=0.62, $p<0.01$), which suggests they have a similar exposure source and provides further evidence for their co-application.[46] In flatscreen TVs, DBDPE appears to have been used with BDE-209 based on product wipes and measurements in a plastic TV casing sample.[46,135] DBDPE on the wristbands was also positively and significantly correlated with TTBP-TAZ levels ($r_s$=0.39, $p<0.05$). With the phase-out of BDE-209, the co-application of DBDPE and TTBP-TAZ in electronics could explain similar exposure pathways, which was observed again in a small sample of recently analyzed television casings.[46] This suggests that DBDPE was and continues to be co-applied with other halogenated FRs in electronics through different generations of electronic production (pre- and post-BDE-209 phase-out). Additionally, EH-TBB and BEH-TEBP were significantly correlated on the wristbands ($r_s$=0.50, $p<0.01$), which was expected given their frequent use together in the Firemaster® mixtures and applications in products.[3,41] In this study, BFR concentrations on bands were generally not impacted by other covariates such as age or sex of the participants or time spent in various microenvironments, although this is a small sample size (Table C2, C3).

**Table 10: Spearman correlation coefficients for BFRs measured on wristbands (*n* = 30).**

| | BDE-28,33 | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-154 | BDE-209 | EH-TBB | BEH-TEBP | DBDPE | TBBPA-DBPE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **BDE-47** | **0.89**# | | | | | | | | | | |
| **BDE-99** | **0.68**# | **0.78**# | | | | | | | | | |
| **BDE-100** | **0.83**# | **0.92**# | **0.86**# | | | | | | | | |
| **BDE-153** | **0.73**# | **0.85**# | **0.70**# | **0.84**# | | | | | | | |
| **BDE-154** | **0.70**# | **0.84**# | **0.81**# | **0.93**# | **0.92**# | | | | | | |
| **BDE-209** | 0.10 | 0.24 | 0.07 | 0.23 | **0.38*** | 0.31 | | | | | |
| **EH-TBB** | 0.15 | 0.19 | 0.21 | 0.13 | -0.03 | 0.07 | -0.06 | | | | |
| **BEH-TEBP** | -0.07 | 0.05 | -0.21 | -0.16 | -0.09 | -0.17 | -0.09 | **0.50**# | | | |
| **DBDPE** | 0.24 | 0.27 | 0.12 | 0.21 | **0.37*** | 0.25 | **0.62**# | 0.03 | 0.06 | | |
| **TBBPA-DBPE** | -0.28 | -0.29 | **-0.37*** | -0.34 | -0.15 | -0.21 | 0.28 | 0.05 | 0.11 | 0.13 | |
| **TTBP-TAZ** | -0.05 | 0.04 | -0.03 | -0.03 | 0.11 | 0.07 | 0.33 | 0.31 | 0.33 | **0.39*** | 0.26 |

*p<0.05, #p<0.01

#### 4.3.1.2 Serum

Serum samples were analyzed for a suite of PBDE compounds. While the serum extraction method used here has only been optimized for PBDEs, we did attempt to screen for the novel BFRs in the serum extracts; however, no discernible peaks were present for novel BFRs. Therefore, it is possible that our extraction method may not have recovered these analytes. Only 6 BDE congeners were detected in >60% of the samples (Table 9). In general, the serum PBDEs were similar to or lower than other reports in the U.S. from recent years.[96,104,134,157] While this decline in certain congeners like BDE-47 appears to reflect the PentaBDE phase-out, continued detection of these congeners in serum suggests persistent exposure, which is especially concerning since these congeners have half-lives on the order of years in serum.[149]

### 4.3.2 Relationship between wristbands and serum

Correlations between wristbands and serum were assessed for the 6 BDE congeners detected in serum. Concentrations of BDE-47, -99, -100, and -153 measured in paired wristbands and serum were positively and significantly correlated ($r_s$=0.39-0.57, $p<0.05$; Table 11, Figure 7), suggesting that silicone wristbands worn for seven days capture relevant personal exposures to PBDEs. The wristband-serum relationships were also statistically significant between congeners, in particular BDE-47, -99, and -100, with wristband levels ($r_s$=0.39-0.61, $p<0.05$; Table 11), which seems reasonable given their likely co-exposure from the PentaBDE commercial mixture. The half-lives of these

particular BDEs in serum range from 1.6 to 6.5 years, with BDE-47 and -100 falling on the lower end of the range and BDE-153 having the longest estimated half-life.[109] Although the wristbands were worn for only a 7-day period, these data suggest that the wristbands capture quantitative individual exposures to compounds with longer half-lives. The significant relationship between wristbands and serum is likely reflective of a chronic exposure to PBDEs in the home environment, which has been previously shown to be consistent at multiple time points in house dust over the course of a year.[158] As dust ingestion is considered to be one of the primary pathways of exposure for PBDEs, it is unlikely that PBDE exposure fluctuates drastically over a short period of time, especially since these compounds were phased out over a decade prior to the sampling period and the participants in this study lived in their homes for at least a year. Similarly, serum PBDEs have been shown to be consistent over a year-long time period, suggesting that the time of blood collection during our study period would likely not impact associations observed between the wristbands and serum.[150] Positive and significant correlations between PBDEs in paired house dust and serum samples have also been demonstrated previously.[87,88] While PBDEs in the environment and serum may be declining over time, the decline would be gradual and expected to be proportional to prior exposure. Therefore, this decline is also not expected to impact the associations observed between wristbands and serum.

**Table 11: Spearman correlation coefficients for PBDEs measured in paired wristbands and serum (*n* = 29).**

| | | Serum | | | | | |
|---|---|---|---|---|---|---|---|
| | | BDE-28,33 | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-154 |
| **Wristband** | BDE-28,33 | 0.28 | **0.41*** | 0.34 | **0.39*** | 0.29 | **0.43*** |
| | BDE-47 | 0.35 | **0.52#** | **0.45*** | **0.39*** | **0.44#** | 0.33 |
| | BDE-99 | **0.57#** | **0.49#** | **0.57#** | **0.45*** | 0.25 | 0.22 |
| | BDE-100 | **0.38*** | **0.58#** | **0.49#** | **0.40*** | 0.31 | 0.21 |
| | BDE-153 | 0.21 | **0.51#** | **0.42*** | **0.42*** | **0.39*** | 0.20 |
| | BDE-154 | 0.34 | **0.61#** | **0.51#** | **0.47#** | 0.34 | 0.15 |
| | BDE-209 | -0.11 | 0.10 | 0.04 | -0.04 | 0.10 | -0.07 |

*p<0.05, #p<0.01

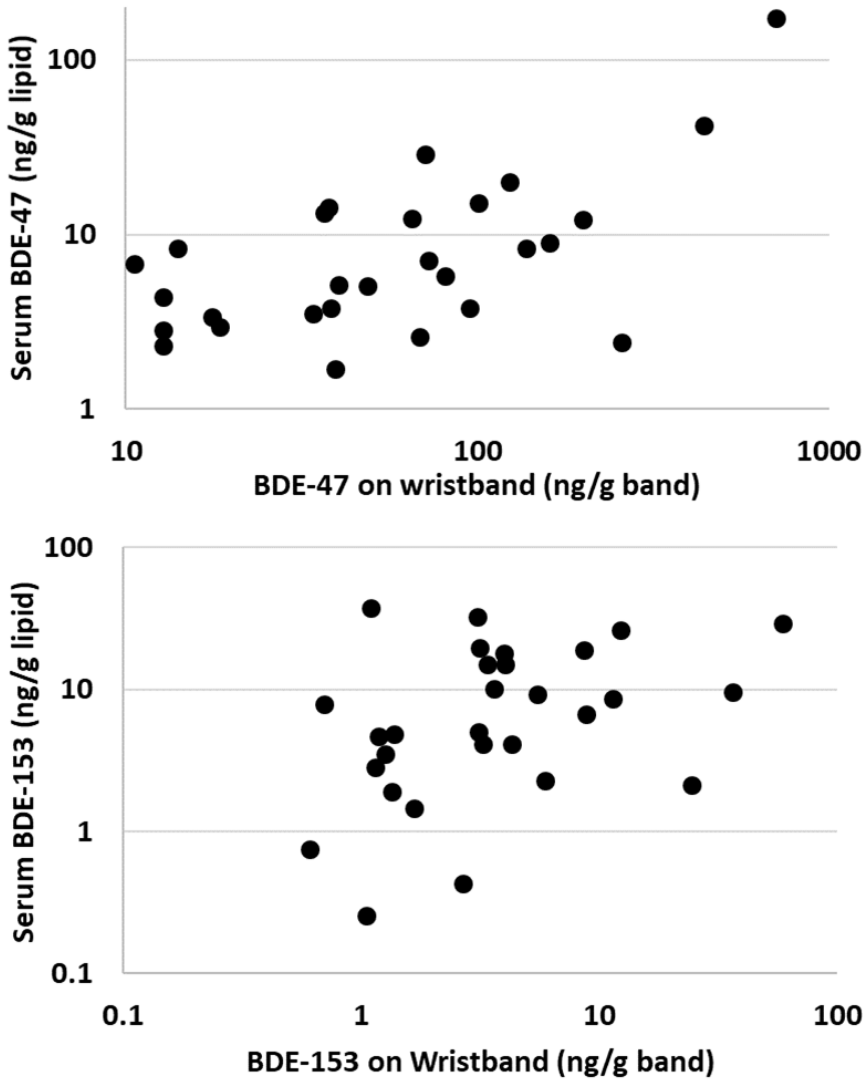



**Figure 7: Associations between wristbands and serum biomarkers for BDE-47 and BDE-153.**

Associations between serum and wristbands were further analyzed by categorizing the BDE levels on the wristbands into tertiles to assess their sensitivity for measuring reflective changes in serum (Figure 8). In general, the trends observed suggest that low, middle, and high BDE levels on the wristbands do indeed reflect

similar and significant associations with serum ($p<0.05$). For example, individuals within the highest tertile of BDE-99 on the wristbands had 3.75 times higher levels of BDE-99 in their serum, compared to the lowest wristband tertile ($p=0.001$; Figure 8). None of the serum biomarkers were associated with BDE-209 on the wristbands, which is unsurprising since BDE-209 is typically used in different applications from the PentaBDE congeners and may have differing pathways of exposure due to physicochemical properties.

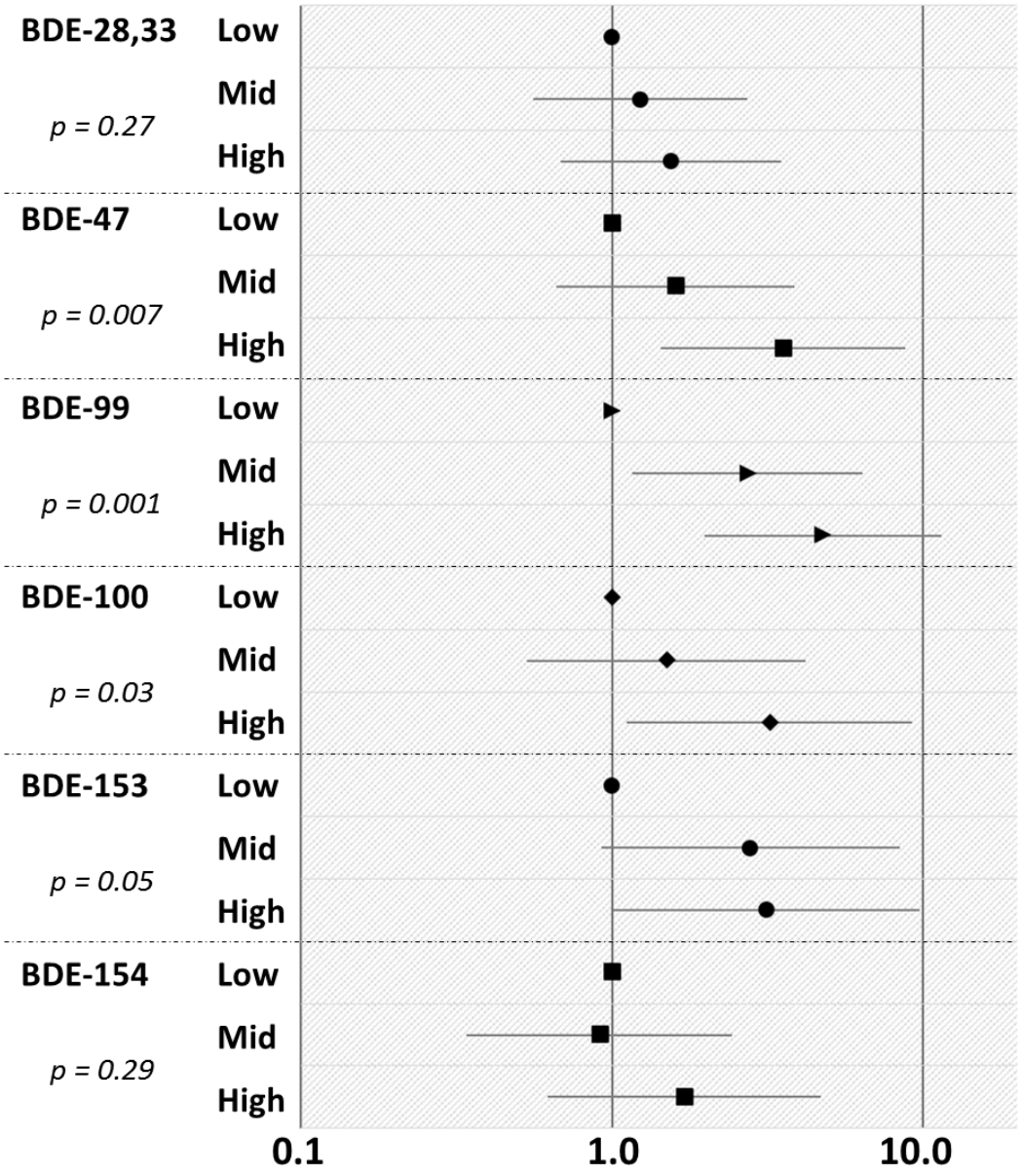



**Figure 8: Multiplicative change ($10^{\beta}$) and 95% confidence intervals in serum biomarkers based on the BDE compounds on wristbands categorized by tertiles. The low category for each congener served as the reference. *P*-values describe the *p* for trend.**

In bivariate analyses, age was positively associated with serum BDE-100 and BDE-154 levels ($p<0.05$; Table C3). In contrast, during the NHANES 2003-2004 cycle,

serum PBDEs were observed to decrease with age until around age 60 after which the levels increase again, possibly due to bioaccumulation or slower metabolism/excretion.[18] Our age range was much narrower, with 63% of our study population falling between 25-35 years old (Table 8). Additionally, the NHANES study was prior to the phase-out of PBDEs in the U.S. so exposure patterns for these compounds may have changed since then, thereby explaining the opposite trend with age.

Associations with BDEs and sex, handwashing frequency, or time spent in various microenvironments were generally not observed in this study, with the exception of a suggestive increase in levels of serum BDEs-28/33, -47, and -99 for individuals who reported spending more time each day in their car ($10^{\beta}$=2.1-2.4, $p<0.1$; Table C2, C3). This suggests that perhaps spending more time in a car on a daily basis could lead to an increase in PBDE exposure, or that cars may serve as a source of exposure to these compounds. We were unable to evaluate bathing differences in this study population since the majority of participants (70%) bathed between 6-8 times per week. Although we could not adjust for many potential confounding variables simultaneously due to the small sample size, we attempted to adjust the regression models examining the association between serum and wristbands (categorized in tertiles) for variables associated with serum (e.g., age). The relationship between wristbands and serum was not expected to be confounded by these variables since most

were not significantly related to wristband PBDE levels, and the results were qualitatively similar (data not shown).

### 4.3.3 Wristband concentrations and log $K_{OA}$

In general, the BFR concentrations measured on wristbands in this study were lower than the PFR concentrations measured in our previous study, which reflects the current trend in household dust.[105–107,133] In wristbands, this trend could either reflect greater use of PFRs in products in the average indoor environment, or differences in emissions due to differences in their physicochemical properties (e.g., vapor pressure). When the geometric means of 15 FR compounds were plotted against their respective octanol-air partitioning coefficient (log $K_{OA}$) values, a significant decreasing trend was observed ($r_s$ = -0.69, p=0.005; Figure 9). Each individual data point is also graphed with the geometric means, and it is evident that a decreasing geometric mean concentration on the wristbands is associated with an increase in the log $K_{OA}$ values. This suggests that lower molecular weight compounds with higher vapor pressures may be more abundant in the air and become absorbed by the wristbands at higher rates. However, it should be noted that in this analysis we were unable to account for application and emission rates from specific products, which would also be a factor in this trend.[159]

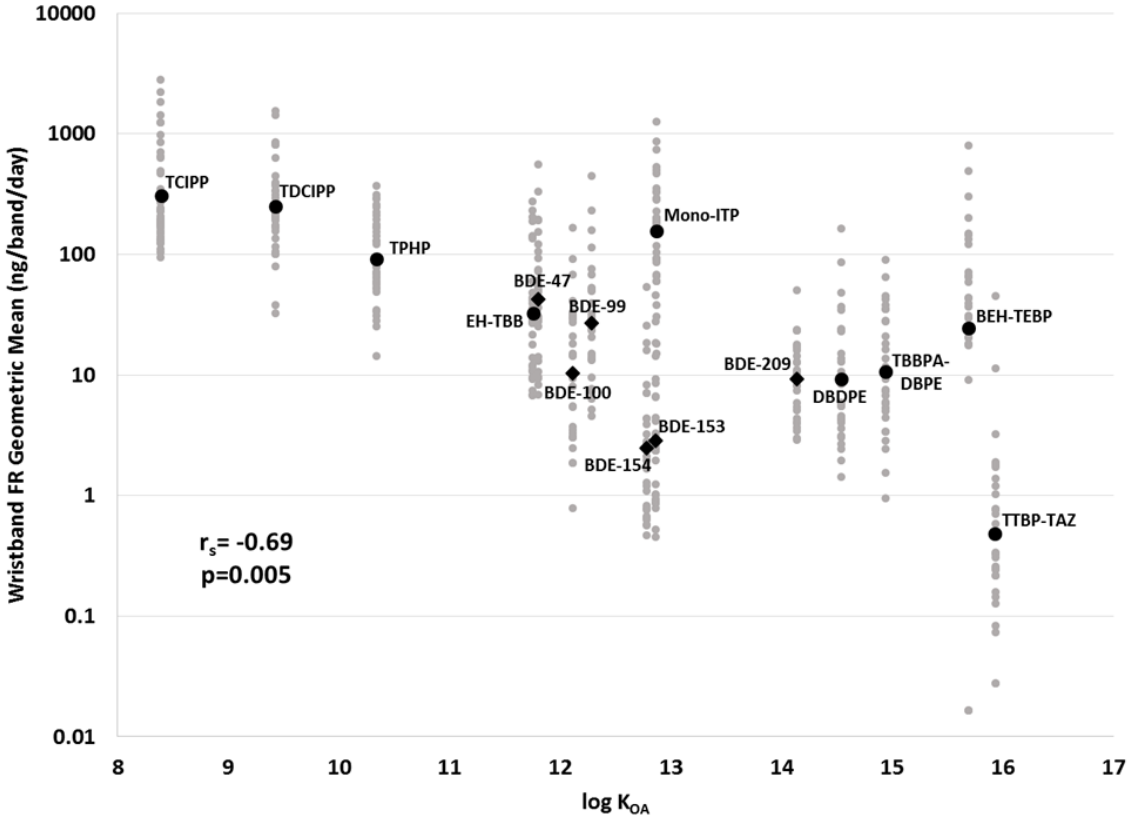



**Figure 9: Concentrations of 15 compounds measured on the wristbands per band per day based on log $K_{OA}$ of the compound. Each individual wristband is plotted in gray with the geometric mean plotted in black. Geometric means of BDE congeners are demarcated by diamonds with all other FRs are circles. The Spearman correlation coefficient was calculated from the geometric means and log $K_{OA}$ values.**

Given their physicochemical properties, it is likely that the high molecular weight compounds such as BDE-209, DBDPE, and TBBPA-DBPE are particle-bound in indoor air (at 25°C) rather than present in the gas phase.[160–163] Previous work in a different laboratory examining log $K_{OA}$ and binding to the wristbands reported that the wristbands effectively captured compounds in the log $K_{OA}$ range of 2 to 13; however, preparation of these samples included washing the wristbands with water and isopropanol which could have removed more particles and therefore compounds with higher log $K_{OA}$ values from the wristbands.[164] Compounds in the log $K_{OA}$ range of 8 to 12 have been examined in the context of hand wipe samples in both adults and children, with dermal absorption suggested to be a primary exposure pathway via partitioning of semi-volatile organic compounds (SVOCs) from air directly to skin surface lipids.[130,165] The fact that the wristbands capture exposure to compounds within this range of log $K_{OA}$ values prompts the question of whether the wristbands themselves may serve as a mimic of the skin surface and therefore capture the dermal absorption exposure pathway, regardless of whether the compounds are in the gas phase or bound to aerosols. As reported by Harner and Shoeib, 80% of BDE-153 would be bound to aerosols at 25°C compared to 17% of BDE-47 at the same temperature.[163] Nonetheless, both of these compounds were significantly correlated between wristband BFR levels and serum biomarkers ($r_s$=0.39 for BDE-153, 0.52 for BDE-47, $p<0.05$, Table 11). While exposure to PFRs have been generally accepted to be via inhalation and dermal

absorption, the same has not been the case for PBDEs.[71,131,166–168] Therefore, wristbands may have the potential to be used in examining the dermal absorption pathway for a large range of SVOCs, which has largely been underestimated in exposure assessment.

### 4.3.4 Limitations

Our results should be examined in the context of several limitations. Only one paired wristband was collected per participant and therefore serves as a cross-sectional sample that attempts to predict a longer-term exposure. Additional studies should determine how wristband deployment periods may affect associations with serum biomarkers. The wristband and serum samples were all collected in August 2016 and from a generally homogenous population around Duke University and Durham County, NC. Because our study population was relatively small, we were unable to fully consider for potential confounders; however, the homogeneity of the population could be advantageous by reducing residual confounding. Nonetheless, the homogenous population may limit generalizability. Future studies with larger sample sizes should evaluate potential confounding variables. In our analyses, we assume serum biomarkers are the gold standard for assessing BDE exposure. As some of the compounds for which we analyzed (e.g., DBDPE) do not have reliable internal dose measurements, it prompts the possibility of using external exposure measures such as wristbands as a gold standard for assessing exposure. Given that the current study and previous studies have shown that wristbands hold the potential to enhance assessment of personal exposures,

further work with true validation studies are needed to reduce the risk of exposure misclassification if used in future epidemiological studies.

### 4.3.5 Implications

Wristbands could potentially be used as an inexpensive and non-invasive method of measuring personal exposure that might replace or complement the complexity of large-scale biomonitoring endeavors. This could provide opportunities for expanded monitoring during critical periods of development or susceptibility, which would be highly beneficial for epidemiological studies. Wristbands also present the potential of measuring integrated exposure to hundreds of compounds with a single sample, thereby allowing for the evaluation of individual exposure to mixtures. Oftentimes, biomarker analysis is limited to single chemicals or classes of compounds due to cost or availability of the biospecimen samples. Despite being considered the gold standard for accurately measuring personal exposure to environmental chemicals, biomarkers often involve invasive and difficult collection techniques and require cumbersome sample processing.[169] In addition, the low levels at which biomarkers are often found in the body present an analytical challenge, and some environmental chemicals lack appropriate biomarkers altogether (e.g., those that are rapidly metabolized).[170] With the ability to simultaneously sequester compounds from a wide range of physicochemical properties, the diversity of chemical exposures that can be measured with a single wristband sample has the potential to significantly increase the

power of environmental epidemiological studies and collect crucial data on exposures to mixtures.

Our results suggest that silicone wristbands may be effective tools for accurately and quantitatively assessing individual PBDE exposure. Because they have been previously effectively used to capture PFR exposure, compounds with shorter half-lives and lower log $K_{OA}$ values compared to PBDEs, this study demonstrates that silicone wristbands are likely effective at capturing personal exposure for a wide range of SVOCs in which inhalation and dermal absorption are predominant exposure pathways.

# 5. Children's residential exposure to organophosphate ester flame retardants and plasticizers: Investigating exposure pathways in the TESIE study

This chapter is adapted with permission from Phillips, A.L. and Hammel, S. C.; Hoffman, K.; Lorenzo, A. M.; Chen, A.; Webster, T. F.; Stapleton, H. M. Children's residential exposure to organophosphate ester flame retardants and plasticizers: Investigating exposure pathways in the TESIE study. *Environ. Int.* 2018, *116*, 176–185 (Publisher: Elsevier). A. L. Phillips and S. C. Hammel are co-first authors on the publication. Specifically, S.C. Hammel contributed to participant recruitment, sample collection, statistical analyses, table and figure design, and writing and editing of the manuscript. The accompanying supporting information is included in Appendix D.

## *5.1 Introduction*

Flame retardants (FRs) are chemicals added to consumer products and building materials to slow or prevent their combustion. Historically, polybrominated diphenyl ethers (PBDEs) were used to treat a wide array of products; however, following their phase-out in the early 2000s, organophosphate esters (OPEs) have been increasingly used to meet residential and commercial flammability standards.[8] In addition to flame retardant applications in furniture, electronics, and insulation, OPEs are heavily used as plasticizers. In fact, it is estimated that the global market for OPEs will grow from $1.3 billion in 2014 to $1.6 billion in 2019, with plastic applications accounting for the majority of this growth.[171] For aryl OPEs, this projected increase will likely be

compounded by the recent Consumer Product Safety Commission (CPSC) ruling banning the use of organohalogen flame retardants in several consumer product categories in the United States.[7] Aryl OPEs are anticipatory substitutes for the banned organohalogen flame retardants, and are already used extensively in commerce.[41]

Because OPEs are applied to products in an additive rather than reactive manner, they can migrate out of the treated product over time, leading to human exposure.[172] Widespread use of OPEs has led to their ubiquitous detection in air and in dust in a variety of indoor environments.[86,173,174] Many recent studies have indicated human exposure to OPEs is near ubiquitous with frequent detection of OPE metabolites in urine.[34,77,175] Other studies have highlighted the potential for OPEs to impact human health as endocrine disruptors, reproductive-, developmental-, and neuro-toxicants.[150-154] This is concerning for young children who often have higher FR exposures compared to other age groups and are at a particularly vulnerable time in development.[35,44,178,179]

Previous studies have indicated that inadvertent ingestion of house dust is the largest contributor of exposure for PBDEs in North American populations, while diet is thought to be a primary source of exposure in European populations.[180–184] Correspondingly, measures of FRs in house dust have often been used as a paradigm for estimating exposure. More recently, hand wipes have been used to characterize human exposure to FRs, and have been shown to be have potential as an exposure metric for

OPEs in particular.[86,105,142] In addition, *in vitro* findings demonstrate that dermal absorption likely plays a role in the exposure pathway for OPEs.[131,185]

Despite ongoing and potentially increasing human exposure to OPEs, very few studies have investigated factors that influence OPE exposure in children, especially for the novel, aryl OPEs. The Toddlers' Exposure to SVOCs in the Indoor Environment (TESIE) study allows for an ideal opportunity to address some of these data gaps. Approximately 200 children, aged 3 to 6 years, participated in the TESIE study, with home visits conducted from 2014 to 2016. The current study utilized paired samples of dust, hand wipes, and urine collected from TESIE participants during home visits to assess determinants of OPE exposure. Figure 10 shows the structures of the parent compounds and their corresponding known metabolites discussed in this paper; structures are not included for tris(2-butoxyethyl) phosphate (TBOEP) and tris(2-chloroethyl) phosphate (TCEP) for which metabolites were not analyzed, as well as for individual isopropylated triarylphosphate (ITP) and *tert*-butylated triarylphosphate (TBPP) isomers. Relationships between urinary OPE metabolite levels and dust concentrations, hand wipe levels, demographic variables (e.g., age and mother's race/ethnicity), and average outdoor temperature were examined to determine their potential impact on children's exposure to OPEs.

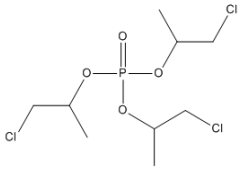
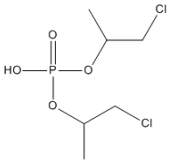
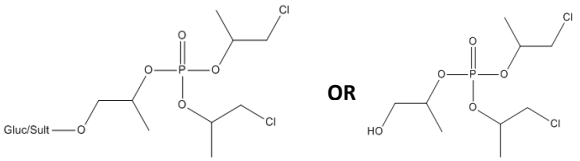
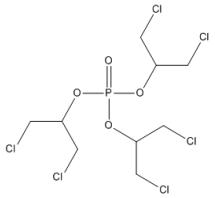
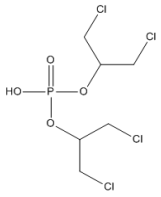
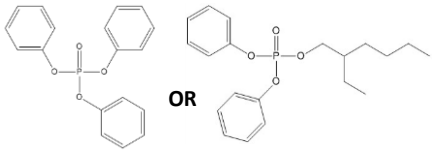
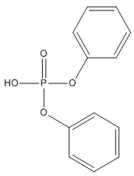
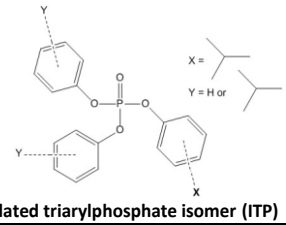
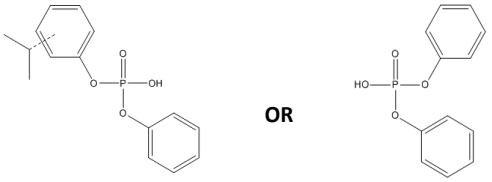
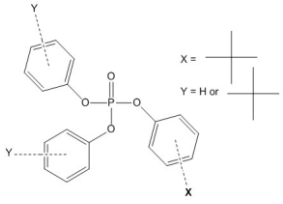
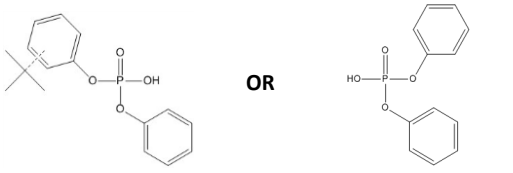
| Parent Compound | Urinary Metabolite |
|---|---|
|  Tris(1-chloro-2-isopropyl) phosphate (TCIPP) |  Bis(1-chloro-2-isopropyl) phosphate (BCIPP)<br>  Bis(1-chloro-2-isopropyl) 1-hydroxy-2-isopropyl phosphate (BCIPHIPP) |
|  Tris(1,3-dichloroisopropyl) phosphate (TDCIPP) |  Bis(1,3-dichloroisopropyl) phosphate (BDCIPP) |
|  Triphenyl phosphate (TPHP) OR 2-Ethylhexyl diphenyl phosphate (EHDPHP) |  Diphenyl phosphate (DPHP) |
|  Isopropylated triarylphosphate isomer (ITP) |  Isopropylphenyl phenyl phosphate (ip-PPP) OR Diphenyl phosphate (DPHP) |
|  *Tert*-butylated triarylphosphate isomer (TBPP) |  *Tert*-butylphenyl phenyl phosphate (tb-PPP) OR Diphenyl phosphate (DPHP) |

**Figure 10: Parent compounds and urinary metabolites for OPEs.**

## *5.2 Materials and methods*

### 5.2.1 Study design

Mothers recruited as part of the Newborn Epigenetics STudy (NEST), a prospective pregnancy cohort study based in central North Carolina, were re-contacted and their children were invited to participate in the Toddler's Exposure to SVOCs in the Indoor Environment (TESIE) study.[186,187] Hoffman et al. 2018 provides a detail comparison of families participating in both NEST and the TESIE study.[187] Briefly, children (n=203) from 190 homes in were recruited and participated in the TESIE study between September 2014 and April 2016 when children were approximately 3-6 years of age. The objective of this study was to measure prenatal and postnatal exposure to SVOCs and examine associations with health outcomes. The study population is described in Table D1 and more extensively in Hoffman et al. 2018.[187] All study protocols and related materials were approved by the Duke Medicine Institutional Review Board for Clinical Investigations. Legal guardians provided informed consent prior to the collection of samples and questionnaire data.

### 5.2.2 Sample Collection

Research personnel visited the homes of enrolled participants to conduct questionnaires with legal guardians and collect samples from the home and children. Families were instructed not to vacuum their homes for two days prior to the scheduled visit. During the home visit, a hand wipe sample was collected from each child using

pre-cleaned cotton twill wipes (4x4 in., MG Chemicals) wrapped in aluminum foil, similar to previously described methods.[122] A gloved researcher collected each sample by soaking the twill wipe with 3 mL isopropyl alcohol and wiping the entire surface area of both of the child's hands from wrists to fingertips, including between each of their fingers. Hand wipes were then rewrapped in foil and stored at -20°C until analysis. To collect a house dust sample, the entire exposed floor area of the main living area was vacuumed using a Eureka Mighty Mite vacuum fitted with a cellulose thimble within the hose attachment.[88] For each visit, an identical vacuum was used to collect the samples. The hose attachment was cleaned with soap and water and solvent rinsed in between each home visit to prevent cross-contamination. In our sampling design, dust passes straight from the hose attachment into the thimble during collection. As such, we do not anticipate OPE contamination from the vacuum itself. Each thimble was wrapped in aluminum foil and stored at -20°C until analysis.

Additionally, during the home visit, families were given collection kits for urine samples. Three spot urine samples were collected from each child by their parent during a 48-hour period. Urine samples were stored frozen in the families' homes during the sampling period. After the three individual samples were collected, the urine was transported to our research laboratory on ice and stored at -20°C. Prior to analysis, the samples were thawed, and equal volumes of each urine sample were pooled to form a composite.

During the home visits, the week of sample collection was recorded. From this week, average outdoor temperature was retrieved from the National Weather Service website to examine the potential impact of temperature on exposure pathways.

### 5.2.3 Hand wipe extraction

Hand wipes were extracted and analyzed similar to methods developed by Van den Eede at al. 2012.[85] Wipes were spiked with the following internal standards: $d_{15}$-tris(1,3-dichloro-2-propyl) phosphate ($d_{15}$-TDCIPP; 45.6 ng) and $^{13}$C-triphenyl phosphate ($^{13}$C-TPHP; 38.0 ng). Hand wipes were extracted in 1:1 dichloromethane:hexane (v/v) by sonication, and extracts were concentrated to ~1 mL using a SpeedVac™ Concentrator. Extracts were cleaned using Florisil® solid-phase extraction cartridges (Supel-clean ENVI-Florisil, 6 mL, 500 mg; Supelco), eluting the F2 fraction containing OPEs with 10 mL ethyl acetate. F1 fractions eluted using 6 mL hexane and F3 fractions eluted using 6 mL methanol were also collected and used for analyses not described in this paper. F2 fractions were concentrated to ~1 mL using a SpeedVac™ concentrator and were reconstituted in hexane prior to GC/MS analysis. Recovery of internal standards was assessed using $d_9$-tris(2-chloroethyl) phosphate ($d_9$-TCEP; 164.8 ng) for $d_{15}$-TDCIPP, and $d_{15}$-triphenyl phosphate ($d_{15}$-TPHP; 164.8 ng) for $^{13}$C-TPHP. Field blanks (n=14) were analyzed in each batch for quality assurance and quality control (Table D2).

### 5.2.4 Dust extraction

Dust samples were sieved to <500 microns prior to extraction. Dust samples were extracted in the same manner as hand wipe samples, with minor adjustments. Dust extracts were split, reserving ~25% for cell-based toxicity assays, 25% for non-targeted analysis, and the remaining 50% for targeted analyses described here. For this reason, internal standards ($d_{15}$-TDCIPP; 173.4 ng and $^{13}$C-TPHP; 173.4 ng) were spiked following extraction. Laboratory blanks (n=6) and house dust standard reference material (n=5; SRM 2585 National Institute of Standards and Technology (NIST), Gaithersburg, MD) were analyzed in each batch for quality assurance and quality control (Table D2). Measurements of OPEs (TCEP, TCIPP, TDCIPP, and TPHP) in SRM 2585 were 86-132% of the values reported in published literature and were deemed acceptable for quality assurance and quality control purposes.[85,188]

### 5.2.5 Urine extraction

Prior to analysis, specific gravity (SG) was measured for each pooled urine sample using a digital handheld refractometer. The measured concentration of all urinary metabolites was corrected for dilution prior to statistical analyses, as recommended by Boeniger et al. 1993.[189] Urine samples were analyzed for bis(2-chloro-isopropyl) phosphate (BCIPP), bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP), bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), diphenyl phosphate (DPHP), mono-isopropyl phenyl phenyl phosphate (ip-PPP), and mono-*tert*-butyl

phenyl phenyl phosphate (tb-PPP) using previously described methods.[35,73,83] Briefly, 5.0 mL of each pooled urine sample was spiked with internal standards $d_{10}$-BDCIPP (10 ng), $d_{10}$-DPHP (8.8 ng), and $d_{15}$-TDCIPP (35 ng). Urine samples were incubated overnight at 37°C with a 1 M sodium acetate buffer solution (pH 5) and an enzyme solution containing β-glucoronidase and sulfatase. Metabolites were extracted using a mixed-mode anion-exchange solid-phase extraction and analyzed using electrospray ionization liquid chromatography-tandem mass spectrometry (Agilent Technologies Model 6410). Recovery of the internal standards were assessed using $^{13}C_2$-DPHP (25 ng) for all three internal standards. Lab blanks (n=11) and a urine standard reference material (n=6; SRM 3673; NIST, Gaithersburg, MD) were analyzed alongside samples for quality assurance and control (Table D2). Measurements in SRM 3673 were 0.59 ± 0.10, 0.31 ± 0.001, 1.11 ± 0.27, 0.55 ± 0.05, and 2.59 ± 0.39 ng/mL for BCIPP, BCIPHIPP, BDCIPP, DPHP, and ip-PPP, respectively. These values are similar to levels reported by Hammel et al. and A. Covaci's group (University of Antwerp, Belgium) during an interlab comparison exercise with this SRM.[77,190]

### 5.2.6 Statistical analyses

All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) for analytes detected in >50% of samples. Method detection limits (MDLs) were calculated using three times the standard deviation of the average lab blanks for dust and urine samples, and field blanks for the hand wipes. MDLs were

normalized to the average mass of dust extracted (0.059 mg) or volume of urine extracted (5 mL), accordingly. Values that were less than MDL were replaced with MDL/2.[191] In a small number of dust samples (<10%), the responses for TCPP, TDCPP, TBOEP and TPHP were off the calibration curve, and were thus estimated using a linear regression analysis for points above the curve. However, TBOEP responses in dust were above the calibration curve in 29% of dust samples and 49% of hand wipe samples, and thus the geometric mean and percentile distributions should be interpreted with some caution. Preliminary analyses indicated that OPE concentrations in dust and on hand wipes, as well as the OPE metabolite concentrations in urine were log-normally distributed. Accordingly, Spearman correlations were used to assess relationships within and between matrices. These were conducted for both unadjusted and specific gravity corrected urinary metabolite levels; since these coefficients were not differentiable, specific gravity corrected results are presented here.

Generalized estimating equations were used to examine predictors of $\log_{10}$-transformed urinary OPE metabolite concentrations, as these models took into account residual within-family correlations potentially introduced by the inclusion of siblings in the models. Variables examined included child's sex, age, mother's race/ethnicity, mother's education level at the time of birth (a proxy for socioeconomic status or SES), average outdoor temperature (continuous variable), dust concentration, and hand wipe level. As suggested by O'Brien et al. 2015, analyses were also performed using specific

gravity as a covariate; results were indistinguishable from those obtained without including specific gravity as a covariate (data not shown).[192] Education was dichotomized as having earned a four-year college degree (bachelor's or graduate) or not. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, or Hispanic. The race/ethnicity of three participants was classified as "Other" and they were excluded from analyses. Child's age was dichotomized at the median (54 months). Hand wipe and dust levels were categorized as quartiles, except for hand wipe TBOEP and B4tBPPP and dust 24DIPPDPP and 4IPPDPP, which were categorized as either tertiles or detected/not detected due to lower detection frequencies for these compounds. When assessed in a univariate analysis, hand washing frequency did not significantly impact OPE levels on hand wipes (data not shown). Hand washing was assessed in the questionnaire during which parents were asked to report the average number of times that their child washed their hands each day (never, 1-2, 3-4, 5-6, 7-9, 10+). Because hand washing frequency was not related to OPE concentrations on hand wipes, it was not included in the multivariate analysis. Exponentiated beta coefficients from the models represent multiplicative change in $\log_{10}$-transformed urinary OPE metabolite concentrations relative to the reference category. Statistical significance was set to $\alpha$=0.05.

## *5.3 Results and discussion*

### 5.3.1 Study population

In total, 203 children from 190 individual homes were recruited for this study, including 1 pair of siblings, 8 sets of twins, and 2 sets of triplets. Approximately 55% of the participants were male and 45% were female, with an overall median age of 54 months or 4.5 years old (Table D1). A more detailed description of the study population can be found in Hoffman et al. 2018.[187] In brief, about 40% of the children were non-Hispanic white, 40% were non-Hispanic black, and the remaining 20% were Hispanic. Maternal educational attainment at birth was split rather equally within the study population, with 56% of mothers having less attainment than a four-year college degree and 44% having earned at least a bachelor's degree.

### 5.3.2 OPEs in individual matrices

#### 5.3.2.1 Hand wipes

OPEs were frequently detected on the 202 hand wipe samples taken from the child participants, with TDCIPP measured in every hand wipe (Table 12). Although it was only detected in 59% of the samples, TBOEP was measured at the highest levels of all the OPEs on the hand wipes (GM=606.8 ng/wipe), which is likely due to its prevalence in plastics and perhaps in floor polishes. The detection frequency of TBOEP was similar to a study with adults in Norway, but the geometric mean in this study was an order of magnitude greater, suggesting differential exposure between adults and

children, or possibly a regional difference between Europe and North America, and possibly China as well, where it was only detected in 8% of samples.[193,194] The chlorinated alkyl phosphates (TCEP, TCIPP, TDCIPP) were all detected in >85% of the hand wipe samples with TDCIPP being the most abundant within this subclass of compounds, similar to a previous study investigating OPEs on children's hand wipes in the U.S.[105] On the whole, levels of the chlorinated organophosphate compounds in this study were higher than hand wipes taken from similarly-aged children also from central North Carolina and were significantly higher than wipes taken from toddlers aged 9-18 months in Europe.[105,195] With the exception of the tert-butylated triaryl phosphates, the aryl phosphate compounds (EHDPHP, TPHP, 2IPPDPP, 4IPPDPP) were detected almost ubiquitously. To the authors' knowledge, this is the first time that the ITP and TBPP isomers have been quantitatively analyzed in hand wipes. Across the board, the observed high detection frequency of the chlorinated compounds and several of the aryl phosphates suggests children's exposure to these compounds is widespread and possibly increasing.

**Table 12: Descriptive statistics for OPEs and their urinary metabolites.**

| Matrix and Compound | Detection Frequency (%) | MDL[a,b] | 10th Percentile | Geometric Mean | 90th Percentile | Max |
|---|---|---|---|---|---|---|
| **Hand Wipe (ng/wipe) n=202** | | | | | | |
| **TCEP** | 87.0 | 2.7 | <MDL | 27.5 | 214.2 | 3,216 |
| **TCIPP** | 88.0 | 19.8 | <MDL | 89.8 | 466.8 | 2,488 |
| **TDCIPP** | 100 | 3.9 | 32.0 | 143.6 | 831.6 | 11,911 |
| **TBOEP** | 59.0 | 497 | <MDL | 740.8 | 3,310 | 8,361 |
| **EHDPHP** | 95.0 | 0.31 | 3.1 | 14.9 | 66.0 | 361.5 |
| **TPHP** | 98.0 | 1.1 | 4.0 | 18.2 | 93.8 | 2,468 |
| **2IPPDPP** | 99.5 | 0.19 | 1.3 | 7.0 | 36.4 | 2,787 |
| **4IPPDPP** | 96.0 | 0.22 | 1.1 | 7.9 | 99.5 | 1,373 |
| **4tBPDPP** | 73.0 | 0.09 | <MDL | 0.53 | 3.8 | 364.5 |
| **B4tBPPP** | 69.0 | 0.37 | <MDL | 2.2 | 27.6 | 965.3 |
| **T4tBPP** | 42.0 | 0.80 | NA[d] | NA[d] | NA[d] | 398.6 |
| **Dust (ng/g) n=188** | | | | | | |
| **TCEP** | 98.4 | 18.7 | 216.8 | 864.1 | 3,511 | 167,532 |
| **TCIPP** | 100 | 45.6 | 1,150 | 4,818 | 28,062 | 468,780 |
| **TDCIPP** | 100 | 12.1 | 797.9 | 4,843 | 26,799 | 257,917 |
| **TBOEP** | 97.9 | 51.5 | 995.6 | 6,862 | 69,520 | 2,209,172 |
| **EHDPHP** | 98.4 | 1.3 | 51.7 | 203.7 | 859.5 | 3,342 |
| **TPHP** | 100 | 12.4 | 726.0 | 2,582 | 12,202 | 290,982 |
| **2IPPDPP** | 80.9 | 10.1 | <MDL | 101.0 | 460.7 | 2,646 |
| **4IPPDPP** | 53.2 | 9.2 | <MDL | 29.8 | 190.6 | 1,267 |
| **24DIPPDPP[c]** | 68.6 | 1.7 | <MDL | 58.4 | 921.9 | 6,775 |
| **B2IPPPP[c]** | 20.7 | 2.7 | NA[d] | NA[d] | NA[d] | 2,143 |
| **B4IPPPP[c]** | 48.4 | 2.6 | NA[d] | NA[d] | NA[d] | 1,183 |
| **B24DIPPPP[c]** | 8.0 | 3.5 | NA[d] | NA[d] | NA[d] | 29,637 |
| **4tBPDPP** | 94.7 | 2.4 | 65.9 | 510.9 | 2,544 | 85,986 |
| **B4tBPPP** | 83.5 | 1.9 | <MDL | 70.2 | 438.5 | 12,777 |
| **T4tBPP** | 29.3 | 2.8 | NA[d] | NA[d] | NA[d] | 525.5 |
| **SG-corrected urine (ng/mL) n=181** | | | | | | |
| **BCIPP** | 80.1 | 0.14 | <MDL | 0.43 | 1.51 | 31.9 |
| **BCIPHIPP** | 97.2 | 0.18 | 0.33 | 1.29 | 4.94 | 19.2 |
| **BDCIPP** | 100 | 0.07 | 1.42 | 5.63 | 23.9 | 80.7 |
| **DPHP** | 99.4 | 0.12 | 0.92 | 2.67 | 9.53 | 50.9 |
| **ip-PPP** | 100 | 0.02 | 2.25 | 6.85 | 17.6 | 61.5 |
| **tb-PPP** | 94.5 | 0.08 | 0.06 | 0.26 | 1.14 | 11.8 |

[a] Dust MDL values were normalized to average mass of dust extracted (0.059 mg).

[b] Urine MDL values were normalized to volume of urine extracted (5 mL).

[c] Compounds were not integrated on hand wipes due to interferences in chromatography

[d] Descriptive statistics were not reported for compounds detected in less than 50% of samples

#### 5.3.2.2 House dust

The majority of the OPEs were highly detected in house dust samples with TCEP, TCIPP, TDCIPP, TBOEP, EHDPHP and TPHP having detection frequencies >97% (Table 12). Of the OPE compounds analyzed, TBOEP levels were the most abundant in the dust and were similar to levels of TCIPP, which is a trend that has been observed frequently in house dust around the world.[108,196,197] Overall, the OPE levels in dust appear to be similar to or higher than previous studies conducted in the United States, particularly in North Carolina.[86,105,133,198] The levels of the ITP and TBPP compounds and EHDPHP in dust were generally at least an order of magnitude lower than the other OPEs measured, which suggests either differential use patterns or lower application levels within products.

#### 5.3.2.3 Urinary metabolites

OPE metabolites were detected in over 80% of all urine samples, indicating widespread exposure to OPEs for the children in the TESIE study. Both BDCIPP and ip-PPP, metabolites of TDCIPP and the ITP compounds respectively, were detected in every sample, with ip-PPP having the highest geometric mean concentration of 6.9 ng/mL (Figure 10, Table 12). Observed high detection frequencies of OPE metabolites emphasizes the need to determine how children are exposed to these compounds. Discussion of the urinary metabolites and their association with demographic variables is presented in greater detail in Hoffman et al., 2018 (Appendix D).[187]

### 5.3.3 Comparing hand wipes and dust to urine

The masses of OPEs measured in hand wipe samples were significantly correlated with their corresponding urinary metabolites ($r_s$=0.16-0.41, $p<0.05$; Table 13). This suggests that hand wipes serve as an effective exposure metric for OPEs, which has previously been shown in studies with both adults and children.[77,86,105] Particularly noteworthy is that this is the first time that OPEs on hand wipes have been shown to be significantly and positively correlated with urinary metabolites for a wide range of compounds, including EHDPHP, ITPs, and TBPPs. These relationships continue to be significant in the highest quartile of OPE mass on hand wipes when adjusted for child's age and sex, mother's race and education, and average outdoor air temperature (Table D4). Recently, the dermal absorption pathway has been shown to be important for many of these OPE compounds.[131] Since hand wipes capture both hand-to-mouth contact and potential dermal absorption, this study provides further evidence that these pathways of exposure are important for OPEs, and particularly for children's exposures.

**Table 13: Spearman correlation coefficients for OPE and OPE metabolite levels measured in paired hand wipes (*n* = 180) and dust (*n* = 179) with ≥60% detection and specific gravity-corrected urine. Shading indicates known parent-metabolite pairs.**

| | | Urine | | | | | |
|---|---|---|---|---|---|---|---|
| | | BCIPP | BCIPHIPP | BDCIPP | DPHP | ip-PPP | tb-PPP |
| **Hand Wipe** | TCEP | 0.00 | **0.27†** | 0.11 | 0.11 | **0.25†** | 0.13 |
| | TCIPP | **0.27†** | **0.16*** | **0.27†** | 0.08 | 0.04 | -0.01 |
| | TDCIPP | 0.11 | 0.13 | **0.41†** | **0.18#** | **0.22#** | 0.14 |
| | EHDPHP | 0.09 | **0.22#** | 0.07 | **0.19#** | 0.11 | 0.08 |
| | TPHP | 0.14 | 0.09 | 0.04 | **0.23#** | 0.07 | **0.23#** |
| | 2IPPDPP | 0.08 | 0.08 | 0.05 | **0.32†** | **0.23#** | **0.31†** |
| | 4IPPDPP | 0.02 | 0.10 | 0.07 | **0.29†** | **0.19#** | **0.25†** |
| | 4tBPDPP | 0.08 | 0.09 | 0.03 | **0.19#** | 0.07 | **0.33†** |
| | B4TBPPP | 0.00 | 0.06 | 0.04 | **0.18#** | 0.11 | **0.38†** |
| **Dust** | TCEP | 0.00 | -0.13 | 0.07 | 0.00 | -0.08 | **-0.16*** |
| | TCIPP | 0.13 | -0.14 | 0.00 | 0.02 | -0.02 | -0.07 |
| | TDCIPP | -0.03 | -0.09 | 0.13 | -0.06 | 0.03 | -0.06 |
| | TBOEP | -0.06 | 0.00 | -0.04 | 0.01 | -0.01 | 0.04 |
| | EHDPHP | 0.03 | -0.08 | 0.10 | 0.13 | 0.02 | -0.02 |
| | TPHP | 0.08 | 0.04 | 0.09 | 0.01 | -0.13 | -0.08 |
| | 2IPPDPP | 0.10 | -0.05 | 0.09 | 0.08 | -0.12 | -0.10 |
| | 24DIPPDPP | 0.02 | **0.16*** | 0.07 | 0.13 | 0.03 | 0.02 |
| | 4tBPDPP | -0.09 | -0.10 | -0.06 | 0.01 | 0.03 | **0.18*** |
| | B4TBPPP | -0.09 | -0.05 | 0.01 | 0.11 | 0.07 | **0.27†** |

*p<0.05, #p<0.01, †p<0.001

The correlation between TDCIPP on hand wipes and urinary BDCIPP was the strongest of any paired samples ($r_s$=0.41, p<0.001) and stronger than the correlation with TDCIPP in dust. After adjusting for other covariates, a significant relationship between TDCIPP and urinary BDCIPP was observed for every quartile of hand wipe mass with a clear increasing trend (*p* for trend=0.001; Figure 11). This suggested that of the OPEs assessed in this study, TDCIPP exposure was best classified by the hand wipes, with the

sensitivity to differentiate exposure within each quartile of TDCIPP mass on hand wipes.

Because TCIPP has two potential metabolites, associations between TCIPP and each of its metabolites, BCIPP and BCIPHIPP, were examined (Figure 10). TCIPP levels on hand wipes were significantly correlated with both urinary metabolites, although the magnitude of correlation was greater for BCIPP compared to BCIPHIPP. Although BCIPHIPP is a urinary metabolite of TCIPP, recent studies suggest that children may have immature or decreased expression of enzymes responsible for converting TCIPP to BCIPHIPP compared to adults.[35,199] When the relationship between TCIPP levels on hand wipes and its two urinary metabolites was evaluated while adjusting for child's sex and age, race, mother's education, and average outdoor temperature, the association between TCIPP and BCIPHIPP was no longer significant while the TCIPP-BCIPP association followed a dose response relationship and was significant in the highest hand wipe quartile (Table D4). This may suggest that BCIPP is a better urinary biomarker of exposure for children compared to adults; however, further studies are warranted to examine the different metabolic activities of TCIPP in children versus adults.

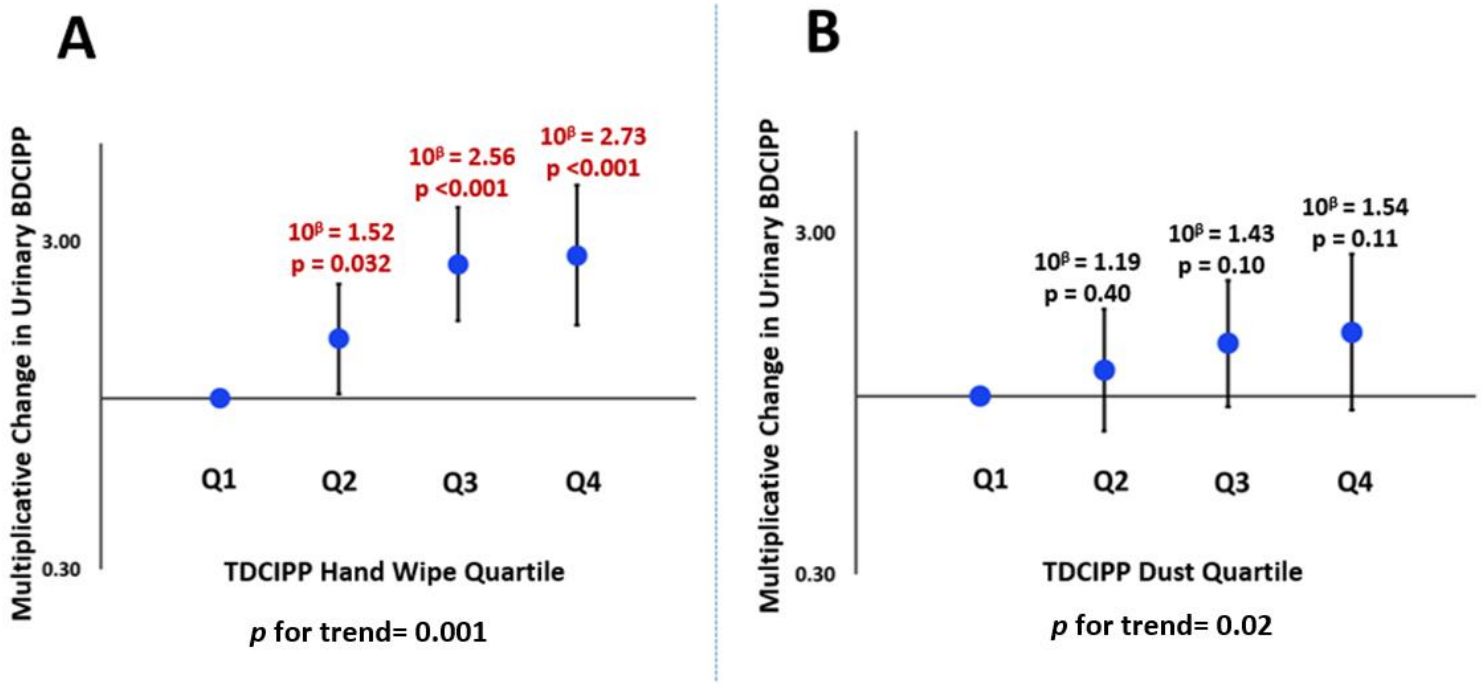



**Figure 11: Regression analyses for predicting urinary BDCIPP from TDCIPP levels on (A) hand wipes and (B) in dust, adjusted for child's sex and age, mother's race and education, and average outside temperature.**

Among the aryl phosphates, TPHP, EHDPHP, and the four ITP and TBPP compounds were all significantly correlated with DPHP ($r_s$=0.18-0.32, p<0.01). This result was not unsurprising since all of these compounds can be metabolized to DPHP. After adjusting for covariates in a regression analysis, the relationship between hand wipes and DPHP remained significant for EHPDP, TPHP, and the two ITP compounds, although generally only for the highest quartile of exposure measured by hand wipes (Table D4). Additionally, the two ITP compounds measured in the hand wipes, 2IPPDPP and 4IPPDPP, were significantly correlated with ip-PPP ($r_s$=0.23, 0.19, p<0.01). This further contributed evidence for ip-PPP as a biomarker of exposure for the ITP compounds, which was previously shown in an *in vivo* animal model.[81] The two TBPP compounds on the hand wipes, 4tBPDPP and B4TBPPP, were strongly correlated with tb-PPP in urine ($r_s$=0.33, 0.38, p<0.001). To the authors' knowledge, this is the first report of frequent detection of tb-PPP in urine. Tb-PPP has been previously suggested to be a metabolite of the TBPP compounds, and the significant correlation here provides evidence in support of this claim.[44] Along with TPHP, the two ITP compounds on hand wipes were also significantly correlated with tb-PPP ($r_s$=0.23-0.31, p<0.01). Because TPHP is a component of the TBPP mixture this association likely reflect co-exposure of the parent compounds even though TPHP is unlikely to be metabolized to tb-PPP.[41,199] The significant correlation of 2IPPDPP and 4IPPDPP with tb-PPP may also be explained by

the detection of trace amounts of ITP compounds in the Firemaster® 600 and TBPP mixtures, thereby also reflecting co-exposure of the parent compounds.[41]

In general, OPE urinary metabolites were not associated with the parent compounds in dust with the exception of the TBPP compounds and tb-PPP metabolite ($r_s$=0.18-0.27, $p<0.05$; Table 13, D5). This suggested that inadvertent dust ingestion may not be the primary route of exposure for the majority of the OPEs. For compounds with relatively higher molecular weights and lower vapor pressures, such as PBDEs and the TBPP compounds, this pathway of exposure may be of greater importance.[88] House dust could also be a source of TBPP compounds on the hand wipes, since both dust and hand wipes were positively associated with urinary tb-PPP. Overall, due to the greater magnitude of the correlation coefficients and results from the regression analyses, hand wipes appear to be a better measure of exposure compared to dust for OPEs. This may be a result of hand wipes capturing exposure to OPEs via hand-to-mouth contacts in addition to various behavioral attributes of the children. Hand wipes also are more likely to integrate exposures from multiple microenvironments whereas dust likely represents exposure solely from one microenvironment, which in this case was the main living area of the home.[89]

### 5.3.4 Comparing OPEs in dust and hand wipes

Several of the OPEs (TCIPP, TBOEP, TPHP, 2IPPDPP, 4tBPDPP, and B4TBPPP) showed positive and significant correlations between paired hand wipes and dust

($r_s$=0.16-0.30, $p<0.05$; Table 14). The ITPs in dust were associated with the ITP compounds on hand wipes ($r_s$=0.15-23, $p<0.05$), suggesting similar sources of exposure due to mixtures applications as well as the potential for indoor dust to be a source of ITPs on children's hands. Additionally, 24DIPPDPP in dust was significantly correlated with both the ITP and TBPP compounds and TPHP on hand wipes, which further points to the potential of co-application of some of these compounds in mixtures. TBOEP on hand wipes and in dust was significantly and positively correlated ($r_s$=0.23, $p<0.05$), which has not been previously observed to the authors' knowledge. The high abundance of TBOEP in both hand wipes and dust suggests that house dust may serve as a primary exposure pathway to children's hands. Surprisingly, no association was observed between hand wipes and dust for TCEP, TDCIPP, and EHDPHP. Inhalation and dermal exposure, and not dust ingestion, have previously been postulated to be the strongest exposure pathway for TDCIPP.[71,167] While dust may still serve as an important measure for assessing exposure to OPEs in the home, hand wipes may be a more holistic exposure metric for OPEs. This was also observed among adults, where hand wipes were a stronger predictor of urinary OPE metabolites than house dust.[86] For children, hand wipes may be an even better predictor of exposure due to their ability to capture behavioral differences, and in particular, increased hand-to-mouth contact compared to adults.

**Table 14: Spearman correlation coefficients for OPE levels measured in paired hand wipes and dust ($n$ = 200) with ≥60% detection.**

| | | Dust | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TCEP | TCIPP | TDCIPP | EHDPHP | TBOEP | TPHP | 2IPPDPP | 24DIPPDPP | 4tBPDPP | B4TBPPP |
| **Hand Wipe** | TCEP | 0.12 | 0.13 | 0.10 | 0.02 | 0.01 | -0.01 | -0.07 | 0.09 | **-0.19**# | **-0.15*** |
| | TCIPP | 0.07 | **0.20**# | 0.07 | -0.02 | 0.05 | 0.07 | 0.03 | -0.09 | **-0.15*** | -0.09 |
| | TDCIPP | 0.04 | 0.04 | 0.03 | -0.04 | 0.09 | 0.04 | -0.01 | 0.09 | -0.04 | 0.00 |
| | EHDPHP | -0.10 | -0.03 | -0.04 | 0.01 | 0.02 | 0.03 | -0.04 | 0.11 | -0.09 | -0.08 |
| | TBOEP | 0.03 | -0.01 | -0.09 | 0.06 | **0.23**# | -0.01 | 0.01 | 0.06 | -0.11 | -0.01 |
| | TPHP | 0.01 | 0.01 | -0.05 | -0.04 | 0.02 | **0.17**# | 0.14 | **0.15*** | 0.01 | 0.06 |
| | 2IPPDPP | -0.01 | -0.01 | -0.06 | 0.01 | 0.04 | 0.05 | **0.16*** | **0.23†** | -0.01 | 0.05 |
| | 4IPPDPP | -0.07 | -0.10 | -0.13 | -0.03 | 0.04 | -0.03 | **0.15*** | **0.19**# | -0.06 | -0.01 |
| | 4tBPDPP | -0.02 | -0.05 | -0.07 | -0.01 | 0.08 | -0.01 | 0.13 | **0.23†** | **0.22**# | **0.27†** |
| | B4TBPPP | -0.07 | -0.05 | -0.03 | -0.01 | 0.05 | -0.01 | 0.07 | **0.20**# | **0.23†** | **0.30†** |

*p<0.05, #p<0.01, †p<0.001

### 5.3.5 Effect of covariates

When using generalized estimating equations to examine associations between urine, hand wipes, and dust, all models were adjusted for the child's age and sex, mother's education and race, and average outdoor temperature. Of these covariates, levels of the OPE compound on hand wipes was generally the most consistently associated variable with the corresponding urinary metabolite (Table 15). Mother's race and education contributed to the models but were not significant except for the relationship between 4tBDPP on hand wipes and tb-PPP in urine, with children whose mothers attained a four-year college degree and were Hispanic having about half as high levels of tb-PPP ($p<0.05$) compared to the reference group. Average outdoor air temperature was a significant predictor of BDCIPP ($10^{\beta}=1.04$, $p<0.0001$), which corresponds to seasonal trends in urinary metabolite concentrations that have been previously described in Hoffman et al. 2017.[34] Our finding suggests that urinary concentrations of BDCIPP will increase by 4% per each 1°C increase in outdoor temperature. Seasonal trends for OPEs in indoor dust have also been observed, with higher levels in warmer months, and have been attributed to the greater volatility of these compounds compared to brominated flame retardants.[200] Because TDCIPP is used in automobile upholstery, it is possible that this trend stems from increased off-gassing inside automobiles with elevated outdoor temperature.[201] Only one family reported not having central air/heating so we would not expect to see significant seasonal differences

in indoor temperature and ventilation in this study. While an impact with every parent-metabolite pair was not observed, the seasonal trends observed suggested an increase in OPE concentrations and exposure during warmer months. This indicates that season and outdoor temperature need to be taken into account during exposure assessments for OPE compounds, as biases in exposure estimates may result within a specific sampling time period.

**Table 15: Results of regression analyses for predicting urinary metabolites based on parent compounds on hand wipes, adjusted for sex, mother's race/ethnicity, mother's education, age, and average outdoor temperature.**

| Predictor | | Parent on Hand wipe – Urinary Metabolite | | | |
|---|---|---|---|---|---|
| | | TCIPP - BCIPP [$10^{\beta}$ (95% CI)- *p*-Value] | TDCIPP - BDCIPP [$10^{\beta}$ (95% CI)- *p*-Value] | 2IPPDPP – DPHP [$10^{\beta}$ (95% CI)- *p*-Value] | 4tBPDPP – tb-PPP [$10^{\beta}$ (95% CI)- *p*-Value] |
| **Age** | ≤54 months (referent) | | | | |
| | >54 months | 0.86 (0.57, 1.30) – 0.47 | 1.21 (0.86, 1.70) – 0.26 | 0.80 (0.57, 1.11) – 0.18 | 1.34 (0.90, 1.99) – 0.15 |
| **Child Sex** | Female (referent) | | | | |
| | Male | 1.04 (0.74, 1.47) – 0.81 | 0.91 (0.68, 1.23) – 0.54 | 0.87 (0.66, 1.15) – 0.33 | 1.12 (0.78, 1.60) – 0.55 |
| **Mother's Education** | No college degree (referent) | | | | |
| | College degree | 1.57 (0.99, 2.49) – 0.054 | 1.32 (0.91, 1.91) – 0.15 | 0.78 (0.50, 1.22) – 0.28 | **0.50 (0.33, 0.75) – 0.001** |
| **Mother's Race** [a] | Non-Hispanic white (referent) | | | | |
| | Non-Hispanic black | 1.24 (0.78, 1.98) – 0.37 | 0.98 (0.61, 1.57) – 0.93 | 0.91 (0.57, 1.46) – 0.70 | 0.77 (0.49, 1.22) – 0.27 |
| | Hispanic | 1.09 (0.61, 1.94) – 0.76 | 0.77 (0.44, 1.34) – 0.36 | 0.51 (0.46, 1.38) – 0.41 | **0.57 (0.34, 0.95) – 0.031** |
| **Average Outdoor Temp** | (°C) | 1.01 (0.99, 1.04) – 0.40 | **1.04 (1.03, 1.07) – <0.0001** | 1.01 (0.99, 1.03) – 0.17 | 1.01 (0.99, 1.04) – 0.27 |
| **Hand Wipe** | Quartile 1 (referent) | | | | |
| | Quartile 2 | 1.09 (0.69, 1.72) – 0.71 | **1.52 (1.04, 2.23) – 0.032** | 1.11 (0.76, 1.60) – 0.59 | **1.51 (1.04, 2.19) – 0.032** |
| | Quartile 3 | 1.19 (0.79, 1.80) – 0.41 | **2.56 (1.72, 3.82) – <0.0001** | 1.12 (0.75, 1.67) – 0.57 | 1.19 (0.74, 1.90) – 0.48 |
| | Quartile 4 | **1.84 (1.19, 2.84) – 0.006** | **2.73 (1.67, 4.48) – <0.0001** | **2.11 (1.31, 3.40) – 0.002** | **2.65 (1.56, 4.49) – 0.0003** |
| | *p*-Value for trend | 0.30 | **0.001** | 0.14 | **0.004** |

[a] Three participants reporting mother's race/ethnicity as "other" were excluded from adjusted models.

### 5.3.6 Exposure pathways

Our results suggest that hand wipes serve as an improved metric of exposure for OPEs compared to house dust. While levels in dust and hand wipes may be significantly correlated, hand wipes serve as a stronger predictor of urinary metabolite concentrations (Tables 13, D4, D5). The correlations between dust and hand wipes suggest that house dust could be a source of OPEs found on children's hands, but this was mostly observed for the higher molecular weight ITP and TBPP compounds. Despite having similar structures, different applications of OPEs in consumer products (e.g., flame retardant or plasticizer), differing levels of OPEs in products, and varying physicochemical properties likely dictate the differences observed in potential exposure pathways. Hand wipes have been postulated to capture exposure via hand-to-mouth contact as well as dermal absorption via sampling of skin-surface lipids. This could be explained by SVOCs partitioning from the air to skin-surface lipids, followed by absorption into the body.[130,165] OPE levels on skin may also reflect contact with dust or surfaces and direct contact with products. Exposure to OPEs contrasts with the brominated flame retardants, and in particular the PBDEs, for which household dust levels have been significantly and positively associated with serum biomarkers implicating dust ingestion as a primary route of exposure.[87,88,122,156] Alternatively, differential OPE and PBDE exposure may partly reflect usage patterns in the home and/or other

microenvironments. As such, additional work to further characterize pathways of exposure for the OPEs is needed.

### 5.3.7 Limitations and Strengths

The results of this study should be interpreted in the context of a few potential limitations. First, the study population was a convenience sample that was selected from a pregnancy cohort. This limits the generalizability of the results to the general population of children within the U.S. but should not impact the internal validity of the study. In addition, the study design provided a cross-sectional analysis of the indoor home environment, which limits our ability to examine long-term exposures to OPEs, and many of these compounds are rapidly metabolized. Here, we used a composite sample comprised of three urine samples per child to examine exposure to OPEs over a 48-hour period. We intended to capture exposure from young children and our study population contains children between ages 3-6 years; however, children who are under the age of 3 may have more hand-to-mouth contact and thus hand wipes may be an even stronger measure of exposure for these individuals. We only sampled dust from one microenvironment, the main living area; this may not correctly measure exposure to dust in other areas of the home or outside the home (e.g., school). Similarly, handwipes were collected at a single point in time. Our past work in adults demonstrated that handwipe OPE concentrations are significantly correlated with pooled urine samples (across 5 days), suggesting that a single handwipe provides information on average

exposure over time.[77] However, levels of OPEs on children's hands likely vary throughout the day and across days. In addition, we did not analyze for OPE metabolites such as DPHP in the house dust or hand wipes, although they have been recently detected in indoor dust samples.[202] We did not assess potential exposure via diet or inhalation; inhalation exposure will be assessed in a future study via passive air samplers that were deployed in a subset of these homes. A model that includes the contribution of these other exposure pathways, various microenvironments, and individual behavior would likely better predict exposure. As we performed multiple statistical tests, some statistically significant results may be due to chance.

Despite these weaknesses, our study has several strengths including the collection of multiple samples (urine, hand wipes, house dust) and the use of a pooled urine sample per child (rather than a single spot urine). It is the first study to report children's exposure to a large suite of novel, aryl OPEs in various matrices. Additionally, this study population is unprecedented in the OPE literature, both in terms of sample size (n=203) and participant age (~3-6 years). Other somewhat similar studies differ from the current study: Hoffman et al. 2015 assessed OPEs on hand wipes and dust in 53 adults.[86] Children's behavior is markedly different from adult behavior and has been known to affect SVOC exposure. Stapleton et al. 2014 also assessed OPEs on hand wipes in 43 children, but comparison to urinary biomarkers was not included.[105] Our study is

the first to assess OPE exposure in a large children's cohort, documenting associations between parent levels on hand wipes and in dust with metabolite levels in urine.

## 5.4 Conclusion

Taken together, our study indicates that OPE exposures are nearly ubiquitous for TESIE participants, and possibly also for other young children in the U.S. Dermal absorption and hand-to-mouth contact are likely important contributors to cumulative OPE exposure, as OPE levels on hand wipes were associated with urinary metabolite concentrations. This is the first study to show that hand wipes are more useful than indoor dust for estimating children's exposure to OPEs, which should be taken into account in future epidemiological studies. While numerous *in vitro* toxicology studies have reported adverse health effects of OPE exposures, *in vivo* studies are needed to investigate potential health effects at the levels of OPE exposure described herein. In particular, developmental toxicity should be considered as children are potentially more vulnerable to OPEs.

# 6. Children's exposure to phthalates and non-phthalate plasticizers in the home: The TESIE study

This chapter is adapted from Hammel, S. C. and Levasseur, J. L.; Hoffman, K.; Phillips, A. L.; Lorenzo, A. M.; Calafat, A. M.; Webster, T. F.; Stapleton, H. M. Children's exposure to phthalates and non-phthalate plasticizers in the home: The TESIE study. *Environ. Int.* Accepted. S. C. Hammel and J. L. Levasseur are co-first authors on the publication. Specifically, S.C. Hammel contributed to participant recruitment, sample collection, statistical analyses, table and figure design, and writing and editing of the manuscript. The accompanying supporting information is included in Appendix E.

## *6.1 Introduction*

Phthalate esters are used in a wide variety of consumer products.[51] High molecular weight phthalates are primarily used as plasticizers in a variety of building materials, industrial products, and consumer products, sometimes at levels as high as 10-30% by mass.[52,55] Low molecular weight phthalates are more often used as solvents or carriers in personal care products, particularly for fragrances.[55,203,204] As such, phthalates are some of the most abundant compounds found in the indoor environment and were detected at the highest concentration compared to several chemical classes in U.S. indoor dust.[53] Because of their widespread use in everyday products, human exposure to phthalates is common, and biomarkers of exposure have been detected in the urine of the majority of the U.S. general population.[54]

Over the last decade, several phthalates have been the focus of global concern and subsequent bans. The U.S. Consumer Product Safety Commission banned diisobutyl phthalate (DiBP), di-n-butyl phthalate (DBP), benzyl butyl phthalate (BBP), bis(2-ethylhexyl) phthalate (DEHP), and di-isononyl phthalate (DiNP) from use in children's toys and child care articles in their Consumer Product Safety Improvement Act of 2008 and subsequent update in 2017.[59] Similar bans have been made for use of DiBP, DBP, BBP, and DEHP in all products in the European Union.[60] Despite the removal of these phthalate esters from new products, their extensive use over the last several decades has ensured that many of these compounds will persist in recycled products and thus in the indoor environment. Due to these global phase-outs and bans, several other plasticizers (*e.g.*, bis(2-ethylhexyl) terephthalate (DEHTP) and bis(2-ethylhexyl) adipate (DEHA)) have been introduced to the market as replacements. Although far less is known about these replacements and their presence indoors, we expect them to be ubiquitously detected in the environment, much like their predecessors.

Phthalates and non-phthalate plasticizers have octanol-air partitioning coefficients ($\log K_{oa}$) calculated or estimated to range from 7 to 13.[84,205] As such, they have a wide range of partitioning behaviors across multiple orders of magnitude. However, with the variation in physical-chemical properties, little is known about the primary pathways by which individuals are exposed, and exposure routes may differ between compounds. In particular, exposures may vary based on their uses in consumer

products and in the home environment (e.g., fragrance in a perfume versus a coating in vinyl flooring). Hand wipes have been previously used to examine dermal absorption of phthalates among children, and significant, positive associations were observed between several parent compounds on hand wipes and their urinary metabolites.[55,204] Indoor dust has also been shown to be correlated with urinary metabolites among children and to contribute to total phthalate exposure through comparisons with the inhalation and dermal absorption pathways.[56,206]

Here, we sought to identify the major exposure pathways for phthalates and other plasticizers among children ages 3-6 years by comparing hand wipes and house dust samples to metabolites measured in pooled urine samples. Further, we examined how specific housing characteristics and behaviors contributed to increased exposure to several phthalate compounds and their replacements.

## *6.2 Materials and methods*

### 6.2.1 Study population

Mothers participating in the Newborn Epigenetics STudy (NEST), a prospective pregnancy cohort study based in Durham, North Carolina (2005-2011), were re-contacted and their children were invited to participate in the Toddler's Exposure to SVOCs in the Indoor Environment (TESIE) study.[187,207] Hoffman et al. 2018 provides a description of recruitment and enrollment procedures for the TESIE study. Briefly, 203 children from 190 different families participated in the TESIE study between September

2014 and April 2016 when children were 3–6 years of age. Study team members conducted home visits with each family enrolled in the TESIE study to collect environmental samples and biospecimens as well as data about the home environment and children's health and behavior. All study protocols and related materials were reviewed and approved by the Duke Medicine Institutional Review Board. Legal guardians provided informed consent prior to the collection of samples and questionnaire data for the TESIE study, and mothers provided informed consent prior to participation in NEST. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subject research.

### 6.2.2 Home environment characteristics

During home visits, research personnel administered questionnaires to parents that focused on housing characteristics, children's health and behavior, and personal care product use. These questions were intended to collect information on the frequency of product use (e.g., nail polish, wipes, lotion) and familial habits (e.g., how often children consumed food from microwaved plastic containers). In addition, information on the square footage of the home and specific rooms in the home was collected in the questionnaires. Researchers visually identified rooms with vinyl flooring and measured the square footage of these individual rooms in each home, providing a calculation of the percentage of the home that contained vinyl flooring. Housing data were later

verified using county property tax records; 2018 tax assessment data (or the most recent year available) were used to verify the total square footage of homes. Tax assessment information was unavailable for public housing units (n=39), which included apartments (n=28), mobile homes/trailers (n=6), and single family homes (n=4 attached, n=1 detached), and thus verification of housing characteristics was not possible for these residences.

### 6.2.3 Hand wipe extraction

Families were instructed not to wash their child's hands for at least 1 hour prior to our home visit. During the visit, research staff collected a hand wipe sample from each child using pre-cleaned cotton twill wipes (4x4 in., MG Chemicals), as described in Chapter 5. Briefly, a gloved researcher soaked the twill wipe with 3 mL isopropyl alcohol and wiped the entire surface area of both of the child's hands. Hand wipes were rewrapped in aluminum foil and stored at -20°C until analysis. Hand wipes were extracted and analyzed as described in Chapter 5. In brief, wipes were spiked with 76 ng of each of the following internal standards: $d_4$-dimethyl phthalate ($d_4$-DMP), $d_4$-diethyl phthalate ($d_4$-DEP), $d_4$-BBP, and $d_4$-DEHP. All analytical standards, both labeled and unlabeled, were sourced from Cambridge Isotope Laboratories, Inc. (Tewksbury, MA). Analytes and corresponding metabolites are presented in Table E1. The wipes were extracted in 1:1 dichloromethane:hexane (v/v) using sonication, and extracts were concentrated to ~1 mL using a SpeedVac™ Concentrator. Extracts were then fractionated

using Florisil® solid-phase extraction cartridges (Supel-clean ENVI-Florisil, 6 mL, 500 mg; Supelco), eluting the F2 fraction (containing phthalates) with 10 mL of ethyl acetate. F1 fractions eluted using 6 mL hexane and F3 fractions eluted using 6 mL methanol were also collected and used for analyses not shown here. F2 fractions were concentrated to ~1 mL and reconstituted in hexane prior to GC/MS analysis. DiNP was quantified using an analytical standard containing a series of DiNP isomers and co-eluted with DEHTP; thus, the peaks following the retention time for DEHTP were integrated. As such, the values for DiNP presented here are conservative estimates for the actual values found on hand wipes. Details regarding the GC/MS conditions and ions monitored are included in Appendix E (Table E2). Recovery of internal standards was assessed using $^{13}C_2$-dicyclohexyl phthalate (98.88 ng) for all of the deuterated internal standards. Field blanks (n=14) were analyzed in each batch for quality assurance and quality control (Table E3). Due to interferences in the chromatography, DEP was not quantified in the hand wipe extracts.

### 6.2.4 Dust extraction

Families were instructed not to clean their homes, specifically mop or vacuum, for at least two days prior to the scheduled visit. For collection of the house dust sample, the entire exposed floor area of the main living area was vacuumed using a Eureka Mighty Mite vacuum fitted with a cellulose thimble within the hose attachment.[88] Each thimble was wrapped in aluminum foil and stored at -20°C until analysis.

Prior to extraction, dust samples were sieved to <500 microns then extracted in the same manner as the hand wipe samples, with minor adjustments. Dust extracts were split by mass, reserving ~25% for cell-based toxicity assays and 25% for non-targeted analysis (not discussed in this manuscript). The remaining 50% was used for targeted analyses as described here. Internal standards ($d_4$-DMP, $d_4$-DEP, $d_4$-BBP, $d_4$-DEHP; all at 1,156.07 ng) were spiked following extraction and prior to any cleanup steps. Laboratory blanks (n=6) and house dust standard reference material (n=5; SRM 2585 National Institute of Standards and Technology (NIST), Gaithersburg, MD) were analyzed in each batch for quality assurance and quality control (Table E3). Measurements of phthalates (DMP, DEP, DiBP, DBP, DEHP, DiNP) in SRM 2585 were 73-103% of the average values reported by Bergh et al. and Luongo and Ostman with the exception of BBP and DiNP, both of which were about 25% of the reported values.[32,208] Our measurements varied more from Mercier et al. and Larsson et al., in the range of 32-108%, and with BBP being about 20% of the reported averages.[209,210] Our measurements were similar to most of the reported values in the literature and deemed acceptable for quality assurance and quality control purposes. During quantification, all the quantified phthalates and non-phthalate plasticizers in the dust samples had at least 50% of samples falling above the calibration curve, and therefore some of the data represent estimates above the calibration curve.

### 6.2.5 Urine extraction

Families were given collection kits for urine samples during the home visit. Three spot urine samples were collected from each child over the course of a 48-hour period, with times of sampling recorded. Urine samples were stored frozen in the families' homes during the sampling period and were transported to our research laboratory on ice and then stored at -20°C. Prior to analysis, the individual samples were thawed and thoroughly mixed, and equal volumes of each urine sample were pooled to form a composite. Specific gravity (SG) was measured in each sample using a digital handheld refractometer (Atago). A modification of previously described methods was used to measure 17 phthalate metabolites and 2 metabolites from the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH).[211,212] Average outdoor temperature was retrieved from the National Weather Service website based on the week of sample collection to examine the potential impact of temperature on exposure pathways. Previous work has observed changes in exposure based on temperature, and thus average outdoor temperature was included as a covariate in comparisons conducted herein.[187]

### 6.2.6 Statistical analyses

All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) for analytes detected in >70% of samples. Method detection limits (MDLs) were determined using three times the standard deviation of the average

lab blank levels for dust samples and field blank levels for the hand wipes. In urine, MDLs were calculated as $3S_0$, where $S_0$ (determined from the replicate analysis of low-level standards) was the standard deviation as the concentration approaches zero.[213] MDLs were normalized to the average mass of dust extracted (0.059 mg). Values that were less than MDL were replaced with MDL/2.[214] Preliminary analyses indicated that plasticizer concentrations in hand wipes and in dust, as well as metabolite concentrations in urine, were right-skewed. Spearman correlations were therefore used to assess relationships within and between matrices. These were performed for both unadjusted and specific gravity corrected urinary metabolite concentrations.[189] These coefficients were not differentiable and therefore only specific gravity corrected results are presented here. Certain parent compounds metabolize to multiple metabolites, and for these chemicals, we evaluated associations based on the molar sum of the metabolites. Investigating these plasticizers on a molar sum basis may allow us to better characterize the relationship between parent compounds in hand wipes or dust and total corresponding urinary metabolites. All analyses were conducted with the individual metabolites as well and displayed similar relationships as their molar sums; thus, the associations of parents with molar sums for these specific compounds are shown here and the individual metabolite data are included in Appendix E.

Participants were asked to provide all samples although circumstances arose in which certain samples could not be collected or analyzed. As such, there was not

complete overlap in the number of participants for each sample type, and therefore relationships were evaluated for the maximum number of paired samples available.

To examine predictors of phthalates and non-phthalate replacements in household dust, hand wipes and urine (metabolites), generalized estimating equations were used. These models account for residual intra-family correlations that may be introduced by including siblings in the models. Additional analyses on the effect of various categorical variables on plasticizer concentration in dust and hand wipes and urinary metabolite concentrations were conducted. These analyses included child's nail polish use, child hand lotion use, frequency of child's food consumption from microwaved plastic, child's use of scented and unscented wipes, and the percentage of vinyl flooring in the home. Outcome variables were all $\log_{10}$-transformed prior to analysis to account for their non-normal distribution.

### 6.2.7 Covariates

Regression analyses were adjusted for covariates based on our *a priori* expectation of association with outcomes and predictors variables of interest. Models evaluating predictors of plasticizers in household dust included mother's race/ethnicity, mother's education level at the time of birth, and average outdoor temperature (continuous). Models investigating predictors of phthalates and phthalate replacements on children's hands and urinary metabolites additionally included the child's age and sex. To investigate the relationship between urinary metabolite and parent compound in

dust or hand wipes, concentrations were divided into quartiles, with the exception of hand wipe levels of DBP which were divided into tertiles due to its less frequent detection.

## *6.3 Results and discussion*

### 6.3.1 Study population and home environment

The demographics of the study population and home characteristics are described in Table 16 and more extensively in Hoffman et al. 2018.[187] Briefly, the TESIE study included 203 children, 55.7% of which were male, from 190 households. The median age of children in the study was 54 months (4.5 years), with child age ranging from 38-73 months. Approximately 41% of mothers identified as non-Hispanic white, while 37% of mothers identified as non-Hispanic black, 20% identified as Hispanic, and 2% identified as other race/ethnicity. Those participants identifying as other race/ethnicity were excluded from the adjusted analysis (n=3). Approximately half of mothers (44%) had completed a four-year college degree program at the time of their child's birth. Biological specimens were collected between September 2014 and April 2016.

**Table 16: Selected demographic characteristics of children participating in the TESIE study, selected product use patterns, and household characteristics of the TESIE study participants.**

| Characteristic | N | % |
|---|---|---|
| Child Sex | | |
| Male | 113 | 55.7% |
| Female | 90 | 44.3% |
| Age | | |
| 38-47 months | 34 | 16.0% |
| 48-59 months | 130 | 64.0% |
| 60-73 months | 39 | 19.2% |
| Ethnicity | | |
| Non-Hispanic white | 84 | 41.4% |
| Non-Hispanic black | 75 | 36.9% |
| Hispanic white | 41 | 20.2% |
| Other | 3 | 1.5% |
| Maternal education | | |
| Less than college graduate | 113 | 55.7% |
| College graduate or more | 90 | 44.3% |
| | **Mean** | **range** |
| Child age | 53.9 | 38-73 |
| Average temp (°C) | 15.5 | -4.4-29.4 |
| **Use information** | **N** | **%** |
| Do not use baby wipes | 98 | 48.3% |
| Use baby wipes (scented) | 33 | 16.3% |
| Use baby wipes (unscented) | 72 | 35.5% |
| Do not use nail polish | 132 | 65.0% |
| Use nail polish | 71 | 35.0% |
| Microwave plastic | 105 | 51.7% |
| Do not microwave plastic | 97 | 47.8% |
| Child does not use lotion | 56 | 27.6% |
| Child uses lotion 1-5 times/month | 40 | 19.7% |
| Child uses lotion 6-29 times/month | 29 | 14.3% |
| Child uses lotion daily | 78 | 38.4% |
| **Vinyl in children's homes** | **N** | **%** |
| *0% vinyl* | 62 | 30.5% |
| *0.1-5% vinyl* | 26 | 12.8% |
| *5.1-10% vinyl* | 21 | 10.3% |
| *10.1-32% vinyl* | 37 | 18.2% |
| *32.1-99.9% vinyl* | 0 | 0.0% |
| *100% vinyl* | 18 | 8.9% |
| *no information* | 39 | 19.2% |

The housing characteristics and product use information are reported in Table 16. Greater than 50% of parents reported that their child used lotion or baby wipes, but nail polish use was less common (35% of parents reported nail polish use at least once per month). Seventy-five percent of home contained at least some vinyl flooring. We categorized the percentage of the home covered in vinyl flooring using measurements of rooms with vinyl (measured by our study team) and the total home square footage (from tax assessment records). Houses with no information on total square footage of the home were included in an "unknown" category for analyses unless the flooring was exclusively vinyl (and thus, measured by our study team). The majority of those homes without information on total square footage were identified as apartments or mobile home/trailers, which meant specific square footage was undeterminable with tax assessment records.

## 6.3.2 Phthalates and non-phthalate plasticizers in individual matrices

### 6.3.2.1 Hand wipes

In general, the phthalate esters and non-phthalate replacements were frequently detected in the children's hand wipes (n=202), with a majority of the compounds detected in >90% of the samples (Table 17). To the authors' knowledge, this study examines the broadest range of phthalates and non-phthalate plasticizers in hand wipe samples to date. Measured in all 202 hand wipe samples, DEHTP, one of the replacements for DEHP, was the most abundant compound (median=2,401 ng/wipe).

This suggests that DEHTP, as it replaces DEHP in its consumer product uses as a plasticizer and in floorings, toys, etc., may be one of the most prominent phthalate compounds to which children are exposed. To the authors' knowledge, this is the first time that DEHTP has been assessed in hand wipe samples. DEHP was also measured at relatively high levels (median=1,842 ng/wipe), which is similar to trends reported previous studies examining both children and adult exposures via hand wipes.[204,215] The higher molecular weight phthalates were generally more abundant on the hand wipes than the lower molecular weight compounds, which suggests that hand-to-mouth behavior may be an important pathway of exposure for these larger phthalate esters.

**Table 17: Descriptive statistics for phthalates and non-phthalate plasticizers with their urinary metabolites.**

| Matrix and Compound | Detection Frequency (%) | MDL[a] | Median | Minimum | 95th Percentile |
|---|---|---|---|---|---|
| **Hand Wipe (ng/wipe) n=202** | | | | | |
| ***Phthalates*** | | | | | |
| **DMP** | 90 | 2.4 | 11 | ND | 120 |
| **DiBP** | 91 | 7.2 | 21 | ND | 123 |
| **DBP** | 49 | 48 | - | ND | 558 |
| **BBP** | 97 | 12 | 138 | ND | 1,110 |
| **DEHP** | 99 | 99 | 1,842 | ND | 12,105 |
| **DiNP** | 80 | 14 | 94 | ND | 1,755 |
| **DEHTP** | 100 | 2.5 | 2,401 | 102 | 16,708 |
| ***Non-phthalate plasticizers*** | | | | | |
| **DEHA** | 36 | 180 | - | ND | 3,043 |
| **TOTM** | 100 | 1.3 | 49 | 0.7 | 480 |
| **Dust (ng/g) n=188** | | | | | |
| ***Phthalates*** | | | | | |
| **DMP** | 38 | 70 | - | - | 1,781 |
| **DEP** | 70 | 234 | 1,937 | ND | 12,239 |
| **DiBP** | 99 | 77 | 4,367 | ND | 33,898 |

| | | | | | |
|---|---|---|---|---|---|
| **DBP** | 99 | 210 | 9,634 | ND | 72,532 |
| **BBP** | 99 | 172 | 13,641 | ND | 132,508 |
| **DEHP** | 100 | 573 | 118,570 | 6,213 | 484,043 |
| **DiNP** | 96 | 188 | 78,751 | ND | 787,600 |
| **DEHTP** | 100 | 167 | 133,649 | 4,506 | 817,386 |
| ***Non-phthalate plasticizers*** | | | | | |
| **DEHA** | 47 | 859 | - | - | 17,168 |
| **TOTM** | 81 | 230 | 4,965 | ND | 36,193 |
| **SG-corrected urine (ng/mL) n=180** | | | | | |
| **MEP** | 100 | 1.2 | 39 | 3.2 | 254 |
| **MiBP** | 100 | 0.80 | 19 | 1.8 | 77 |
| **MHiBP** | 100 | 0.40 | 7.1 | 0.90 | 25 |
| **MBP** | 100 | 0.40 | 20 | 2.5 | 91 |
| **MHBP** | 98 | 0.40 | 2.8 | ND | 14 |
| **MCPP** | 99 | 0.40 | 3.8 | ND | 18 |
| **MBzP** | 100 | 0.30 | 17 | 1.3 | 361 |
| **MEHP** | 72 | 0.80 | 1.9 | ND | 11 |
| **MEOHP** | 100 | 0.20 | 13 | 1.9 | 48 |
| **MEHHP** | 100 | 0.40 | 20 | 1.9 | 80 |
| **MECPP** | 100 | 0.40 | 31 | 8.8 | 121 |
| **MCOP** | 100 | 0.30 | 21 | 2.2 | 175 |
| **MNP** | 53 | 0.90 | 1.2 | ND | 7.6 |
| **MCNP** | 100 | 0.20 | 4.3 | 0.78 | 24 |
| **MONP** | 100 | 0.40 | 6.3 | 0.5 | 49 |
| **MHINCH** | 97 | 0.40 | 2.6 | ND | 14 |
| **MCOCH** | 86 | 0.50 | 1.5 | ND | 6.9 |
| **MECPTP** | 100 | 0.20 | 65 | 14 | 551 |
| **MEHHTP** | 100 | 0.40 | 8.7 | 1.7 | 62 |

[a] Dust MDL values were normalized to average mass of dust extracted (0.059 mg).

#### 6.3.2.2 House dust

The phthalates and alternative plasticizers were commonly and abundantly detected in the indoor house dust with 6 of the analytes detected in >95% of samples (Table 17). Like hand wipes, DEHTP was the most abundant compound measured in the house dust (median=133 μg/g dust) followed closely by DEHP (median=118 μg/g dust). Indoor dust levels of DEHTP in this study are much higher than previous reports of the

terephthalate in Germany from the early 2000s and similar to more recent measurements in Swedish preschool dust.[210,216] Studies examining indoor dust in the United States similarly report DEHP to be the most abundant phthalate compound of those measured with phthalates being the most abundant class of compounds.[53,217,218] Compared to OPEs in the same samples, the phthalates and alternatives were measured at 2-3 orders of magnitude higher, suggesting that exposure through dust for these compounds would be much higher than any organophosphate plasticizers.[219] In this study, DMP was not frequently detected, which suggests that with its lower molecular weight, this compound is either not common to materials/products in the home environment, or it did not significantly partition to the indoor dust.

#### 6.3.2.3 Urinary metabolites

Of the 19 phthalate and non-phthalate plasticizer metabolites assessed in the pooled urine samples, all of the metabolites were detected in >50% of samples with 13 detected in every sample (Table 17). Similar to the hand wipes and dust, one of the DEHTP metabolites, MECPTP, was the most abundant of all metabolites measured in the urine samples (median= 65 ng/mL) followed by MEP (median= 39 ng/mL), the metabolite of DEP. Concentrations of the DEHTP metabolites were much higher than previous reports among U.S. adults from samples taken over the last twenty years, which suggests that children's exposure to DEHP could be higher than for adults.[220] More detailed examination of the phthalate metabolites compared to NHANES children

from a similar age group was previously discussed in Hoffman et al. 2018.[221] In addition, concentrations of unadjusted urinary MBzP in this study population (geometric mean = 25 ng/mL) were similar to those observed in inner-city children who experienced respiratory inflammation and wheeze (95% CI: 16-34 ng/mL).[222] In addition, these observed concentrations of MBzP were considerably higher than those measured in children aged 3-5 years by NHANES 2015-2016 (geometric mean = 8.27 ng/mL).[223] While respiratory-related symptoms and measurements were not investigated here, this suggests that the urinary concentrations of the major BBP metabolite observed here could be related to respiratory health outcomes among TESIE study children in the central North Carolina region.

The urinary metabolites with the largest 95$^{th}$ percentile values were MBzP (major metabolite of BBP) and MECPTP (one metabolite of DEHTP). The reference dose (RfD) of BBP is listed at 200 $\mu g/kg_{bw}/day$.[224] Based on an assumed urinary excretion of 13 mL/hr for children ages 3-4 years and the recorded body weights of the children, we were able to determine relative doses of BBP based on urinary measurements of MBzP (Table E7).[225] The 95$^{th}$ percentile exposure of BBP for children in this study is approximately 4% of the listed RfD for BBP (Median = 0.15% of BBP RfD; Maximum = 31% of BBP RfD). Currently, no RfD has been set for DEHTP. As a result, we calculated an approximate RfD using a NOAEL of 79 $mg/kg_{bw}/day$.[226] Assuming two uncertainty factors of 10, each for inter- and intra-species variability, we estimated an RfD for

DEHTP of 790 μg/kg$_{bw}$/day. Comparing this RfD for DEHTP to the dose of DEHTP, calculated based on the summed metabolites (MECPTP and MEHHTP), the 95$^{th}$ percentile exposure of DEHTP in children in this study is approximately 2% of our estimated RfD for DEHTP (Median = 0.2% of DEHTP RfD; Maximum = 7% of DEHTP RfD). Further details regarding the calculations and assumptions made in calculating these values are included in the Supporting Information.

### 6.3.3 Comparing hand wipes and dust to urine

Spearman correlations coefficients for phthalates and non-phthalate plasticizers and their metabolites, both on a molar sum basis and individually, can be found in Tables 18 and E4.

**Table 18: Spearman correlation coefficients for phthalate, non-phthalate plasticizers, and their corresponding metabolite levels measured in paired hand wipes (*n* = 179) and dust (*n* = 178) with ≥70% detection and specific-gravity corrected urine.**

| | | Urine | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MEP | Σ*DiBP*[a] | Σ*DBP*[b] | MCPP | MBzP | Σ*DEHP*[c] | Σ*DiNP*[d] | MCNP | MHINCH | MCOCH | Σ*DEHTP*[e] |
| **Hand Wipe** | DMP | 0.07 | 0.10 | 0.07 | 0.07 | 0.10 | 0.08 | -0.02 | 0.05 | 0.05 | 0.06 | 0.05 |
| | DiBP | 0.10 | **0.33†** | 0.10 | 0.07 | 0.08 | 0.05 | 0.04 | 0.00 | 0.01 | -0.03 | 0.02 |
| | BBP | **0.16*** | **0.23#** | **0.35†** | 0.08 | **0.56†** | 0.11 | 0.03 | 0.00 | 0.02 | -0.03 | 0.03 |
| | DEHP | 0.04 | 0.14 | 0.09 | **0.18*** | **0.16*** | **0.25†** | **0.19*** | 0.07 | 0.01 | -0.02 | -0.03 |
| | DiNP | 0.11 | **0.18*** | 0.15 | **0.25†** | **0.15*** | **0.20#** | **0.27†** | **0.17*** | 0.04 | -0.03 | -0.03 |
| | DEHTP | 0.13 | **0.17*** | 0.10 | 0.01 | **0.18*** | 0.02 | 0.05 | 0.04 | 0.13 | 0.13 | 0.13 |
| | TOTM | -0.09 | 0.10 | -0.02 | 0.09 | 0.08 | 0.05 | **0.16*** | 0.09 | 0.08 | 0.04 | -0.03 |
| **Dust** | DEP | 0.10 | -0.05 | -0.10 | **0.19*** | 0.03 | -0.05 | 0.12 | 0.07 | 0.04 | -0.01 | 0.14 |
| | DiBP | **0.31†** | **0.42†** | **0.33†** | **0.31†** | **0.25†** | **0.23#** | **0.23#** | **0.21#** | 0.10 | 0.06 | **0.18*** |
| | DBP | **0.17*** | **0.19*** | **0.26†** | 0.10 | 0.13 | 0.14 | 0.04 | 0.06 | 0.11 | 0.07 | **0.19*** |
| | BBP | **0.33†** | **0.29†** | **0.26†** | 0.06 | **0.44†** | **0.21#** | 0.04 | 0.05 | 0.10 | 0.06 | **0.27†** |
| | DEHP | 0.00 | 0.13 | 0.12 | **0.22#** | 0.04 | **0.18*** | **0.15*** | **0.17*** | 0.04 | 0.01 | 0.08 |
| | DiNP | 0.03 | 0.08 | 0.11 | **0.24#** | 0.05 | **0.18*** | **0.19*** | 0.13 | **0.16*** | 0.11 | **0.18*** |
| | DEHTP | 0.12 | 0.12 | 0.08 | **0.17*** | 0.11 | 0.01 | 0.13 | 0.13 | 0.13 | 0.14 | **0.33†** |
| | TOTM | -0.01 | 0.08 | -0.05 | 0.05 | 0.01 | -0.11 | -0.07 | -0.02 | -0.01 | -0.02 | 0.00 |

*p<0.05, #p<0.01, †p<0.001

[a] Σ*DiBP*= Molar sum of MHiBP and MiBP

[b] Σ*DBP* = Molar sum of MHBP and MBP, MCPP is a non-specific metabolite

[c] Σ*DEHP* = Molar sum of MEHP, MEOHP, MEHHP, and MECPP

[d] Σ*DiNP* = Molar sum of MCOP and MONP

[e] Σ*DEHTP* = Molar sum of MECPTP and MEHHTP

Overall, the strongest correlation between a parent plasticizer and a urinary metabolite was observed between BBP and its major metabolite MBzP ($r_s$=0.56 and 0.44 in hand wipes and dust, respectively, $p<0.001$, Table 18). As MBzP is known to be a primary metabolite of BBP, this strong correlation implies that both hand wipe mass and dust concentrations of BBP are effective metrics for estimating residential exposure. The next strongest correlation was between DiBP and the molar sum of all DiBP urinary metabolites (Table 18). This trend held for both hand wipe masses and dust concentrations ($r_s$=0.33 and 0.42, respectively, $p<0.001$) again implying that measuring exposure using either hand wipe mass and dust concentration measurements are effective at estimating exposure. We also observed statistically significant positive relationships between DEHP and DiNP in hand wipes and summed urinary metabolites ($p<0.01$) and for DEHP, DiNP and DEHTP in dust and total corresponding urinary metabolites. Again, this implies that measuring these phthalates in hand wipes and house dust is a useful metric of exposure in children and suggests that the home environment is a major source of exposure to these chemicals.

Table 18 also presents correlations between parent compounds and other metabolites that are not directly related through metabolism pathways. This may imply a co-exposure or co-occurrence of particular parent compounds in residential products or articles resulting in dissimilar urinary metabolite associations. Previous studies have demonstrated similar results, citing that such correlations may exist due to diet or other

lifestyle habits not accounted for in this investigation.[223] In particular, dust DiBP was significantly and positively correlated with 9 of the 11 measured urinary metabolites and molar sums presented in Table 18; however, DiBP can metabolize to MHiBP and MiBP in humans, which are displayed as the molar sum ΣDiBP.[227] A similar, though less dramatic, pattern was found for BBP and DiNP, both of which were positively and significantly correlated with 4 measured urinary metabolites other than its corresponding one.

Regression analyses adjusting for additional covariates (including child's age and sex, mother's education and race, and average outdoor temperature) showed similar patterns to the Spearman correlation analyses (Figure 12). These additional covariates were used for consistency across similar studies with the same dataset that investigated different classes of chemicals.[219] In general, higher levels of parent compounds in dust or hand wipes were associated with higher concentrations of urinary metabolites. For example, a significant relationship between BBP and urinary MBzP was observed for the top two quartiles of hand wipe levels, with an increasing trend across all categories (Figure 12). A similar trend was observed for BBP in dust, suggesting that of all the phthalates evaluated with biomarkers available, BBP exposure as measured by hand wipes and dust was most strongly associated with its urinary metabolite. This suggests that house dust may be a significant source of BBP because both hand wipes and dust were positively associated with urinary MBzP at the highest quartiles. Additionally,

while hand wipes are more likely to integrate exposures across multiple microenvironments, BBP levels in house dust and paired hand wipes were significantly correlated ($r_s$=0.27, p=0.0001), which signifies that BBP is ubiquitous throughout indoor environments, and the home environment may be a primary contributor to the levels found on children's hands.

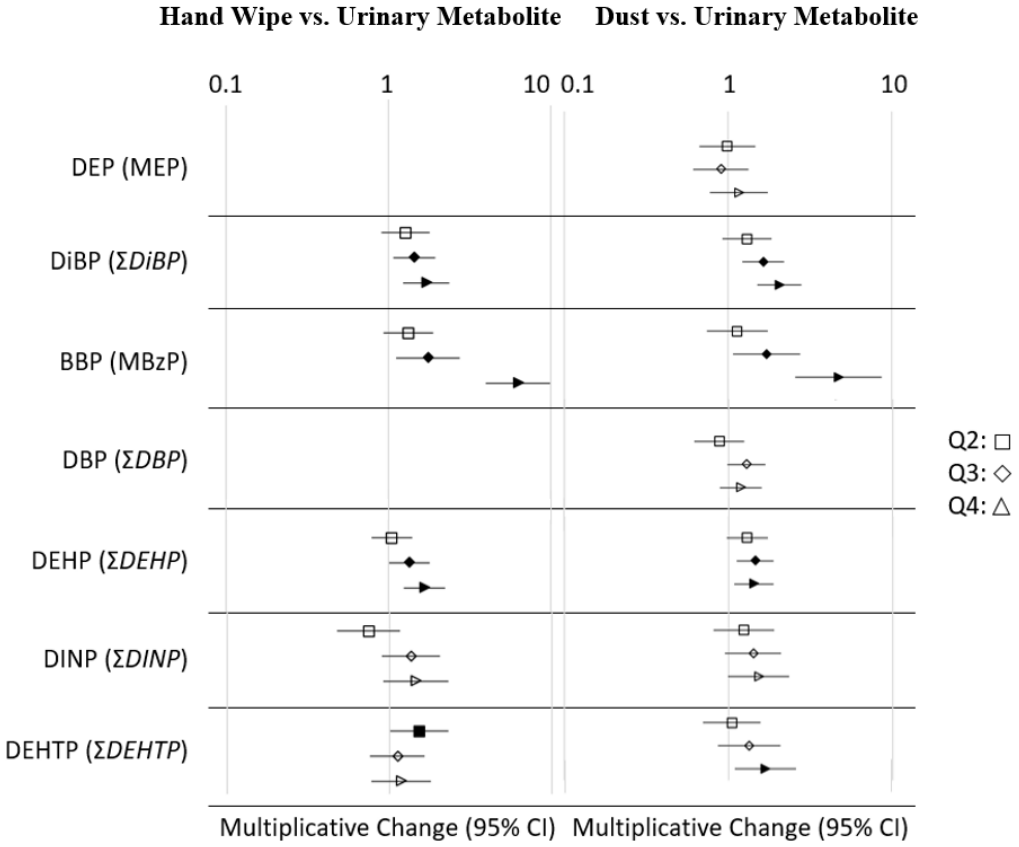



**Figure 12: Multiplicative change results of regression analyses (adjusted for covariates child's sex and age, mother's education and race, and average outdoor temperature) and 95% confidence intervals for predicting phthalate urinary metabolites based on mass of parent phthalate on hand wipes and concentration in dust. Associated urinary metabolites are provided in figure text. Q1 (reference category) not shown. Bolded shapes signify statistically significant (p < 0.05) associations. DEP in hand wipes was not included due to interferences in the chromatography, and DBP in hand wipes was not analyzed due to low detection limit.**

Hand wipe levels of these phthalate and non-phthalate plasticizers may also provide important information on children's exposures in particular. Children have more hand-to-mouth contacts than adults, and this may be an important pathway of exposure for plasticizers that can be captured by the hand wipes in addition to dermal absorption. Further, previous studies have shown that inhalation of indoor air alone can possibly account for only 10% of total exposure to phthalates such as BBP, thereby indicating that for many of these compounds, the majority of individual exposure would be via other pathways (e.g., dust, dermal absorption, or hand-to-mouth contact).[206] The significant and positive correlations between BBP in dust and hand wipes to its urinary metabolite, MBzP, in particular, suggest that residential indoor environmental exposures are meaningful when assessing the total BBP exposure experienced by children. This is particularly noteworthy due to the potential adverse health outcomes for and sensitivity of vulnerable populations, such as pregnant women and children, to BBP.[228]

Similar to the Spearman correlation analyses, models that examined the effect of hand wipes levels of both DiBP and DEHP on their corresponding molar summed urinary metabolites were associated after adjusting for covariates in regression analyses. Positive relationships between dust concentration and urinary metabolites for DiBP, DEHP, DiNP, and DEHTP are also observed. Observed relationships between both DiBP and DEHP in hand wipes and dust as compared to their corresponding urinary metabolites suggest that these sampling techniques are effective exposure metrics for

residential phthalate exposures. Further detailed information on all phthalates and plasticizer alternatives in the three exposure matrices evaluated can be found in Appendix E (Tables E5 and E6).

### 6.3.4 Housing characteristics and exposure matrices

The presence of vinyl flooring in the home was of particular interest since vinyl has been shown to be a source of certain phthalates such as BBP, DiNP and DEHP.[228–230] PVC flooring can contain up to 30% (w/w) of phthalate plasticizers such as BBP;[52] however, since they are not covalently bound to the flooring, these phthalates can leach into the home environment and lead to residential exposure.[228,231,232] Previous studies have observed significantly elevated levels of house dust BBP and urinary MBzP in pregnant women in homes with PVC flooring compared to other flooring types.[228,233] While vinyl flooring could be a source of BBP in the home, it is important to note that we did not directly test the vinyl flooring for phthalates in this study. According to a recent publication, DEHTP is a common plasticizer used in a wide variety of applications such as coatings, adhesives, and sealants in products often found in residential environments (e.g., flooring, cable insulations, and toys). It is marketed as an alternative plasticizer in response to recent phthalate bans worldwide.[234] Therefore, DEHTP may be commonly found in more recent vinyl flooring installations. This may suggest that the homes we sampled with 100% vinyl was older and contained BBP as a plasticizer. A majority of the

homes with 100% vinyl flooring in this study were public housing, and thus they may not have been renovated in some time.

Figure 13 compares the measurements of phthalate and non-phthalate plasticizers on hand wipes and in dust between homes with no vinyl flooring (0%) and homes with 0.1-5%, 5.1-10%, 10.1-33%, or 100% vinyl flooring in the TESIE study. For children living in 100% vinyl homes, levels of BBP measured on their hand wipes were 350% higher than those living in homes without any vinyl flooring, ($10^{\beta}$ = 4.5, 95% CI = 2.2 – 9.3, $p < 0.0001$), while dust concentrations of BBP were associated with a 450% increase as compared to homes with no vinyl flooring ($10^{\beta}$ = 5.5, 95% CI = 2.7 – 11.4, $p < 0.0001$) (Figure 13). These BBP trends in dust were significant across all homes with any vinyl flooring, though a significant result was only observed for hand wipes for children living in homes with 100% vinyl flooring. Though no other phthalates or non-phthalate plasticizers measured in hand wipes showed statistically significant associations in homes with 100% vinyl flooring, DiNP concentrations in dust were also significantly higher in homes with 10.1-32% vinyl flooring ($10^{\beta}$ = 1.9, 95% CI = 1.2 – 3.0, $p<0.05$).

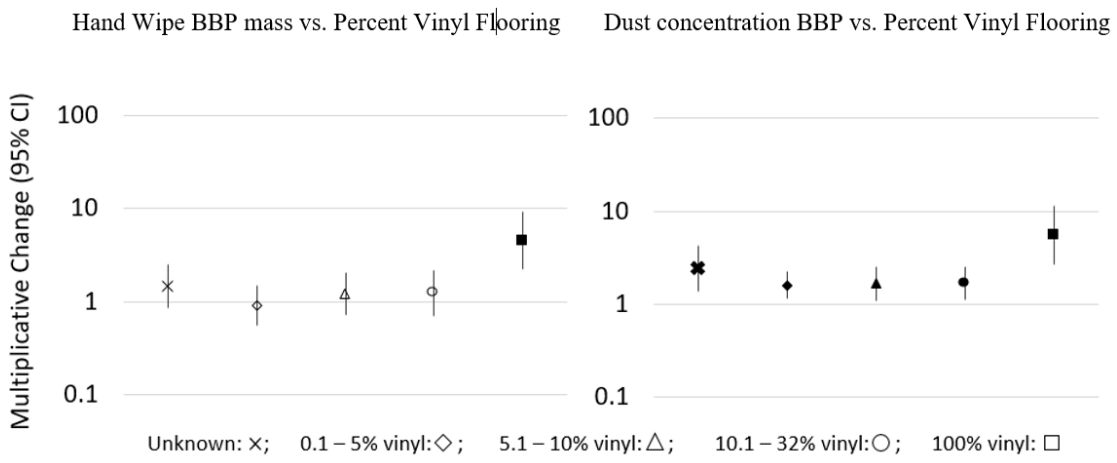



**Figure 13: Multiplicative change results of regression analyses (adjusted for covariates child's sex and age, mother's education and race, and average outdoor temperature) and 95% confidence intervals of vinyl flooring as a predictor of hand wipe BBP mass and dust concentration BBP. The magnitude of increase in BBP compared to percentage of vinyl flooring in the home are compared to homes with 0% vinyl flooring (reference category), which is represented at a multiplicative change of 1. Bolded shapes signify significant ($p < 0.05$) associations.**

As shown in Figure 14, MBzP was substantially higher in children living in houses with 100% vinyl flooring ($10^{\beta} = 16.3$, 95% CI = 6.7 – 39.4, $p < 0.0001$). Urinary MBzP was also elevated among children living in homes where the percentage of vinyl was unknown, most of which were apartment buildings or mobile homes/trailers ($10^{\beta} = 2.0$, 95% CI = 1.1 – 3.5, $p<0.05$). Although not as strongly associated as with MBzP, similar associations with urinary metabolites were observed among children living in homes with 100% vinyl flooring for metabolites of DEP, DBP, DEHP, and DINCH ($10^{\beta} = 1.9 – 3.0$, $p < 0.05$; 95% CI per metabolite). The positive associations observed for other urinary metabolites in children from 100% vinyl homes suggest that these compounds may be present in vinyl flooring along with BBP, thus leading to co-exposure, or may

represent additional products or articles more frequently found in homes that have 100% vinyl flooring. As many of the homes with 100% vinyl flooring in this study were likely public housing developments, there may be implications regarding socioeconomic status that are important when considering exposures to endocrine disrupting compounds such as phthalates.

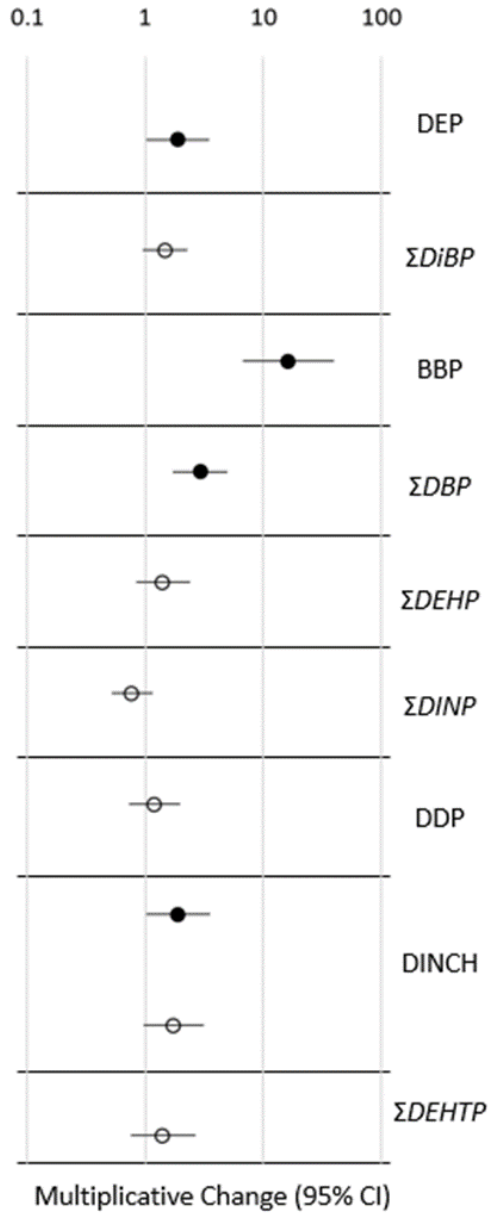



**Figure 14: Multiplicative change results of regression analyses (adjusted for covariates child's sex and age, mother's education and race, and average outdoor temperature) and 95% confidence intervals of 100% vinyl flooring as a predictor of urinary phthalate or phthalate alternative metabolite concentration, listed by parent compound. The magnitude of urinary metabolite found in people living in 100% vinyl flooring homes is compared to homes with 0% vinyl flooring (reference category), which is represented at a multiplicative change of 1. Bolded shapes signify significant ($p < 0.05$) associations.**

Other housing characteristics (e.g., age of home) and behavioral patterns (e.g., frequency of personal care product use, consumption of food from microwaved plastic) were queried and examined in our analyses; however, the results of these investigations were largely null (presented in supporting information). This is somewhat contradictory to what has been reported previously. For example, Hsieh and colleagues recently reported positive association between the use of person care products, including lotion, and urinary phthalate metabolite concentrations among pregnant women.[235] While adult women may have different behaviors and product use habits than children, similarly elevated phthalate urinary metabolites among children has been associated with products such as liquid soap, hair care products, face creams, and sunscreen.[236,237] Due to possible recall bias present in the questionnaire results, our overall results may be biased towards the null because of exposure misclassifications. Thus, despite observing a lack of significant associations in this study, other studies suggest that product use, behavior, and other aspects of the home environment could still be important for evaluating exposure to phthalates and non-phthalate plasticizers.

### 6.3.5 Limitations and strengths

The results of this study should be interpreted in the context of several potential limitations. First, we analyzed the home environment at a single point in time, potentially limiting our ability to evaluate longer-term exposures. In addition, we only sampled dust from the main living area in the home, which may not accurately capture

exposure to chemicals in other areas of the home or outside the home (e.g., school). We did not assess potential exposure via diet or inhalation. A model that includes the contribution of these other exposure pathways, various microenvironments, and individual behavior may strengthen observed associations with urinary biomarkers. As a biomarker of exposure to phthalates and non-phthalate replacements, we used a composite sample comprised of three urine samples per child collected over a 48-hour period. However, many of the metabolites that we assessed have relatively short half lives in the human body and it is likely that exposure over longer periods is more variable. Our study population was a convenience sample from an established pregnancy cohort. While that may limit the generalizability of the results to the broader population, it should not impact the internal validity of the study. With the wealth of data available herein, we cannot rule out residual confounding of our results due to factors such as socioeconomic status (SES). Mother's education was used as a proxy for SES, though this proxy may be unable to account for other nuanced effects of SES. In addition, statistical significance was set at $\alpha = 0.05$, and adjustments were not made for multiple comparisons. However, this has been recommended and generally accepted in the epidemiologic literature.[238]

Our study has several important strengths, including the relatively large size for an exposure study of children and a diverse study population. The collection of paired samples (urine, hand wipes, house dust), the use of a pooled urine sample per child

(rather than a single spot urine), and the analysis for a large suite of phthalates and non-phthalate replacement plasticizers are additional strengths of our work.

## 6.4 Conclusion

Phthalate parent compounds were detected in nearly all of the hand wipe and dust samples collected in this study, and metabolites were detected in all children's urine samples, indicating ubiquitous exposures for children in the TESIE study. Exposure to these compounds likely come from residential environments, and this investigation of vinyl flooring and phthalate metabolite levels may shed light on the pathway of exposure for certain phthalates. Our results suggest that hand wipes and dust provide good estimates of indoor home exposure to phthalates, with dust providing improved metrics of exposure for some of the higher molecular weight phthalates and hand wipes being better for examining exposure to lower molecular weight phthalates. This result also could be dependent on product usage in the home and the chemicals have vastly different usages across the class. Through a more detailed examination of how vinyl flooring may have contributed to children's exposure in this study, we hope that future work can evaluate ways to reduce or eliminate exposure to these compounds, especially in light of their potential adverse health impacts.

# 7. Examining children's exposures to flame retardants and plasticizers using silicone wristbands

## *7.1 Introduction*

Semi-volatile organic compounds (SVOCs) are ubiquitously found in indoor environments because of their extensive use in consumer products as flame retardants, plasticizers, preservatives, fragrances, etc. Their unique partitioning characteristics allow for their presence in both the gas and condensed phases within room temperature conditions.[165] As such, human exposure to these compounds is widespread and likely chronic.[62,84,112,239] Many of these compounds are suspected to impact endocrine function, reproduction, neurodevelopment, and obesity, among other adverse health effects.[29,30,116,240–244] This is of particular concern for children who typically have higher exposures to these chemicals and are at greater risk for adverse health impacts that could persist into adulthood.

Over the last several years, determining how people, and specifically children, are exposed to SVOCs has been a prominent interest in order to understand how one can reduce individual exposures. Inadvertent ingestion of dust, hand-to-mouth contact, inhalation, and dermal absorption have all been posited to be important pathways of exposure for SVOCs.[66,105,130,131,167,182,245,246] In an effort to capture these pathways in external exposure measures and determine exposure levels that can be attributed to indoor environments, dust and indoor air have been extensively sampled, particularly in the home.[32,62,84,112,142,247] Hand wipes, which are hypothesized to capture hand-to-mouth

contact and dermal absorption, have also been used to reliably measure exposure to organophosphate esters (OPEs), phthalates, and brominated flame retardants when compared to their respective biomarkers in urine and serum.[55,86,88,105] More recently, silicone wristbands have been used as personal passive samplers to measure a wide range of consumer product and industrial chemicals among adults and children.[77,125,146,148,164,248–252] In adults, levels on the wristbands have been shown to be significantly and positively associated with biomarker concentrations for OPEs (Chapter 3), polybrominated diphenyl ethers (PBDEs; Chapter 4), and polycyclic aromatic hydrocarbons (PAHs); in children, a similarly positive association was observed between wristband nicotine and urinary cotinine.[77,249,250,252] While these studies demonstrate that wristbands may be representative of internal dose across three classes of compounds, children and adults may have disparate pathways and sources of exposure based on differences in product use, behaviors, and time spent in different microenvironments.

Here, we sought to utilize silicone wristbands (n=77) to evaluate children's exposure to 65 chemicals across 3 classes of SVOCs (OPEs, phthalates and non-phthalate plasticizers, and brominated flame retardants) through associations with available biomarkers in urine and serum in an existing study population in central North Carolina. Our previous work in the same but expanded study population (n=203) demonstrated that hand wipes were an improved measure over indoor dust for OPEs

(Chapter 5) and that hand wipes and dust both have good utility in evaluating children's exposure to phthalates (Chapter 6). Thus, for OPEs and phthalates, we compared wristbands with paired hand wipes and house dust samples to assess their effectiveness in predicting urinary metabolite concentrations. Our primary objective was to determine if silicone wristbands are viable exposure assessment tools with respect to more traditional analytical paradigms, particularly for the evaluation of children's exposure.

## *7.2 Materials and methods*

### 7.2.1 Study population

Mothers in the Newborn Epigenetics STudy (NEST), a prospective pregnancy cohort study based in central North Carolina (2005-2011), were re-contacted and asked to participate with their children in the Toddler's Exposure to SVOCs in the Indoor Environment (TESIE) study.[186,187] Hoffman et al. 2018 provides a more detailed description of recruitment and enrollment of participants within the full TESIE study, which included 203 children from 190 families who participated between September 2014 and April 2016. Silicone wristbands were deployed halfway through the study, starting in August 2015. In this subset of the TESIE study population, 77 children ages 3-6 years from 74 different families wore pre-cleaned wristbands for 7 days. Study team members conducted home visits with each of the enrolled families to collect environmental samples (dust and handwipes) from within the home and biospecimens (urine and blood) from the children. Furthermore, additional information about the

home environment and children's health and behavior were recorded using a researcher-initiated questionnaire. All study protocols and related materials were reviewed and approved by the Duke Medicine Institutional Review Board. Legal guardians provided informed consent prior to any collection of samples or questionnaire data for the TESIE study, and mothers had provided informed consent prior to their participation in NEST.

### 7.2.2 Wristband collection and analysis

Commercially available, adjustable wristbands were purchased in a variety of colors (diasstro adjustable silicone wristband bracelets, Amazon.com) and cleaned as described in Hammel et al. 2016 (Chapter 3), with two 12-hour Soxhlet extractions with 1:1 ethyl acetate/hexane (v/v) and 1:1 ethyl acetate/methanol (v/v) and passive drying in a fume hood.[77] Wristbands were individually wrapped in aluminum foil and placed in an air-tight, labeled 40 mL amber jar. The children were asked to wear the wristbands continuously for 7 days through all daily activities including bathing and sleeping. Following the sampling period, legal guardians were asked to retrieve the wristbands, rewrap them in foil, and replace them in the amber jar. Wristbands were stored at -20°C until analysis.

Wristband samples (n = 77) were extracted and analyzed for a suite of organophosphate esters, phthalates and non-phthalate plasticizers, and brominated flame retardants. Using solvent-rinsed, stainless-steel scissors and forceps,

approximately one-third of each wristband or field blank (n=8) was cut from the total wristband, with the remainder of each band being returned to its respective amber jar and stored at -20°C for future analyses. This segment was carefully cut into another 3 equal parts to facilitate extraction, accurately weighed and placed into a labeled 50 mL glass centrifuge tube. The wristband segments were spiked with the following internal standards: $d_{12}$-TCEP (100 ng), $d_{15}$-TDCIPP (100 ng), $^{13}$C-TPHP (100 ng), $d_4$-DMP (200 ng), $d_4$-DEP (200 ng), $d_4$-BBP (200 ng), $d_4$-DEHP (200 ng), FBDE-69 (100 ng), $^{13}$C-EH-TBB (100 ng), $^{13}$C-BEH-TEBP (100 ng), and $^{13}$C-BDE-209 (50 ng). $D_{12}$-TCEP, $d_{15}$-TDCIPP, $^{13}$C-TPHP, $^{13}$C-EH-TBB, $^{13}$C-BEH-TEBP, and $^{13}$C-BDE-209 were purchased from Wellington Laboratories (Guelph, ON). $D_4$-DMP, $d_4$-DEP, $d_4$-BBP, and $d_4$-DEHP were purchased from Cambridge Isotope Laboratories (Tewksbury, MA). FBDE-69 (100 ng) was purchased from AccuStandard (New Haven, CT). Using a method similar to Hammel et al. 2018 (Chapter 4), the samples were extracted 3 times with 10 mL 1:1 hexane/dichloromethane (v/v) then concentrated to 1.0 mL using a Thermo Scientific SpeedVac Concentrator.[252] The 1.0 mL extracts were fractionated using Florisil® solid-phase extraction cartridges (Supelclean ENVI-Florisil, 6 mL, 500 mg bed weight; Supelco), eluting the first fraction (F1) with 8 mL hexane for the brominated flame retardants, the second fraction (F2) with 10 mL ethyl acetate for organophosphate esters and phthalates, and the third fraction (F3) with 8 mL methanol for PFASs (data not included here). Each fraction was once again concentrated to 1.0 mL using the SpeedVac

Concentrator, with the F3 fractions transferred to autosampler vials (ASVs) and stored at -20°C for future analysis. The F2 fractions were transferred to ASVs for analysis by gas chromatography/mass spectrometry in electron ionization (GC/MS-EI) for the chlorinated OPEs, phthalates, and non-phthalate plasticizers. The phthalates and non-phthalate plasticizers were quantified using a 10:1 dilution in hexane to account for the high concentrations on the wristbands. The ITP and TBPP compounds were analyzed using GC Orbitrap GC/MS/MS for high resolution separation of the isomers and reduction of interferences. The F1 fractions were analyzed for BFRs using GC/MS in electron capture negative ionization (ECNI). The F1 fractions were further purified by fractionating the samples through 8.0 g of deactivated silica gel (60-200 mesh), which were impregnated with 5% concentrated sulfuric acid by mass. The first fraction was eluted with hexane and the second with ethyl acetate. The first fractions of the F1 fractions were concentrated to 1 mL using a nitrogen evaporator system and transferred to ASVs for analysis for PBDEs using GC/MS-ECNI. The second fractions of the F1 fractions were solvent-exchanged to hexane, concentrated to 1 mL with the nitrogen evaporator, transferred to ASVs, and stored at -20°C for future analysis.

Recovery of internal standards was evaluated using $d_{18}$-TCIPP (100 ng) for $d_{12}$-TCEP and $d_{15}$-TDCIPP; $d_{15}$-TPHP (100 ng) for $^{13}$C-TPHP; $^{13}$C-DCPH (100 ng) for the deuterated phthalate standards; $^{13}$C-CDE-141 (100 ng) for FBDE-69, $^{13}$C-EH-TBB, and $^{13}$C-BEH-TEBP; and FBDE-208 (100 ng) for $^{13}$C-BDE-209. $D_{15}$-TPHP and $^{13}$C-CDE-141 were

purchased from Wellington Laboratories (Guelph, ON). $D_{18}$-TCIPP and $^{13}$C-DCPH were purchased from Cambridge Isotope Laboratories (Tewksbury, MA). FBDE-208 was purchased from AccuStandard (New Haven, CT). For the OPE internal standards, recoveries of $d_{12}$-TCEP, $d_{15}$-TDCIPP, and $^{13}$C-TPHP were on average 121 ± 1%, 92.5 ± 2%, 86.0 ± 2%, respectively. For the phthalate internal standards $d_4$-DMP, $d_4$-DEP, $d_4$-BBP, and $d_4$-DEHP, recoveries were on average 70.6 ± 7%, 102 ± 13%, 118 ± 8%, and 93.2 ± 5%, respectively. For the BFR internal standards, recoveries of FBDE-69, $^{13}$C-EH-TBB, $^{13}$C-BEH-TEBP, and $^{13}$C-BDE-209 were on average 103 ± 1%, 115 ± 3%, 75.9 ± 2%, and 102 ± 1%, respectively. In addition, lab blanks (n=5) and field blanks (n=8) were analyzed with the wristband samples for quality assurance and quality control.

### 7.2.3 Hand wipe and dust collection and extraction

Phillips & Hammel et al. 2018 (Chapter 5) provided a more detailed description of collection and analysis for hand wipes and dust.[219] In brief, hand wipe samples were collected from each child using pre-cleaned twill wipes which were soaked with 3 mL isopropyl alcohol. The entirety of the children's hand surface area was wiped, from wrists to fingertips and in between the fingers. The wipes were wrapped in aluminum foil and stored at -20°C until analysis. House dust samples were collected by using a Eureka Mighty Mite vacuum fitted with a cellulose thimble in the hose attachment to vacuum the entire exposed floor area of the main living area. The thimbles were wrapped in aluminum foil and stored at -20°C until analysis. Both hand wipes and dust

were spiked with internal standards and solvent extracted by sonication then cleaned using Florisil® SPE cartridges. Field blanks for hand wipes and lab blanks and house dust standard reference material (SRM 2585, NIST, Gaithersburg, MD) for dust were analyzed alongside the samples for quality assurance and quality control. Samples were analyzed for OPEs and phthalates using GC/MS-EI.

### 7.2.4 Urine collection and extraction

During home visits, families were provided with collection kits for urine samples. Three spot urine samples were collected from each child during a 48-hour sampling period, after which they were stored frozen in the families' homes until transportation back to our research laboratory where they were stored at -20°C. Prior to analysis, the samples were thawed, and equal volumes of the spot urine samples were combined to form a pooled sample. The composite sample was analyzed for OPE metabolites in our laboratory, with a detailed description of methods previously described in Phillips & Hammel et al. 2018 (Chapter 5), and for phthalate and non-phthalate plasticizer metabolites by the CDC laboratory, as described previously in Hammel & Levasseur et al. 2019 (Chapter 6).[219]

### 7.2.5 Serum collection and analysis

Serum samples were collected from children during home visits by a certified phlebotomist using venipuncture or a finger stick based on the preference of the legal guardian and child. All samples were collected in serum separator tubes then

centrifuged at 3500 RPM for 5 minutes and stored at -20°C until analysis. PBDEs were quantified in serum at the CDC using previously described methods, using gas chromatography/isotope dilution high-resolution mass spectrometry.[253] Similar to the urinary metabolites, standard QA/QC practices were used for the assessment of PBDEs and MDLs as described previously.

### 7.2.6 Statistical analyses

All analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC) for analytes detected in >60% of samples, and results were assessed at a level of $\alpha$=0.05 for significance. Method detection limits (MDLs) were determined using three times the standard deviation of the average field blank levels for wristbands and hand wipes, and lab blanks for dust, urine, and serum samples. MDLs were normalized to the average field blank sample mass of wristbands (1.52 g), average mass of dust extracted (0.06 mg), or volume of urine extracted (5 mL), accordingly. Values below the MDL were replaced with MDL/2.[103] Preliminary analyses examining the chemical concentrations in the external exposure measures (wristbands, hand wipes, and dust) and biomarker concentrations in biospecimens (urine and serum) indicated that the levels were non-normally distributed across the board. As such, Spearman correlations were used to assess the relationships between matrices. For the comparisons to urinary metabolites, these were performed for both unadjusted and specific gravity-corrected urinary metabolite levels.[189] The correlation coefficients were non-

differentiable and thus only the specific gravity-corrected values are presented here. Certain parent compounds, specifically TCIPP and several of the phthalates and non-phthalate plasticizers, metabolize to multiple metabolites. For TCIPP, we evaluated the associations for its two metabolites separately since preliminary data from another study suggests that BCIPP and BCIPHIPP levels vary significantly based on age, race/ethnicity, or other factors. For the phthalates and non-phthalate plasticizers, associations were evaluated on molar sums of the metabolites, which allowed for better characterization of the relationships between the parents and total metabolites. Therefore, only these relationships, rather than the associations with individual metabolites, are displayed.

Some families in the TESIE study elected not to provide a blood sample. Given that the wristbands were introduced halfway through the study there is not a complete overlap in the number of participants for each sample type, and relationships were evaluated for the maximum number of paired samples available. For the OPEs and phthalates, relationships utilizing hand wipes and dust were restricted to participants who had also provided wristband samples. Due to the small overlap in wristbands and serum samples (n=15 pairs), the correlations for detected PBDEs on wristbands and serum were evaluated but relationships were not compared to hand wipes and dust.

Linear regression models were used to further evaluate how the external exposure assessment tools contributed to biomarker concentrations for OPEs and phthalates. These models included house dust and hand wipes or wristbands. All

variables were $\log_{10}$-transformed for inclusion in the models; consequently, to ease interpretation, the beta estimates were used as relative comparisons rather than for evaluating on the basis of units of change. Variance inflation factors were calculated for all variables, indicating that the individual matrices did not experience multicollinearity and could reasonably be included in the models together, as presented.

### 7.2.7 Estimated daily intake

In an attempt to calculate exposure estimates from each of the external exposure assessment tools, estimated daily intakes were calculated from the chemical concentrations measured on each matrix. These values were normalized to the child's body weight, which was determined during the home visit, and calculated using data provided from the U.S. EPA Exposure Factors Handbook and from the questionnaires with the child's legal guardian.[254] The following equations were used to calculate exposure estimates from dust, hand wipes, and wristbands:

$$Exposure\ Estimate\ from\ Dust\ (ng\ day^{-1}kg^{-1}) = \frac{Concentration\ of\ analyte\ in\ dust\ (ng/g) \times\ Dust\ Ingestion\ Rate \times Fraction\ of\ Day\ in\ Home}{Body\ Weight}$$

Where child dust ingestion rate for 2-6yo is estimated at 0.060 g $day^{-1}$ and fraction of day is calculated for median of category recorded in questionnaire divided by 24 hours.

$$Exposure\ Estimate\ from\ Hand\ Wipes\ (ng\ day^{-1}kg^{-1})$$

$$= \frac{Mass\ of\ Analyte\ on\ Hand\ Wipe\ \times\ TE\ \times\ SAC\ \times EF}{Body\ Weight}$$

Where TE is the fraction of compound transferred per contact (50%), SAC is the portion of hand involved in each contact event (10%), and EF is the frequency of contact over 24 h period based on Stapleton et. al 2008.[122]

$$EF = \frac{16\ contacts}{hr} \times \frac{Active\ hours}{day}\ where\ Active\ hours = 24 - Median\ Sleep\ time$$

Activity logs could have been used for calculating contacts. However, based on the data, 65% of participants have either no data or zero observed hand to mouth contacts. Therefore, 16 hand to mouth contacts are included in this model based on the average for children>24 months old from Tulve et. al 2002.[255]

$$Exposure\ Estimate\ from\ Wristbands\ (ng\ day^{-1}kg^{-1})$$

$$= \frac{\frac{Concentration\ of\ Analyte\ on\ Wristband\ (ng/g) \times Total\ Mass\ of\ Wristband}{t}}{Body\ Weight}$$

Where t is sampling time based on the wristband log (1, 3, 5, 7 days) and total mass is 3 times the mass of wristband piece. For samples missing t data (n=28), the average sampling time (5 days) was used.

These exposure estimates or estimated daily intake from each form of media were calculated for 12 OPE compounds and 7 phthalate/non-phthalate plasticizers that were highly detected in the wristbands and had corresponding urinary metabolite data

available. Spearman correlations with biomarkers were assessed with these exposure estimates, and their magnitudes of correlation were compared between matrices.

## *7.3 Results and discussion*

### 7.3.1 Study population

The demographics of the study population subset in which wristbands were deployed are described in Table 19. Details about the full TESIE study population were more extensively described in Hoffman et al. 2018. This subset of the TESIE study included 77 children from 74 homes, with about two-thirds of the children being male. The median age in this study population was 57 months (4.75 years) and included children ranging from 50 to 67 months. Notably different from the total TESIE study population, the majority of the children's mothers identified as Hispanic (43%), while 31% and 25% identified as non-Hispanic black and white, respectively. Also, more of the mothers in this subset had attained a high school degree or less (65%), compared to the 55% in the original TESIE population. Wristband collection started a year into the TESIE study, and thus, all samples described here were collected between August 2015 and April 2016.

**Table 19: Demographics of TESIE Children (n = 77) included in the Wristband Data Subset**

| Characteristic | N | % |
|---|---|---|
| Child Sex | | |
| Male | 46 | 59.7% |
| Female | 31 | 40.3% |
| Age | | |
| 50-55 months | 30 | 39.0% |
| 56-59 months | 24 | 31.2% |
| 60-67 months | 23 | 29.9% |
| Ethnicity | | |
| Non-Hispanic white | 19 | 24.7% |
| Non-Hispanic black | 24 | 31.2% |
| Hispanic white | 33 | 42.9% |
| Other | 1 | 1.3% |
| Maternal education | | |
| Less than high school graduate | 31 | 40.3% |
| High school graduate or GED | 19 | 24.7% |
| College graduate or more | 27 | 35.1% |
| | **Mean** | **range** |
| Child age (months) | 57.1 | 50-67 |
| Average temp (°C) | 15.6 | -1.1-27.2 |
| Child Body Weight (kg) | 19.7 | 15.3-35.5 |
| **Children's Behaviors** | **N** | **%** |
| Time spent at home | | |
| 3-5 hours | 2 | 2.6% |
| 6-8 hours | 11 | 14.3% |
| 9-12 hours | 20 | 26.0% |
| 13-18 hours | 27 | 35.1% |
| 19-22 hours | 5 | 6.5% |
| 23-24 hours | 12 | 15.6% |
| Time spent sleeping | | |
| 0-6 hours | 1 | 1.3% |
| 7-9 hours | 34 | 44.2% |
| 10-12 hours | 41 | 53.2% |
| >12 hours | 1 | 1.3% |
| Hand-to-Mouth contacts (per 15 min) Activity Log | | |
| 0 times | 30 | 39.0% |
| 1-2 times | 15 | 19.5% |
| 3-8 times | 9 | 11.7% |

| | | |
|---|---|---|
| 11-26 times | 4 | 5.2% |
| No data | 19 | 24.7% |
| Time wristband worn | | |
| 1-2 days (<25% of week) | 8 | 10.4% |
| 3-4 days (~50% of week) | 6 | 7.8% |
| 5-6 days (~75% of week) | 8 | 10.4% |
| 7 days (whole week) | 27 | 35.1% |
| Missing Log | 28 | 36.4% |

## 7.3.2 Levels of compounds on wristbands

### 7.3.2.1 Organophosphate esters

Wristbands were analyzed for 22 organophosphate esters, and 13 of them were detected in >80% of the wristband samples (Table 20). The chlorinated alkyl phosphates (TCEP, TCIPP, TDCIPP) were detected in >80% of the wristbands, with TDCIPP being the most abundant within this subclass (GM = 184.1 ng/g) (Figure 15). EHDPHP was the only OPE that was detected in every wristband collected. Measured in all but one sample, TPHP was the most abundant OPE overall on the wristbands (GM = 742.6 ng/g) (Table 20, Figure 16), which is likely due to its prevalence of use in consumer products as both a plasticizer and flame retardant. When compared to deployed wristbands among children of a similar age range in Oregon, we observed a different trend, as Kile et al. detected TDCIPP at the highest levels of the 4 OPEs measured (TDCIPP, TPHP, TCIPP, and TCEP).[125] The mean levels of TPHP on the children's wristbands were roughly similar, with Kile et al. observing 134 ng/g/day and our study reporting 168 ng/g/day. While the distribution of the data in both cases were log-normal, suggesting

that the means would not be the most effective manner of comparing wristband levels, the similar means could indicate that both study populations likely had TPHP levels on the wristbands that were within the same order of magnitude. Also, the Oregon children were recruited from preschools, indicating that they spent part of their day in school, whereas not all of the children in our study attended school during the daytime. This would suggest that the difference in where children from these two study populations spent their time could lead to the differing trends observed in their OPE exposure. Compared to OPE levels measured in an adult cohort from a similar region of central North Carolina (Chapter 2), we again observed a dissimilar trend among the children's wristbands.[77] Among adults, the most abundant OPE measured was TCIPP, which was followed by TDCIPP then TPHP. This indicates that children may have different exposure sources and pathways from adults, particularly for TCIPP, which could be due to differences in consumer product use and the shift away from using TDCIPP in products (e.g., child car seats, home furnishings) to TCIPP.[8]

**Table 20: Descriptive Statistics of Analytes on Wristbands (n = 77; ng/g wristband)**

| Class and Compound | Detection Frequency (%) | MDL[a] | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| ***OPEs*** | | | | | | |
| **TCEP** | 81.8 | 8.85 | 35.84 | 35.80 | ND | 319.7 |
| **TCIPP** | 98.7 | 0.89 | 62.71 | 55.16 | 17.03 | 848.5 |
| **TDCIPP** | 98.7 | 0.92 | 184.1 | 179.7 | 38.04 | 1,443 |
| **EHDPHP** | 100.0 | 0.06 | 62.95 | 73.61 | 21.74 | 306.9 |
| **TPHP** | 98.7 | 1.18 | 742.6 | 872.9 | 224.4 | 3,681 |
| **2IPPDPP** | 98.7 | 1.37 | 292.1 | 373.4 | 66.24 | 1,499 |
| **3IPPDPP** | 94.8 | 0.66[b] | 30.64 | 40.83 | 4.46 | 237.0 |

| Class and Compound | Detection Frequency (%) | MDL[a] | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| **4IPPDPP** | 98.7 | 0.66[b] | 94.54 | 112.5 | 21.53 | 537.9 |
| **24DIPPDPP** | 98.7 | 0.88 | 186.3 | 236.0 | 45.01 | 1,644 |
| **B2IPPPP** | 98.7 | 0.66[b] | 115.0 | 141.1 | 25.62 | 707.4 |
| **B3IPPPP** | 98.7 | 0.66[b] | 237.9 | 309.8 | 39.83 | 2,053 |
| **B4IPPPP** | 49.4 | 0.66[b] | 1.59 | - | ND | 39.55 |
| **B24IPPPP** | 50.6 | 32.88 | 43.26 | 36.53 | ND | 355.0 |
| **2tBPDPP** | 5.2 | 0.66[b] | 0.37 | - | ND | 0.47 |
| **4tBPDPP** | 98.7 | 0.66[b] | 107.3 | 119.5 | 29.83 | 477.6 |
| **B2tBPPP** | 0.0 | 0.66[b] | - | - | ND | ND |
| **B4tBPPP** | 88.3 | 0.66[b] | 13.64 | 20.68 | ND | 137.8 |
| **T4tBPP** | 10.4 | 0.66[b] | 0.44 | 0.33 | ND | 3.91 |
| ***Phthalates*** | | | | | | |
| **DMP** | 98.7 | 0.04 | 24.62 | 22.59 | 8.37 | 127.3 |
| **DEP** | 98.7 | 1.40 | 803.8 | 739.1 | 254.0 | 4,489 |
| **DiBP** | 98.7 | 0.55 | 1,003 | 976.2 | 311.1 | 6,081 |
| **DBP** | 98.7 | 4.27 | 252.9 | 274.3 | 114.4 | 668.2 |
| **BBP** | 100.0 | 0.45 | 986.1 | 1,059 | 211.8 | 9,895 |
| **DEHP** | 100.0 | 2.24 | 7,510 | 9,010 | 2,198 | 42,296 |
| **DiNP** | 98.7 | 4.73 | 6,319 | 7,073 | 1,848 | 26,058 |
| **DEHTP** | 100.0 | 1.19 | 7,629 | 8,493 | 2,293 | 33,857 |
| ***Non-phthalate plasticizers*** | | | | | | |
| **DEHA** | 100.0 | 3.05 | 805.6 | 999.9 | 188.6 | 3,998 |
| **TOTM** | 98.7 | 0.57 | 105.6 | 124.7 | 26.31 | 419.9 |
| ***PBDEs*** | | | | | | |
| **BDE-30** | 58.4 | 0.03 | 0.06 | 0.05 | ND | 2.31 |
| **BDE-17** | 88.3 | 0.02 | 0.30 | 0.44 | ND | 1.87 |
| **BDE-25** | 87.0 | 0.04 | 0.20 | 0.20 | ND | 2.26 |
| **BDE-28,33** | 98.7 | 0.07 | 4.50 | 5.11 | 0.99 | 26.58 |
| **BDE-75** | 87.0 | 0.52 | 3.33 | 3.93 | ND | 16.14 |
| **BDE-49** | 59.7 | 1.27 | 1.92 | 1.74 | ND | 17.20 |
| **BDE-71** | 51.9 | 2.36 | 3.05 | 2.35 | ND | 19.99 |
| **BDE-47** | 100.0 | 0.16 | 123.4 | 144.5 | 18.98 | 855.2 |
| **BDE-66** | 98.7 | 0.02 | 1.43 | 1.49 | 0.25 | 12.30 |
| **BDE-100** | 98.7 | 0.28 | 24.54 | 28.38 | 3.60 | 198.0 |
| **BDE-119** | 9.1 | 1.87 | 1.10 | - | ND | 2.89 |
| **BDE-99** | 98.7 | 1.40 | 86.22 | 91.45 | 13.54 | 940.4 |
| **BDE-116** | 75.3 | 0.13 | 0.42 | 0.37 | ND | 3.44 |
| **BDE-85,155** | 98.7 | 0.10 | 3.93 | 4.42 | 0.71 | 36.58 |
| **BDE-154** | 98.7 | 0.01 | 5.79 | 6.08 | 1.00 | 62.63 |
| **BDE-153** | 98.7 | 0.10 | 5.82 | 6.30 | 1.05 | 37.54 |
| **BDE-138** | 94.8 | 0.02 | 0.49 | 0.53 | 0.08 | 5.12 |

| Class and Compound | Detection Frequency (%) | MDL[a] | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| **BDE-156** | 18.2 | 0.01 | 0.01 | - | ND | 0.13 |
| **BDE-183** | 94.8 | 0.02 | 0.64 | 0.77 | 0.15 | 6.33 |
| **BDE-191** | 84.4 | 0.01 | 0.15 | 0.24 | ND | 1.11 |
| **BDE-181** | 41.6 | 0.02 | 0.03 | - | ND | 0.39 |
| **BDE-190** | 49.4 | 0.03 | 0.04 | - | ND | 0.63 |
| **BDE-200,203** | 54.5 | 0.14 | 0.16 | 0.15 | ND | 0.99 |
| **BDE-205** | 39.0 | 0.02 | 0.02 | - | ND | 0.20 |
| **BDE-206** | 85.7 | 0.66 | 1.62 | 1.64 | ND | 6.18 |
| **BDE-209** | 100.0 | 0.16 | 30.04 | 34.78 | 11.84 | 107.1 |
| ***Novel BFRs*** | | | | | | |
| **EH-TBB** | 98.7 | 2.38 | 131.9 | 131.5 | 22.69 | 1,126 |
| **BEH-TEBP** | 100.0 | 0.10 | 197.6 | 218.1 | 56.42 | 973.4 |
| **OBIND** | 92.2 | 0.04 | 0.60 | 0.81 | 0.13 | 2.73 |
| **DBDPE** | 100.0 | 0.02 | 8.89 | 8.14 | 2.75 | 77.57 |
| **TBBPA-DBPE** | 97.4 | 0.25 | 39.37 | 50.59 | 12.07 | 256.7 |
| **TTBP-TAZ** | 29.9 | 0.05 | 0.05 | - | ND | 0.72 |

[a] Wristband MDLs were normalized to avg mass of field blank wristbands extracted (1.5224 g).
[b] MDLs were estimated at 1.0 ng since the compound was not detected on the QE data.

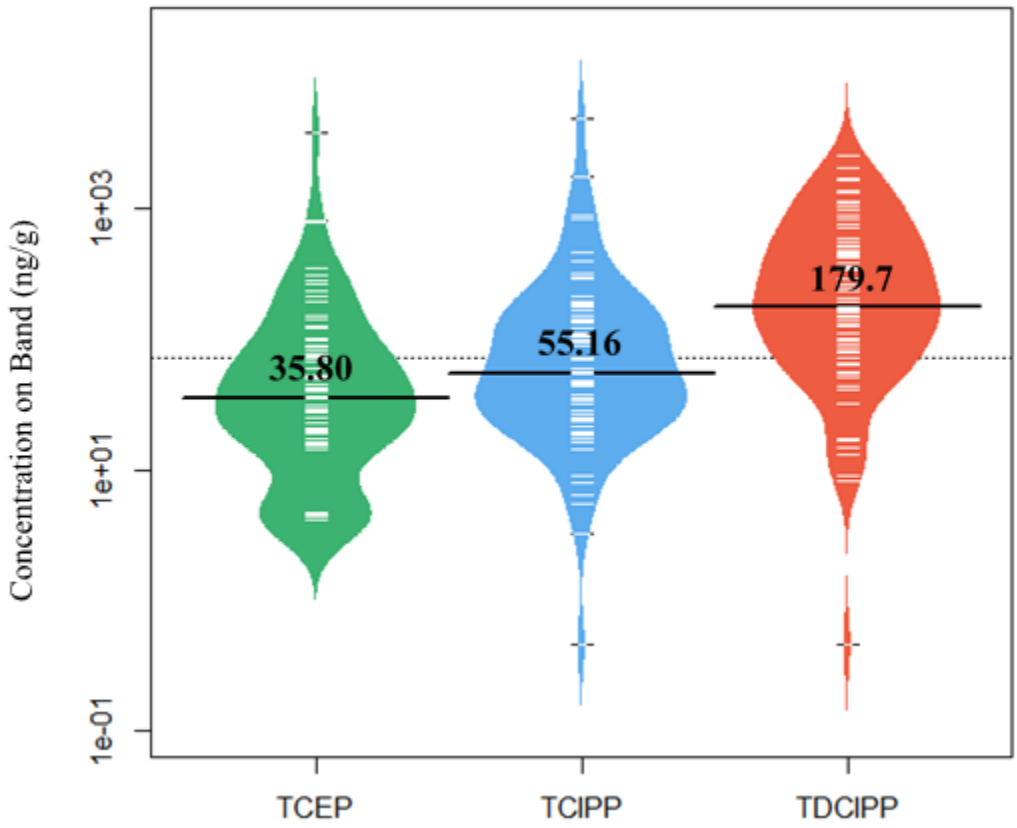



**Figure 15: Chlorinated OPE bean plot of concentrations (ng/g wristband) on the children's wristbands. Bean plots utilize data point and plot an estimated distribution of the dataset, centered on the median (represented by the black line).**

Of the isopropylated triaryl phosphates (ITPs), 6 of 8 were detected in >90% of the wristband samples, the other 2 being detected in ~50%. 2IPPDPP was the most abundant ITP on the wristbands (GM = 292.1 ng/g), which is the dominant ITP in Firemaster® 550 (FM550) and the ITP mixture (Table 20, Figure 16).[41] However, the next most abundant ITP with a similar level to 2IPPDPP is B3IPPPP (GM = 237.9 ng/g); this compound is not a large component of any of the flame retardant mixtures previously characterized which suggests that it must have a separate source for personal exposure.

Only 2 of the 5 tert-butylated triaryl phosphates (TBPPs) were quantified in >80% of the wristband samples, with 4tBPDPP being the most abundant (GM = 107.3 ng/g; Table 20). While 4tBPDPP is not a major component of FM600, it is the dominant compound in the TBPP mixture, suggesting that FR applications could be contributing the high levels of this compound on the wristbands.[41] To the authors' knowledge, the isopropylated and tert-butylated triaryl phosphate esters have not been previously quantitatively measured on wristbands and particularly for children.

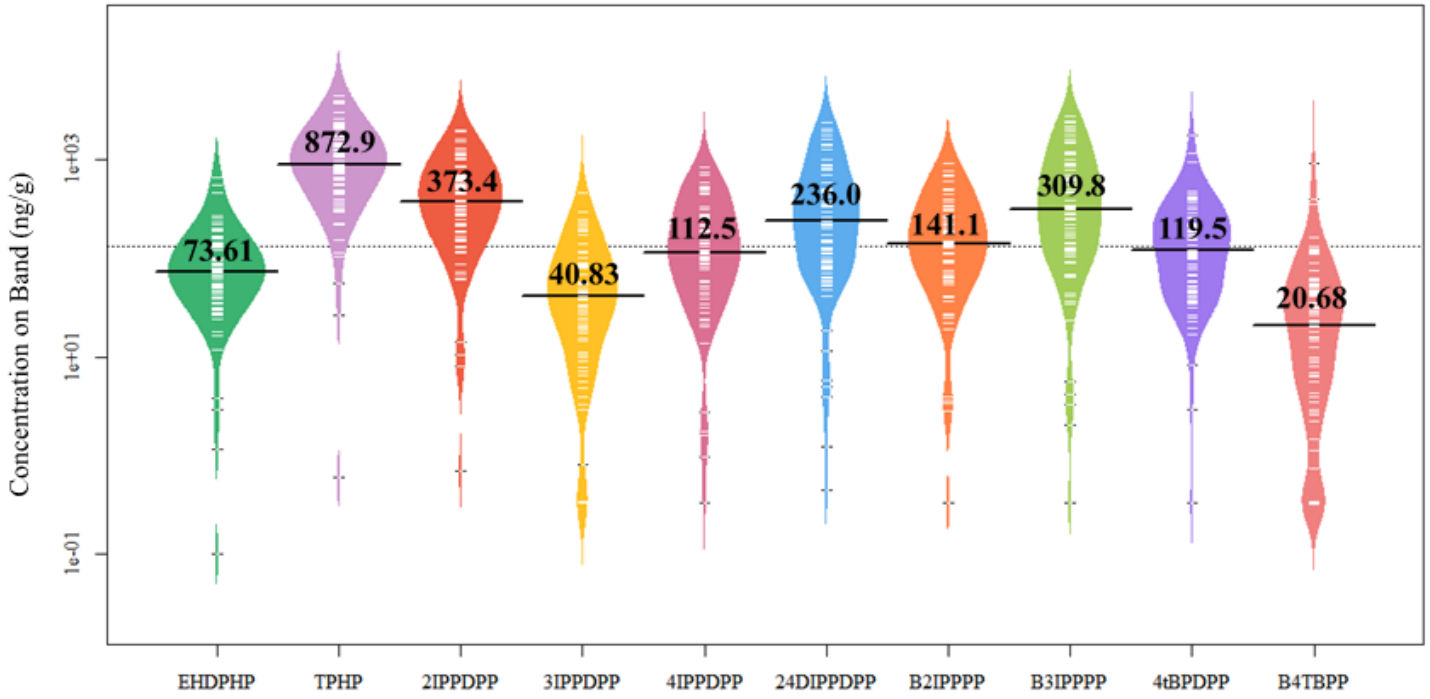



**Figure 16: Aryl phosphate bean plot of concentrations (ng/g wristband) on the children's wristbands.**

#### 7.3.2.2 Phthalates and non-phthalate plasticizers

Of the chemical classes evaluated here, the phthalates and non-phthalate plasticizers were the most abundant class measured on the wristbands. Every one of the 10 compounds quantified were measured in >98% of the wristbands (Table 20). Previous work measuring phthalates on the wristbands have reported between 50-95% detection for 6 phthalates presented here.[248,251] However, comparisons between our study and these previous studies could not be conducted because only positive or negative detections of phthalates were reported as results from a GC/MS scan and not concentrations on the wristbands. Measured in every wristband, DEHP and one of its replacements, DEHTP, were the most abundant compound within this class and were measured at similar levels on the wristbands (GM = 7,510 and 7,629 ng/g, respectively) (Figure 17). This suggests that DEHTP may be a prominent chemical that children are exposed to as it replaces DEHP as a plasticizer in floorings and children's toys; nonetheless, children's exposure to DEHP remains high compared to the other compounds within this group of chemicals. Generally, the higher molecular weight compounds were more abundant on the wristbands compared to the lower molecular weight phthalate compounds, suggesting that the wristbands may have captured a substantial concentration of particle-bound compounds. Based on particle-gas partitioning coefficients (Kp) calculated by Weschler et al., 2008 using saturation vapor pressures of phthalates, about 16% of BBP and 86% of DEHP would be particle-bound at

room temperature.[161,163] Since DiNP and DEHTP were both less volatile than DEHP, it is likely that both of these compounds were primarily picked up by the wristbands bound to particles as well.

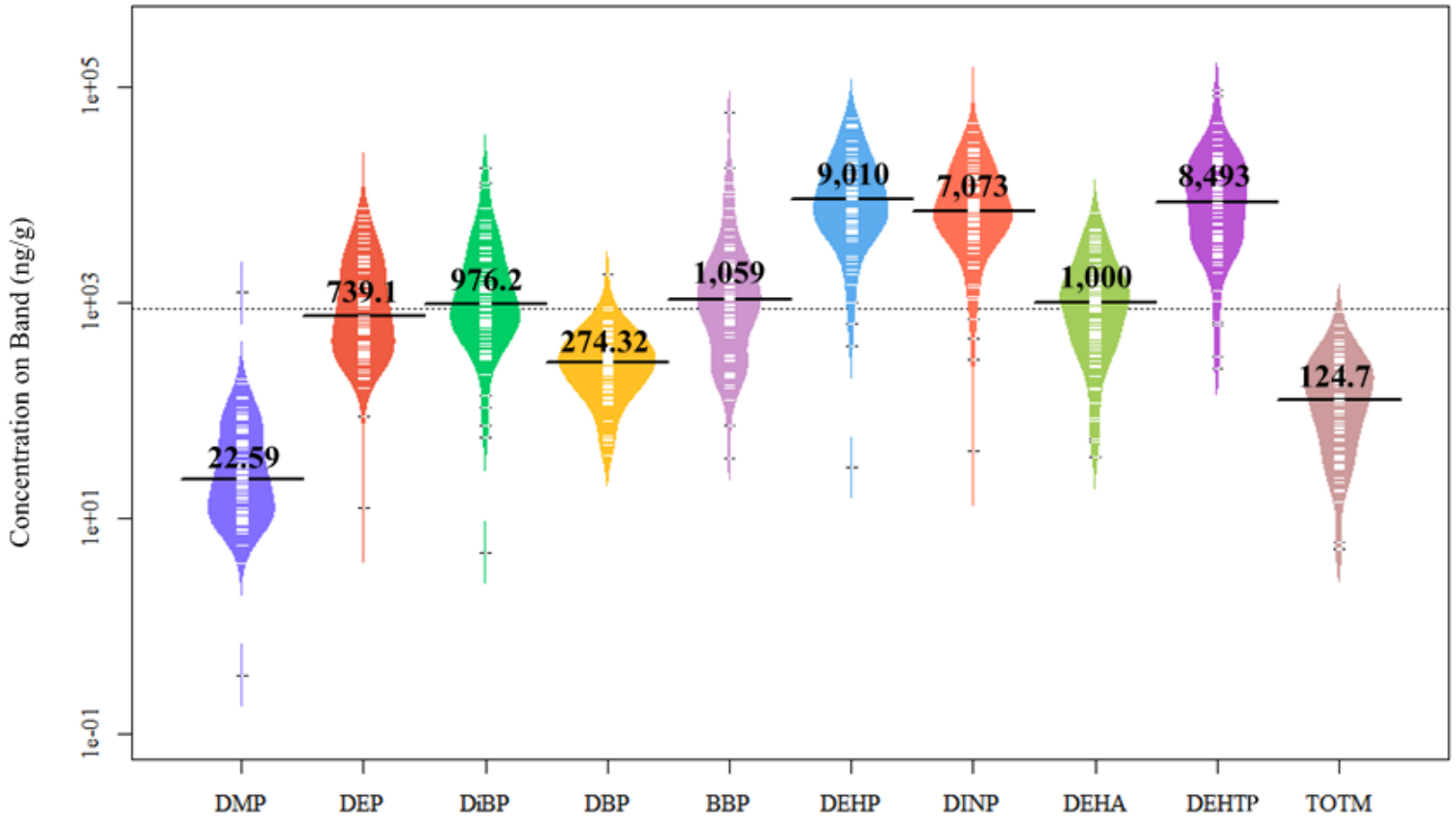



**Figure 17: Phthalate and non-phthalate plasticizer bean plot of concentrations (ng/g wristband) on the children's wristbands.**

#### 7.3.2.3 Brominated flame retardants

Within our GC/ECNI-MS method, we sought to quantify 27 BDEs and 6 novel BFRs. Of these 33 compounds, 19 BDEs and 5 novel BFRs were detected in >70% of samples. Similar to Kile et al. who measured BDEs on wristbands from preschool-aged children, BDE-47 was the most abundant BDE detected on the wristbands (GM = 123.4 ng/g; Table 20). However, overall, BEH-TEBP and EH-TBB had the highest levels measured of the BFRs on the wristbands (GM = 197.6 and 131.9 ng/g, respectively). These two brominated compounds are components of the Firemaster® mixtures although BEH-TEBP has also been reported to be used separately as a flame retardant and plasticizer in other products such as flexible polyvinyl chloride, adhesives, and wire and cable insulation.[256,257] When compared to an adult cohort also from central North Carolina (Chapter 3), the same number of BFRs were detected in >70% of samples; however, OBIND was measured at low levels in 92% of samples here (compared to 40% in the adult cohort), and TTBP-TAZ was highly detected in the adult wristbands but not in the children's bands. As both of these compounds serve as replacements for BDE-209 in electronics, this potentially suggests a difference in use of electronics between children and adults.[132] While similar compounds were detected among the children and adults, the geometric mean levels on the children's wristbands were typically an order of magnitude higher compared to levels measured on the adult wristbands. Like the comparisons between the adults and children for OPEs on wristbands, this suggests

differential exposure to these FRs based on microenvironment, product use, etc. and potentially higher exposure to BFRs among children.

## 7.3.3 Biomarker measurements

### 7.3.3.1 Urinary metabolites

OPE and phthalate metabolites were detected in a majority of the children's pooled urine samples, with every metabolite except MNP being detected in >65% of samples (Table 21). When comparing the urine values within this subset of the TESIE study to the entire study population, detection frequencies and geometric mean levels are very similar. Of all of the urinary metabolites measured here, MECPTP, one of the metabolites of DEHTP, was the most abundant (GM = 93.40 ng/mL). Detailed discussion of the urinary metabolites and their relationships with demographic variables is presented in Hoffman et al., with additional points discussed in Phillips & Hammel et al. 2018 (Chapter 5) and Hammel & Levasseur et al. 2019 (Chapter 6).[187,219]

**Table 21: Descriptive Statistics of Specific Gravity-Corrected Urinary Metabolites from Subset with Paired Wristbands (ng/mL).**

| Class and Metabolites | Detection Frequency (%) | MDL[a] | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| *OPEs (n=75)* | | | | | | |
| **BCIPP** | 69.3 | 0.14 | 0.302 | 0.290 | ND | 1.250 |
| **BCIPHIPP** | 98.7 | 0.18 | 1.931 | 2.270 | 0.448 | 8.080 |
| **BDCIPP** | 100.0 | 0.07 | 4.745 | 4.780 | 1.290 | 33.12 |
| **DPHP** | 100.0 | 0.12 | 2.878 | 2.720 | 0.998 | 18.97 |
| **ip-PPP** | 100.0 | 0.02 | 8.509 | 8.780 | 3.218 | 27.39 |
| **tb-PPP** | 98.7 | 0.08 | 0.382 | 0.360 | 0.094 | 2.649 |
| *Phthalates (n=74)* | | | | | | |
| **MEP** | 100.0 | 1.2 | 65.56 | 60.81 | 19.24 | 258.0 |
| **MHiBP** | 100.0 | 0.40 | 7.308 | 7.651 | 3.010 | 22.91 |
| **MiBP** | 100.0 | 0.80 | 21.71 | 22.64 | 8.757 | 76.44 |
| **MHBP** | 98.6 | 0.40 | 3.850 | 3.946 | 1.133 | 14.82 |
| **MBP** | 100.0 | 0.40 | 24.58 | 22.34 | 10.06 | 75.19 |
| **MCPP** | 97.3 | 0.40 | 3.545 | 3.298 | 1.468 | 12.58 |
| **MBzP** | 100.0 | 0.30 | 25.49 | 20.17 | 5.615 | 298.4 |
| **MEHP** | 67.6 | 0.80 | 1.612 | 1.791 | ND | 7.732 |
| **MEOHP** | 100.0 | 0.20 | 13.49 | 13.00 | 5.583 | 40.06 |
| **MEHHP** | 100.0 | 0.40 | 21.07 | 20.44 | 8.771 | 76.24 |
| **MECPP** | 100.0 | 0.40 | 34.94 | 33.91 | 14.88 | 116.5 |
| **MCOP** | 100.0 | 0.30 | 21.21 | 17.97 | 6.865 | 152.6 |
| **MONP** | 100.0 | 0.40 | 5.384 | 5.057 | 1.906 | 36.38 |
| **MCNP** | 100.0 | 0.20 | 4.295 | 4.231 | 1.618 | 14.08 |
| **MNP** | 33.8 | 0.90 | 0.930 | - | ND | 4.102 |
| **MECPTP** | 100.0 | 0.20 | 93.40 | 89.69 | 23.31 | 949.9 |
| **MEHHTP** | 100.0 | 0.40 | 11.88 | 10.14 | 3.672 | 79.77 |
| *Non-phthalate plasticizers (n=74)* | | | | | | |
| **MHINCH** | 95.9 | 0.40 | 3.086 | 3.039 | 0.960 | 14.68 |
| **MCOCH** | 89.2 | 0.50 | 1.622 | 1.588 | ND | 6.414 |

[a] OPE urinary MDL values were normalized to volume of urine extracted (5.0 mL).

### 7.3.3.2 Serum biomarkers

Four PBDEs were detected in nearly all of the children's serum samples within this TESIE subset that had paired wristbands available (Table 22). BDE-47 was the most

abundant of the BDEs in serum (GM = 15.34 ng/g lipid), and BDE serum levels are comparable to those observed among children of similar ages in the U.S. and specifically in North Carolina, despite the ten-year gap in time.[88,258] While there may be a slight decline in the mean levels among children for specific congeners (e.g., BDE-47), these levels are still much higher than U.S. adult measurements from recent years, suggesting persistent exposure to these chemicals despite the global phase-out.[18,96,104,157,252] BDE-209 was only detected in 40% of the serum samples within this subset.

**Table 22: Descriptive Statistics of PBDEs in Children's Serum Samples from Subset with Paired Wristbands (n = 15; ng/g lipid)**

| Serum Biomarkers | Detection Frequency (%) | MDL | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| **BDE-47** | 100.0 | 1.11 | 15.34 | 15.74 | 5.605 | 77.59 |
| **BDE-99** | 93.3 | 0.67 | 3.169 | 2.972 | 1.377 | 23.57 |
| **BDE-100** | 100.0 | 0.50 | 3.922 | 3.702 | 1.782 | 19.66 |
| **BDE-153** | 100.0 | 0.50 | 5.938 | 5.902 | 2.644 | 18.82 |
| **BDE-209** | 40.0 | 2.52 | 2.065 | - | ND | 5.737 |

### 7.3.4 Levels of compounds on hand wipes and dust

OPE and phthalate/non-phthalate plasticizer levels on the hand wipes and in dust within this TESIE subset were very similar to the total dataset (Table 23, 24). As a result, these compounds in individual matrices are not discussed here. Several of the ITP and TBPP compounds as well as DEP were not reported on hand wipes due to the unavailability of certain standards at the time of analysis (ITPs and TBPPs) or chromatographic interferences (DEP). More extensive discussions of the OPEs in hand

wipes and dust are presented in Phillips & Hammel, et al. 2018 (Chapter 5) and of phthalates in hand wipes and dust in Hammel & Levasseur, et al. 2019 (Chapter 6).

**Table 23: Descriptive Statistics of Hand Wipes from Subset with Paired Wristbands (n = 77; ng/wipe)**

| Class and Compound | Detection Frequency (%) | MDL | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| ***OPEs*** | | | | | | |
| **TCEP** | 100.0 | 2.7 | 59.57 | 47.50 | 11.46 | 882.6 |
| **TCIPP** | 87.0 | 19.8 | 84.57 | 71.60 | ND | 761.5 |
| **TDCIPP** | 100.0 | 3.9 | 144.6 | 132.4 | 27.77 | 2,328 |
| **EHDPHP** | 92.2 | 0.31 | 16.13 | 22.90 | 2.253 | 109.2 |
| **TPHP** | 98.7 | 1.1 | 16.24 | 18.29 | 3.305 | 123.6 |
| **2IPPDPP** | 98.7 | 0.19 | 6.044 | 5.630 | 1.010 | 64.40 |
| **3IPPDPP**[a] | - | - | - | - | - | - |
| **4IPPDPP** | 92.2 | 0.22 | 5.563 | 5.923 | 0.555 | 100.7 |
| **24DIPPDPP**[b] | - | - | - | - | - | - |
| **B2IPPPP**[b] | - | - | - | - | - | - |
| **B3IPPPP**[a] | - | - | - | - | - | - |
| **B4IPPPP**[b] | - | - | - | - | - | - |
| **B24IPPPP**[b] | - | - | - | - | - | - |
| **2tBPDPP**[b] | - | - | - | - | - | - |
| **4tBPDPP** | 76.6 | 0.09 | 0.560 | 0.816 | ND | 7.180 |
| **B2tBPPP**[b] | - | - | - | - | - | - |
| **B4tBPPP** | 76.6 | 0.37 | 3.024 | 3.978 | ND | 47.42 |
| **T4tBPP** | 48.1 | 0.80 | 1.247 | - | ND | 14.05 |
| ***Phthalates*** | | | | | | |
| **DMP** | 84.4 | 2.4 | 11.39 | 12.95 | ND | 150.2 |
| **DEP**[b] | - | - | - | - | - | - |
| **DiBP** | 81.8 | 7.2 | 18.63 | 19.32 | ND | 127.4 |
| **DBP** | 53.2 | 48 | 86.68 | 65.22 | ND | 3,976 |
| **BBP** | 100.0 | 12 | 159.5 | 149.9 | 33.46 | 1,111 |
| **DEHP** | 97.4 | 99 | 1,165 | 1,154 | 233.7 | 8,298 |
| **DiNP** | 72.7 | 14 | 61.57 | 58.77 | ND | 916.5 |
| **DEHTP** | 100.0 | 167 | 2,251 | 2,177 | 541.9 | 16,838 |
| ***Non-phthalate plasticizers*** | | | | | | |
| **DEHA** | 35.1 | 180 | 211.4 | - | ND | 2,543 |
| **TOTM** | 98.7 | 1.3 | 33.80 | 33.55 | 8.428 | 298.9 |

[a] Standards were not available at time of hand wipe quantification.

[b] Compounds were not reported due to chromatographic interferences.

**Table 24: Descriptive Statistics of Dust from Subset with Paired Wristbands (n=77; ng/g dust).**

| Class and Compound | Detection Frequency (%) | MDL[a] | Geometric Mean | Median | 10th Percentile | 95th Percentile |
|---|---|---|---|---|---|---|
| *OPEs* | | | | | | |
| **TCEP** | 100.0 | 18.7 | 927.0 | 786.7 | 192.0 | 6,800 |
| **TCIPP** | 100.0 | 45.6 | 4,593 | 3,724 | 911.5 | 62,810 |
| **TDCIPP** | 100.0 | 12.1 | 6,694 | 5,878 | 953.2 | 103,510 |
| **EHDPHP** | 98.7 | 1.3 | 162.9 | 198.0 | 31.37 | 840.8 |
| **TPHP** | 100.0 | 12.4 | 2,315 | 1,799 | 566.7 | 43,794 |
| **2IPPDPP** | 71.4 | 10.1 | 70.29 | 67.64 | ND | 491.9 |
| **3IPPDPP**[b] | - | - | - | - | - | - |
| **4IPPDPP** | 41.6 | 9.2 | 22.89 | - | ND | 159.4 |
| **24DIPPDPP** | 68.8 | 1.7 | 64.75 | 119.5 | ND | 851.0 |
| **B2IPPPP** | 13.0 | 2.7 | 4.867 | - | ND | 214.3 |
| **B3IPPPP**[b] | - | - | - | - | - | - |
| **B4IPPPP** | 44.2 | 2.6 | 11.98 | - | ND | 97.80 |
| **B24IPPPP** | 5.2 | 3.5 | 1.597 | - | ND | - |
| **2tBPDPP** | 0.0 | 1.5 | - | - | - | - |
| **4tBPDPP** | 92.2 | 2.4 | 427.6 | 501.9 | 47.58 | 2,673 |
| **B2tBPPP** | 0.0 | 2.4 | - | - | - | - |
| **B4tBPPP** | 80.5 | 1.9 | 64.27 | 93.00 | ND | 1,127 |
| **T4tBPP** | 24.7 | 2.8 | 3.680 | - | ND | 35.66 |
| *Phthalates* | | | | | | |
| **DMP** | 32.5 | 70 | 177.5 | - | ND | 2541 |
| **DEP** | 70.1 | 234 | 1,936 | 2,355 | ND | 10,556 |
| **DiBP** | 98.7 | 77 | 4,988 | 4,859 | 1,720 | 34,314 |
| **DBP** | 100.0 | 210 | 11,511 | 10,718 | 4,160 | 75,946 |
| **BBP** | 98.7 | 172 | 18,665 | 15,298 | 3,992 | 164,989 |
| **DEHP** | 100.0 | 573 | 113,030 | 114,897 | 32,853 | 594,449 |
| **DiNP** | 97.4 | 188 | 90,954 | 80,737 | 19,797 | 857,776 |
| **DEHTP** | 100.0 | 167 | 131,758 | 133,081 | 41,485 | 580,903 |
| *Non-phthalate plasticizers* | | | | | | |
| **DEHA** | 36.4 | 859 | 2,113 | - | ND | 18,523 |
| **TOTM** | 75.3 | 230 | 3,513 | 4,664 | ND | 44,866 |

[a] Dust MDL values were normalized to average mass of dust extracted (0.059 mg).

[b] Standards were not available at time of dust quantification.

### 7.3.5 Comparing wristbands to biomarkers

#### 7.3.5.1 OPEs

In general, OPE concentrations on the wristbands were positively correlated with their corresponding urinary biomarkers (Table 7). In particular, TDCIPP, 3 ITP isomers, and both TBPP isomers were significantly associated with their primary urinary metabolites, BDCIPP, ip-PPP, and tb-PPP, respectively ($r_s$=0.25-0.52, $p<0.05$; Figure 18). This suggests that wristbands do capture meaningful personal OPE exposures in children. These results, particularly for TDCIPP and mono-isopropylated triaryl phsophates (2IPPDPP, 3IPPDPP, and 4IPPDPP), were similar to those evaluated in the adult pilot cohort (Chapter 3), although in that study, the mono-isopropylated triaryl phosphates were measured on the wristbands in a semi-quantitative manner and a significant result at $\alpha$=0.05 was not observed ($r_s$=0.29, p=0.07).[77] For these compounds, the pathways of exposure captured by the wristbands could be similar for both children and adults. The primary difference in relationships evaluated between the children and adults is the association between TCIPP on the wristbands and its urinary metabolites. Here, TCIPP on the wristbands was not significantly correlated with either of its metabolites measured in the children's urine, BCIPP and BCIPHIPP. In the adult pilot study, BCIPP was only detected in 18% of samples and was not evaluated in statistical analyses; BCIPHIPP was significantly and positively correlated to TCIPP on the wristbands with a similar magnitude of correlation to TDCIPP-BDCIPP ($r_s$=0.6, $p<0.0001$).[77] This suggests that the metabolism of TCIPP could change with age, which

was previously proposed by Van den Eede et al. 2015 and demonstrated by the difference in detections between adults and children from the same region. An additional possibility for this difference is that adults and children are not exposed to TCIPP in the same manner, whether by source or pathway, and children may be exposed to TCIPP via a pathway not captured by the wristbands.

**Table 25: OPE Correlation Tables with Raw Wristband Levels (ng/g) and Specific Gravity-Corrected Biomarkers (n=75), DF>60%; shading indicates potential parent-metabolite pairs.**

| | | Urine | | | | | |
|---|---|---|---|---|---|---|---|
| | | BCIPP | BCIPHIPP | BDCIPP | DPHP | ip-PPP | tb-PPP |
| **Wristband** | TCEP | 0.13 | **-0.29**$^{\#}$ | 0.09 | -0.06 | -0.06 | 0.04 |
| | TCIPP | 0.18 | -0.06 | 0.03 | -0.18 | 0.06 | -0.09 |
| | TDCIPP | 0.07 | 0.10 | **0.52**$^{\dagger}$ | 0.04 | 0.14 | 0.16 |
| | EHDPHP | 0.13 | -0.06 | 0.11 | -0.08 | 0.05 | 0.07 |
| | TPHP | 0.05 | -0.02 | 0.09 | 0.12 | 0.21 | **0.26*** |
| | 2IPPDPP | 0.05 | 0.00 | 0.03 | 0.05 | 0.22 | 0.17 |
| | 3IPPDPP | 0.05 | 0.04 | 0.11 | 0.07 | **0.27*** | 0.20 |
| | 4IPPDPP | 0.04 | 0.06 | 0.14 | 0.10 | **0.31**$^{\#}$ | 0.22 |
| | 24DIPPDPP | 0.02 | 0.02 | -0.01 | 0.04 | 0.20 | 0.15 |
| | B2IPPPP | 0.06 | 0.02 | 0.03 | 0.06 | 0.22 | 0.17 |
| | B3IPPPP | 0.05 | 0.02 | 0.03 | 0.07 | **0.25*** | 0.17 |
| | 4tBPDPP | -0.09 | -0.06 | 0.03 | 0.03 | 0.18 | **0.35**$^{\#}$ |
| | B4TBPP | -0.04 | 0.00 | 0.12 | 0.05 | 0.18 | **0.35**$^{\#}$ |
| **Hand Wipe** | TCEP | 0.13 | 0.07 | 0.14 | 0.10 | -0.02 | 0.12 |
| | TCIPP | **0.24*** | 0.13 | 0.22 | 0.07 | 0.03 | 0.03 |
| | TDCIPP | 0.19 | 0.19 | **0.48**$^{\dagger}$ | **0.22*** | 0.21 | 0.05 |
| | EHDPHP | 0.19 | 0.21 | 0.09 | 0.13 | -0.03 | -0.06 |
| | TPHP | 0.15 | 0.05 | -0.01 | 0.18 | 0.11 | 0.14 |
| | 2IPPDPP | 0.15 | 0.15 | 0.09 | 0.18 | 0.20 | 0.07 |
| | 4IPPDPP | 0.06 | 0.19 | 0.12 | **0.23*** | 0.19 | 0.21 |
| | 4tBPDPP | -0.06 | 0.07 | -0.06 | -0.02 | 0.02 | 0.16 |
| | B4tBPPP | -0.10 | -0.03 | -0.03 | 0.07 | -0.03 | **0.28*** |
| **Dust** | TCEP | -0.02 | -0.15 | 0.16 | 0.14 | -0.11 | -0.05 |
| | TCIPP | -0.05 | **-0.32**$^{\#}$ | -0.10 | 0.08 | -0.03 | -0.06 |
| | TDCIPP | -0.06 | **-0.32**$^{\#}$ | 0.13 | -0.04 | -0.05 | -0.07 |
| | EHDPHP | -0.07 | -0.07 | 0.04 | 0.05 | -0.10 | -0.07 |
| | TPHP | 0.05 | -0.10 | 0.13 | 0.00 | 0.03 | -0.14 |
| | 2IPPDPP | -0.06 | 0.00 | 0.07 | 0.14 | 0.13 | -0.08 |
| | 24DIPPDPP | -0.01 | 0.22 | 0.05 | 0.05 | 0.12 | -0.06 |
| | 4tBPDPP | -0.08 | -0.09 | 0.07 | -0.04 | 0.19 | 0.05 |
| | B4tBPPP | -0.05 | -0.04 | 0.04 | 0.03 | 0.12 | 0.11 |

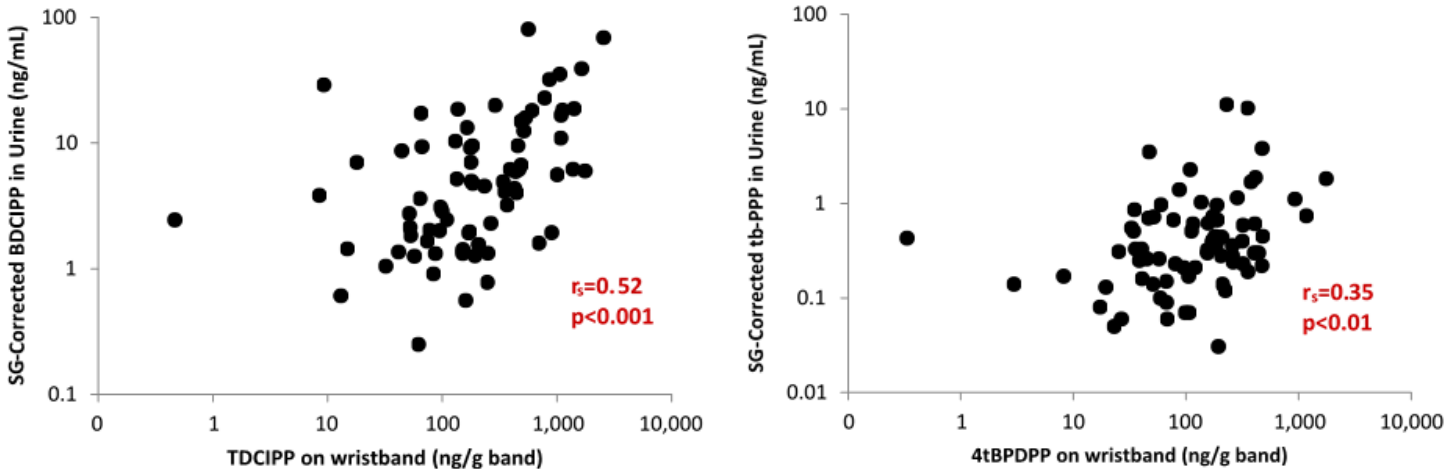



**Figure 18: Correlation plots of TDCIPP and 4tBPDPP on wristbands with their corresponding urinary metabolites.**

The ITP isomers measured on the wristbands were all positively correlated with their corresponding urinary metabolite, ip-PPP ($r_s$=0.2-0.3, $p<0.1$; Table 25), with 3 of the 6 isomers significantly associated at $\alpha$=0.05. Little is known about personal exposure to ITPs, particularly in children, and few studies have characterized exposure to ITPs in the general population, since their metabolites are not currently measured in NHANES. Also, the sources of these compounds other than FR applications in foam are largely unknown. Thus, the positive associations between ITPs on wristbands and urinary biomarkers observed here suggest that the wristbands could provide some initial insights for how humans are exposed to them in their daily environments. TBPP isomers were measured for the first time on the wristbands and were positively and significantly associated with their corresponding metabolite, tb-PPP ($r_s$=0.35, $p<0.01$; Figure 18). Like the ITP isomers, little data is available regarding personal exposure to TBPP isomers, and the positive and moderate correlation coefficient suggests that the ambient environment is a source of exposure. None of the potential parent compounds for DPHP (EHDPHP, TPHP, ITPs, TBPPs) were significantly correlated with the urinary metabolite, suggesting that there could be other sources of exposure to DPHP which were not measured in this study (e.g., other OPEs or diet). This is dissimilar to what was observed with the adult cohort where TPHP on wristbands was positively and significantly associated with DPHP in pooled urine samples ($r_s$=0.43, $p<0.01$). TPHP was the most abundant OPE measured on the children's wristbands, and the lack of a

correlation with urinary DPHP suggests that children may be exposed to TPHP in a different manner than adults, which could potentially be diet since this exposure pathway not captured by the wristbands.

#### 7.3.5.2 Phthalates

Similar to OPEs, several phthalate and non-phthalate plasticizer levels on wristbands were positively correlated with their corresponding urinary metabolites (Table 26). Of the 7 plasticizer compounds that had data available for urinary biomarkers, 4 were significantly associated with urine measures ($r_s$=0.24-0.56, $p<0.05$), with BBP on the wristbands being the most highly correlated ($r_s$=0.56, $p<0.001$; Figure 19). While a few studies have evaluated phthalates on wristbands, no published literature to date has compared wristbands levels to biomarkers of exposure. These results suggest that the wristbands may capture meaningful personal exposure to phthalates, particularly in children over a 7-day period, as they have been shown previously for OPEs in adults and here for children. This is particularly of interest for DEP, which is a fairly volatile compound typically used in fragrances and for which previous studies have not evaluated links with its urinary metabolite, MEP.[55,203] Here, we observed a significant and positive association between wristband DEP and urinary MEP ($r_s$=0.53, $p<0.001$; Figure 19), suggesting that children are likely exposed to DEP via inhalation or dermal absorption. For the higher molecular weight phthalates and DEHTP, a DEHP replacement, the relationships between the wristbands and urinary

metabolites were positive, with DiNP being significantly associated with the molar sum of its metabolites ($r_s$=0.24, $p<0.05$). DEHP on the wristbands was positively associated with the molar sum of its metabolites ($r_s$=0.22, p=0.06), although it did not reach statistical significance. This observation suggest that the wristbands capture some portion of a child's overall DEHP exposure which could occur through alternative pathways, despite the primary exposure pathway for DEHP being attributed to diet.[259] To our knowledge, measurements of DEHTP in external exposure measures have not been previously evaluated with their urinary biomarkers. In this study, DEHTP wristband concentrations were not associated with its urinary biomarker, suggesting that the exposure pathway is not effectively captured by the wristbands ($r_s$=0.15, $p>0.05$; Table 26). Lastly, no directional relationship was observed for wristband DBP compared to the molar sum of its specific metabolites (MHBP and MBP) or its nonspecific metabolite (MCCP).

**Table 26: Phthalates Correlation Tables with Raw Wristband Levels (ng/g) and Specific-Gravity Corrected Urinary Metabolites (n=74), DF>60%, shading indicates potential parent-metabolite pairings.**

| | | Urine | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MEP | Σ*DiBP*[a] | Σ*DBP*[b] | MCPP | MBzP | Σ*DEHP*[c] | Σ*DiNP*[d] | MCNP | MHINCH | MCOCH | Σ*DEHTP*[e] |
| **Wristband** | DMP | **0.23*** | 0.21 | 0.17 | -0.09 | 0.15 | -0.03 | -0.16 | -0.06 | 0.06 | 0.03 | -0.01 |
| | DEP | **0.53†** | 0.09 | 0.02 | 0.08 | -0.01 | 0.09 | 0.06 | 0.09 | 0.06 | 0.08 | 0.04 |
| | DiBP | -0.06 | **0.32#** | -0.07 | -0.04 | -0.03 | 0.05 | 0.07 | -0.12 | 0.03 | -0.02 | 0.05 |
| | DBP | 0.05 | -0.05 | 0.04 | -0.02 | 0.03 | 0.09 | 0.06 | -0.03 | -0.10 | -0.16 | 0.05 |
| | BBP | **0.30#** | 0.13 | 0.22 | 0.09 | **0.56†** | 0.15 | 0.08 | 0.09 | 0.14 | 0.05 | 0.20 |
| | DEHP | 0.05 | 0.05 | -0.12 | 0.00 | -0.01 | 0.22 | -0.01 | -0.11 | -0.02 | -0.02 | 0.18 |
| | DiNP | 0.05 | 0.01 | -0.16 | 0.10 | -0.11 | 0.09 | **0.24*** | 0.08 | 0.10 | 0.06 | 0.09 |
| | DEHTP | 0.06 | -0.06 | -0.21 | -0.21 | -0.14 | -0.10 | -0.11 | -0.17 | 0.05 | 0.05 | 0.15 |
| | DEHA | 0.03 | 0.06 | -0.11 | 0.07 | -0.02 | 0.08 | 0.12 | 0.00 | 0.16 | 0.14 | 0.07 |
| | TOTM | -0.01 | 0.05 | -0.17 | -0.03 | -0.12 | 0.09 | -0.02 | -0.08 | 0.18 | 0.17 | 0.14 |
| **Hand Wipe** | DMP | 0.07 | 0.04 | 0.00 | 0.14 | 0.02 | 0.02 | -0.01 | 0.05 | 0.03 | 0.07 | -0.08 |
| | DiBP | -0.02 | **0.27*** | 0.02 | -0.06 | 0.11 | -0.06 | -0.16 | **-0.23*** | -0.01 | -0.09 | -0.03 |
| | BBP | **0.23*** | **0.36#** | **0.33#** | 0.06 | **0.56†** | 0.06 | 0.01 | 0.04 | 0.00 | -0.11 | 0.11 |
| | DEHP | -0.06 | 0.07 | 0.04 | 0.03 | 0.13 | 0.14 | 0.03 | -0.10 | -0.08 | -0.13 | -0.01 |
| | DiNP | 0.03 | 0.19 | 0.01 | 0.19 | 0.09 | 0.11 | 0.22 | 0.03 | 0.01 | -0.01 | -0.02 |
| | DEHTP | 0.14 | 0.16 | 0.08 | -0.10 | 0.20 | -0.03 | -0.04 | -0.02 | 0.14 | 0.15 | 0.06 |
| | TOTM | 0.00 | **0.23*** | 0.05 | -0.05 | 0.12 | -0.01 | 0.03 | -0.03 | 0.20 | 0.14 | 0.14 |
| **Dust** | DEP | 0.17 | -0.03 | 0.07 | 0.14 | 0.10 | 0.05 | 0.17 | 0.08 | 0.12 | 0.03 | 0.03 |
| | DiBP | 0.09 | **0.27*** | **0.29*** | **0.27*** | 0.17 | 0.18 | 0.22 | 0.08 | 0.01 | -0.08 | 0.15 |
| | DBP | -0.06 | -0.02 | **0.28*** | **0.27*** | 0.18 | 0.15 | 0.21 | 0.12 | -0.10 | -0.12 | 0.05 |
| | BBP | 0.14 | 0.08 | 0.16 | 0.15 | **0.23*** | -0.05 | 0.10 | 0.08 | 0.00 | 0.00 | **0.34#** |
| | DEHP | 0.00 | 0.06 | 0.14 | 0.17 | 0.07 | 0.16 | 0.03 | 0.08 | 0.08 | 0.11 | 0.11 |
| | DiNP | -0.07 | 0.01 | 0.11 | **0.30#** | 0.04 | 0.19 | 0.20 | 0.10 | 0.10 | 0.09 | 0.11 |
| | DEHTP | 0.00 | 0.04 | 0.01 | 0.17 | 0.05 | 0.05 | 0.14 | 0.15 | 0.16 | 0.21 | **0.35#** |
| | TOTM | 0.05 | 0.12 | 0.04 | 0.08 | 0.13 | 0.01 | -0.13 | 0.10 | 0.09 | 0.07 | 0.06 |

*p<0.05, #p<0.01, †p<0.001

[a] Σ*DiBP*= Molar sum of MHiBP and MiBP; [b] Σ*DBP* = Molar sum of MHBP and MBP, MCPP is a non-specific metabolite; [c] Σ*DEHP* = Molar sum of MEHP, MEOHP, MEHHP, and MECPP; [d] Σ*DiNP* = Molar sum of MCOP and MONP; [e] Σ*DEHTP* = Molar sum of MECPTP and MEHHTP

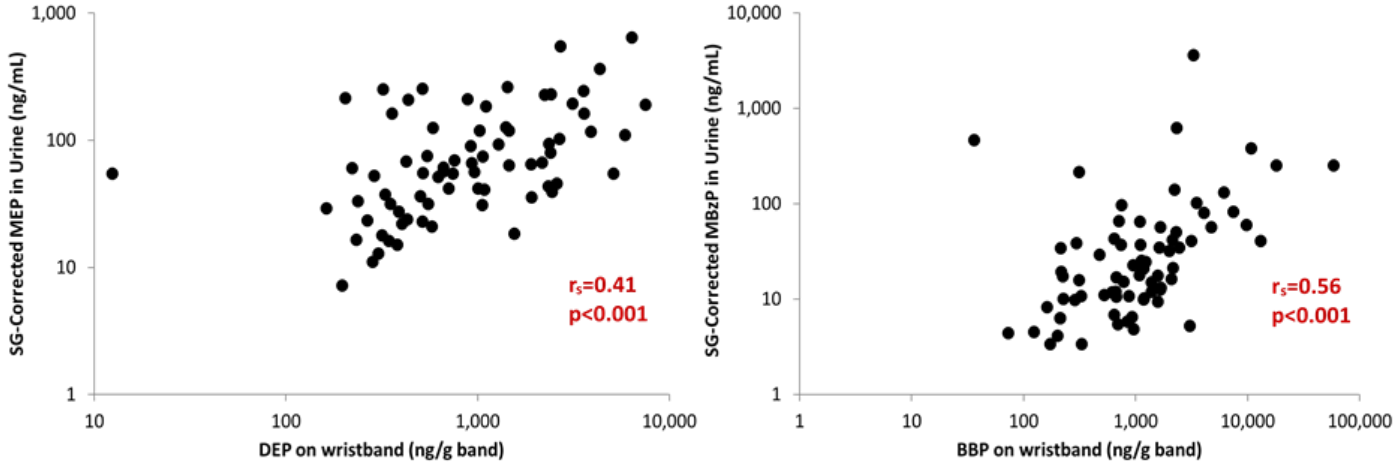



**Figure 19: Correlation plots of DEP and BBP on wristbands with their urinary metabolites.**

#### 7.3.5.3 PBDEs

Serum levels of BDE-47, -99, and -100 were significantly correlated with the corresponding BDEs on the wristbands ($r_s$=0.54-0.73, $p<0.05$; Table 27). Similar associations were observed in an adult cohort from central North Carolina, where the highest correlation was observed for BDE-47 on wristbands and in serum (Chapter 3).[252] In the adult cohort, BDE-153 was significantly correlated ($r_s$=0.39; $p<0.05$) whereas it was not significant among children in our study. However, the magnitudes of the correlation coefficients were the same, indicating that given a larger sample size of children and greater statistical power, a similarly significant result may have been observed. The estimated half-life of BDE-153 (6.5 years) in serum is also longer than the age of the children in this cohort, which could explain why the magnitude of correlation observed here was smaller than the rest of the BDEs.[109] While the results presented here show promise for the use of wristbands to evaluate PBDE exposure and other possible compounds with serum biomarkers, we are limited by our small sample size and would require a larger study to determine how well they would effectively measure exposure among children.

**Table 27: PBDE Correlation Tables with raw wristband levels (ng/g) and lipid-normalized serum (ng/g lipid) (n = 15)**

| | | Serum | | | | |
|---|---|---|---|---|---|---|
| | | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-209 [a] |
| **Wristband** | BDE-17 | **0.65**# | 0.50 | 0.41 | 0.24 | 0.06 |
| | BDE-25 | 0.26 | 0.24 | 0.19 | **0.66**# | 0.17 |
| | BDE-28,33 | **0.73**# | **0.63**# | 0.48 | 0.41 | 0.09 |
| | BDE-75 | -0.05 | -0.13 | 0.21 | 0.17 | 0.29 |
| | BDE-47 | **0.73**# | **0.64*** | **0.51*** | 0.49 | 0.02 |
| | BDE-66 | **0.69**# | **0.53*** | 0.43 | 0.29 | 0.14 |
| | BDE-99 | **0.63*** | **0.63*** | **0.53*** | 0.30 | 0.14 |
| | BDE-100 | **0.70**# | **0.66**# | **0.54*** | 0.38 | 0.12 |
| | BDE-85,155 | **0.64*** | **0.63*** | **0.59*** | 0.35 | 0.15 |
| | BDE-153 | **0.61*** | **0.68**# | **0.70**# | 0.39 | 0.15 |
| | BDE-154 | **0.67**# | **0.68**# | **0.63*** | 0.36 | 0.19 |
| | BDE-138 | **0.61*** | **0.65*** | **0.68**# | 0.33 | 0.22 |
| | BDE-183 | 0.15 | 0.39 | **0.54*** | 0.23 | 0.19 |
| | BDE-191 | **-0.51*** | -0.46 | 0.00 | 0.09 | 0.38 |
| | BDE-206 | 0.18 | 0.18 | 0.27 | 0.30 | **0.68**# |
| | BDE-209 | 0.10 | 0.09 | 0.15 | 0.19 | **0.71**# |

*p<0.05, #p<0.01, †p<0.001

a Detection frequency (40%) was below the level at which statistical analyses were conducted. The results are presented here but not interpreted due to the reliability of this analysis given the low detection of BDE-209 in serum.

## 7.3.6 Comparing wristbands to hand wipes and dust

For OPEs measured in each matrix (wristbands, hand wipes, and dust), the wristband levels were, in general, significantly correlated with hand wipes ($r_s$=0.23-0.52, p<0.05), with the exception of TCIPP, and were not correlated with house dust (Table 10). While hand wipes were slightly more correlated with dust compared to wristbands, these correlations were not statistically significant overall. Similarly, for phthalates, wristband levels were significantly correlated with hand wipes ($r_s$=0.24-0.42, p<0.05), with the exception of DiBP (Table 11). Again, dust was in general not significantly

associated with wristbands or hand wipes. For both classes evaluated here, the most volatile compound available with paired exposure biomarkers, TCIPP and DiBP, were not significantly correlated between hand wipes and wristbands. This suggests that the wristbands are capturing another pathway of exposure, whether inhalation or another, that is not measured by the hand wipes. The associations between concentrations in hand wipes and wristbands indicate that while the levels are not extremely correlated, the two matrices could be capturing similar exposure pathways. Currently, wristbands have been hypothesized to effectively measure or "capture" primarily inhalation and dermal absorption exposure pathways. However, hand wipes are posited to capture exposures that occur via hand-to-mouth contact and dermal absorption; thus, the overlap in dermal exposure pathways could explain the positive and significant associations observed in this study between wristbands and hand wipes, although more research is needed on other chemical classes to confirm this statement.

**Table 28: Intramatrix Spearman Correlations for selected OPEs (n=77).**

| OPEs | | Wristbands | | | | | | | | | Dust | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TCIPP | TDCIPP | EHDPHP | TPHP | 2IPPDPP | 4IPPDPP | 24DIPPDPP | 4tBPDPP | B4tBPPP | TCIPP | TDCIPP | EHDPHP | TPHP | 2IPPDPP | 4tBPDPP | B4tBPPP |
| **Hand wipe** | TCIPP | 0.14 | | | | | | | | | 0.22 | | | | | | |
| | TDCIPP | | **0.34**[#] | | | | | | | | | -0.03 | | | | | |
| | EHDPHP | | | **0.23*** | | | | | | | | | -0.13 | | | | |
| | TPHP | | | | **0.30**[#] | | | | | | | | | 0.21 | | | |
| | 2IPPDPP | | | | | **0.38**[†] | | | | | | | | | **0.29**[#] | | |
| | 4IPPDPP | | | | | | **0.27*** | | | | | | | | | | |
| | 4tBPDPP | | | | | | | | **0.41**[†] | | | | | | | 0.21 | |
| | B4tBPPP | | | | | | | | | **0.52**[†] | | | | | | | **0.30**[#] |
| **Dust** | TCIPP | 0.07 | | | | | | | | | | | | | | | |
| | TDCIPP | | 0.03 | | | | | | | | | | | | | | |
| | EHDPHP | | | -0.01 | | | | | | | | | | | | | |
| | TPHP | | | | 0.14 | | | | | | | | | | | | |
| | 2IPPDPP | | | | | 0.12 | | | | | | | | | | | |
| | 24DIPPDPP | | | | | | | 0.09 | | | | | | | | | |
| | 4tBPDPP | | | | | | | | **0.27*** | | | | | | | | |
| | B4tBPPP | | | | | | | | | **0.32**[#] | | | | | | | |

*p<0.05, [#]p<0.01, †p<0.001

**Table 29: Intramatrix Spearman Correlations for Phthalates (n=77).**

| Phthalates | | Wristbands | | | | | | | Dust | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | DEP | DiBP | DBP | BBP | DEHP | DiNP | DEHTP | DEP | DiBP | DBP | BBP | DEHP | DiNP | DEHTP |
| **Hand wipes** | DiBP | | 0.18 | | | | | | | 0.15 | | | | | |
| | BBP | | | | **0.42†** | | | | | | | **0.23*** | | | |
| | DEHP | | | | | **0.24*** | | | | | | | 0.03 | | |
| | DiNP | | | | | | **0.36#** | | | | | | | 0.13 | |
| | DEHTP | | | | | | | **0.29#** | | | | | | | 0.04 |
| **Dust** | DEP | **0.23*** | | | | | | | | | | | | | |
| | DiBP | | 0.19 | | | | | | | | | | | | |
| | DBP | | | 0.18 | | | | | | | | | | | |
| | BBP | | | | **0.34#** | | | | | | | | | | |
| | DEHP | | | | | 0.05 | | | | | | | | | |
| | DiNP | | | | | | 0.06 | | | | | | | | |
| | DEHTP | | | | | | | 0.10 | | | | | | | |

*p<0.05, #p<0.01, †p<0.001

### 7.3.7 Estimated daily intake

Exposure estimates for 12 OPEs and 7 phthalate and non-phthalate plasticizers were calculated using data collected from the wristbands, hand wipes and dust samples (Table 30). Among the OPEs, TPHP was calculated to have the largest estimated daily intake (EDI) on the wristbands (GM = 37.8 ng/day/kg body weight), TDCIPP was most abundant from the hand wipes (GM = 90.7 ng/day/kg bw) and dust (GM = 10.7 ng/day/kg bw). DEHTP and DEHP were the largest contributors in all three matrices in terms of estimated exposure, with DEHTP being the greatest from the hand wipes (GM = 1,383 ng/day/kg bw). In general, these trends reflected the raw concentrations measured in each media, which were discussed previously, and thus, they are not interpreted extensively here. Correlations for both OPEs and phthalates appeared to be fairly similar in magnitude and trends among the wristbands, hand wipes, and dust when comparing the EDIs to raw concentrations (Table 31, 32). If anything, these EDIs displayed poorer correlations with biomarkers of exposure than using the raw concentrations. Overall, the exposure estimates appeared to make the results more difficult to interpret, especially in the context of the large array of assumptions (e.g., child's time spent in the home, active hours, time period during which wristband was worn) made to determine these exposure estimates. In addition, a greater understanding of the pathways measured by the wristbands would help provide more accurate exposure estimates. Despite the results of these analyses being presented here, the raw

concentrations from each exposure matrix was used to evaluate the effectiveness of the matrices for determining individual exposures and to determine which exposure assessment tool was captured personal exposures best of the three.

**Table 30: Geometric means of Estimated Daily Intakes for Each Matrix.**

| Class and Compound | Geometric Mean of Estimated Daily Intakes (ng/day/kg body weight) | | |
|---|---|---|---|
| | Wristband | Hand Wipes | Dust |
| *Organophosphate Esters* | | | |
| **TCIPP** | 3.22 | 52.69 | 7.61 |
| **TDCIPP** | 9.55 | 90.68 | 10.68 |
| **EHDPHP** | 3.26 | 9.80 | 0.27 |
| **TPHP** | 37.80 | 9.92 | 3.76 |
| **2IPPDPP** | 14.77 | 3.71 | 0.12 |
| **3IPPDPP** | 1.55 | - | - |
| **4IPPDPP** | 4.78 | 3.48 | - |
| **24DIPPDPP** | 9.36 | - | 0.10 |
| **B2IPPPP** | 5.81 | - | - |
| **B3IPPPP** | 11.98 | - | - |
| **4tBPDPP** | 5.50 | 0.34 | 0.71 |
| **B4tBPPP** | 0.70 | 1.84 | 0.11 |
| *Phthalates & Non-phthalate Plasticizers* | | | |
| **DEP** | 42.09 | - | 3.24 |
| **DiBP** | 52.75 | 11.32 | 8.01 |
| **DBP** | 12.97 | - | 18.84 |
| **BBP** | 51.02 | 94.13 | 30.07 |
| **DEHP** | 391.69 | 692.94 | 186.34 |
| **DiNP** | 324.49 | 61.57 | 144.21 |
| **DEHTP** | 394.01 | 1,382.6 | 218.99 |

**Table 31: OPE Correlation Tables with Estimated Intake Matrices (n=73). The red font indicates ITP and TBPP isomers which have overlaps between wristbands, hand wipes, and dust.**

| | | Urine | | | | | |
|---|---|---|---|---|---|---|---|
| | | BCIPP | BCIPHIPP | BDCIPP | DPHP | ip-PPP | tb-PPP |
| **Wristband** | TCIPP | 0.13 | -0.01 | -0.08 | **-0.23*** | 0.02 | -0.16 |
| | TDCIPP | 0.04 | 0.16 | **0.37**$^{\#}$ | -0.04 | 0.12 | 0.01 |
| | EHDPHP | 0.06 | -0.08 | -0.01 | -0.22 | -0.01 | -0.07 |
| | TPHP | 0.07 | 0.01 | 0.01 | -0.02 | 0.18 | 0.08 |
| | 2IPPDPP | 0.07 | 0.03 | -0.04 | -0.07 | 0.19 | 0.03 |
| | 3IPPDPP | 0.08 | 0.04 | 0.07 | -0.04 | 0.21 | 0.07 |
| | 4IPPDPP | 0.07 | 0.08 | 0.07 | -0.02 | **0.25*** | 0.09 |
| | 24DIPPDPP | 0.05 | 0.04 | -0.05 | -0.05 | 0.15 | 0.05 |
| | B2IPPPP | 0.08 | 0.04 | -0.03 | -0.05 | 0.19 | 0.05 |
| | B3IPPPP | 0.05 | 0.05 | -0.02 | -0.04 | 0.22 | 0.05 |
| | 4tBPDPP | -0.06 | -0.06 | -0.05 | -0.12 | 0.10 | 0.18 |
| | B4TBPPP | -0.06 | -0.02 | 0.06 | -0.06 | 0.13 | **0.24*** |
| **Hand wipe** | TCIPP | **0.25*** | 0.15 | 0.17 | 0.05 | -0.04 | -0.01 |
| | TDCIPP | 0.20 | 0.21 | **0.47**$^{\dagger}$ | 0.22 | 0.14 | 0.02 |
| | EHDPHP | 0.19 | 0.21 | 0.05 | 0.08 | -0.11 | -0.09 |
| | TPHP | 0.13 | 0.06 | -0.05 | 0.17 | 0.04 | 0.13 |
| | 2IPPDPP | 0.15 | 0.13 | 0.04 | 0.15 | 0.12 | 0.05 |
| | 4IPPDPP | 0.05 | 0.17 | 0.09 | 0.22 | 0.13 | 0.20 |
| | 4tBPDPP | -0.08 | 0.07 | -0.11 | -0.04 | -0.04 | 0.15 |
| | B4tBPPP | -0.10 | 0.00 | -0.04 | 0.05 | -0.10 | **0.28*** |
| **Dust** | TCIPP | -0.08 | **-0.40**$^{\dagger}$ | -0.09 | 0.02 | -0.08 | -0.07 |
| | TDCIPP | -0.06 | **-0.37**$^{\#}$ | 0.16 | -0.06 | -0.01 | -0.10 |
| | EHDPHP | -0.07 | -0.14 | 0.06 | 0.03 | -0.13 | -0.06 |
| | TPHP | 0.01 | -0.11 | 0.12 | -0.10 | 0.05 | -0.18 |
| | 2IPPDPP | -0.06 | -0.12 | 0.09 | 0.05 | 0.07 | -0.09 |
| | 24DIPPDPP | -0.01 | 0.14 | 0.07 | 0.02 | 0.09 | -0.04 |
| | 4tBPDPP | -0.08 | -0.16 | 0.08 | -0.07 | 0.17 | 0.06 |
| | B4tBPPP | -0.05 | -0.15 | 0.02 | 0.00 | 0.08 | 0.11 |

**Table 32: Phthalate Correlation Tables with Estimated Intake Matrices (n=72).**

| | | Urine | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | MEP | Σ*DiBP*[a] | Σ*DBP*[b] | MCPP | MBzP | Σ*DEHP*[c] | Σ*DiNP*[d] | Σ*DEHTP*[e] |
| **Wristband** | DEP | **0.43**† | 0.00 | -0.06 | -0.02 | -0.05 | 0.00 | -0.04 | 0.00 |
| | DiBP | -0.10 | **0.26*** | -0.12 | -0.11 | -0.09 | -0.03 | 0.00 | 0.09 |
| | DBP | -0.01 | -0.10 | -0.02 | -0.10 | 0.01 | 0.00 | -0.04 | 0.01 |
| | BBP | **0.26*** | 0.10 | 0.14 | 0.04 | **0.48**† | 0.10 | 0.04 | 0.21 |
| | DEHP | 0.02 | 0.03 | -0.17 | -0.08 | -0.07 | 0.13 | -0.08 | 0.17 |
| | DiNP | 0.03 | -0.01 | -0.16 | 0.00 | -0.12 | 0.03 | 0.09 | 0.07 |
| | DEHTP | 0.00 | -0.07 | **-0.23*** | **-0.27*** | -0.13 | -0.14 | -0.18 | 0.11 |
| **Hand Wipe** | DiBP | 0.00 | **0.26*** | 0.05 | -0.03 | 0.14 | -0.09 | -0.19 | -0.01 |
| | BBP | **0.24*** | **0.37**# | **0.32**# | 0.09 | **0.56**† | 0.03 | 0.01 | 0.10 |
| | DEHP | -0.04 | 0.09 | 0.07 | 0.07 | 0.14 | 0.13 | 0.03 | -0.02 |
| | DiNP | 0.06 | 0.22 | 0.01 | 0.21 | 0.09 | 0.10 | 0.21 | -0.02 |
| | DEHTP | 0.13 | 0.14 | 0.09 | -0.10 | 0.22 | -0.08 | -0.07 | 0.09 |
| **Dust** | DEP | 0.02 | -0.07 | 0.07 | 0.07 | 0.11 | 0.01 | 0.11 | 0.01 |
| | DiBP | -0.02 | **0.25*** | **0.28*** | 0.19 | 0.17 | 0.11 | 0.14 | 0.10 |
| | DBP | -0.16 | -0.01 | **0.26*** | 0.19 | 0.15 | 0.08 | 0.16 | 0.03 |
| | BBP | 0.05 | 0.08 | 0.17 | 0.09 | **0.24*** | -0.11 | 0.03 | **0.27*** |
| | DEHP | -0.13 | 0.07 | 0.13 | 0.09 | 0.08 | 0.08 | -0.02 | 0.07 |
| | DiNP | -0.19 | -0.02 | 0.12 | 0.22 | 0.05 | 0.14 | 0.12 | 0.07 |
| | DEHTP | -0.08 | -0.01 | -0.01 | 0.11 | 0.05 | -0.02 | 0.10 | **0.34**# |

*p<0.05, #p<0.01, †p<0.001

[a] Σ*DiBP*= Molar sum of MHiBP and MiBP

[b] Σ*DBP* = Molar sum of MHBP and MBP, MCPP is a non-specific metabolite

[c] Σ*DEHP* = Molar sum of MEHP, MEOHP, MEHHP, and MECPP

[d] Σ*DiNP* = Molar sum of MCOP and MONP

[e] Σ*DEHTP* = Molar sum of MECPTP and MEHHTP

## 7.3.8 Evaluating external exposure matrices in the context of urinary biomarkers

### 7.3.8.1 OPEs

In general, OPEs on wristbands and hand wipes shared similar positive correlations with their corresponding urinary metabolites, although in nearly every case, wristbands had a slightly larger magnitude of correlation compared to hand wipes (Tables 25, 33). However, the slight difference in magnitude observed may not indicate a

statistical difference between the two matrices since they are likely to fall within the same confidence interval. The sole exception was TCIPP on hand wipes being significantly correlated with the BCIPP metabolite, with no significant associations observed with the wristbands. Both of these measures were clearly more effective than house dust at evaluating children's exposure to OPEs, with no significant and positive associations observed between dust OPEs and urinary metabolites (Table 25, 33). Table 15 includes the suggested "best media" for evaluating each of the 12 OPEs with corresponding urinary metabolites based on the Spearman correlation coefficients. For the 2 chlorinated OPEs, hand wipes appeared to be a reliable measure of exposure, with TDCIPP being roughly equivalent for both wristbands and hand wipes. In the case of EHDPHP and TPHP, none of the 3 exposure assessment tools utilized appeared to be effective for measuring children's exposures to these compounds. This could be due to the fact that the metabolite used to evaluate exposure to these compounds, DPHP, has multiple parents and is also used in consumer products as a plasticizer.[260] For EHDPHP, DPHP is a possible metabolite but not the most abundant, based on previous metabolism studies.[261] For every ITP and TBPP isomer with the exception of 2IPPDPP, wristbands were observed to be a slightly improved measure compared to hand wipes. It should be noted that these isomers were quantified using different instrumentation for the wristbands compared to the hand wipes and dust, using a higher mass resolution instrument for the wristbands allowed for a decrease in interferences and thus increased

sensitivity. Still, we interpret these results with some caution, as fewer compounds were able to be quantified on the hand wipes and dust due to decreased sensitivity from the single quadrupole instrument as well as decreased sensitivity within the matrices themselves.

**Table 33: Parent-Biomarker correlations with chemical uses, physicochemical properties, and best exposure media.**

| | | WB Corr | HW Corr | Dust Corr | Parent Compound Use[%] | MW | VP | Log Kow | Log Koa | Best Media? |
|---|---|---|---|---|---|---|---|---|---|---|
| **OPEs (n=75)** | TCIPP-BCIPP | 0.18 | **0.24*** | -0.05 | FR, Plastics, Insulation, Building Materials, Adhesives, Product Manufacture, Consumer Use | 327.6 | 4.44E-3 | 2.59 | 8.39 | Hand wipe |
| | TDCIPP-BDCIPP | **0.52[†]** | **0.48[†]** | 0.13 | FR, Plastics, Furniture, Building Materials, Consumer Use | 430.9 | 2.60E-6 | 3.65 | 9.42 | Wristband & Hand wipe |
| | EHDPHP-DPHP | -0.08 | 0.13 | 0.05 | Plastics, Pesticides, FR, Paint, Rubber, Consumer Use, Chemical Manufacture | 362.4 | 5.00E-5 | 5.73 | 10.00 | None |
| | TPHP-DPHP | 0.12 | 0.18 | 0.00 | Nail products, Plastics, FR, Automobiles, Product Manufacture, Lubricants | 326.3 | 6.28E-6 | 4.59 | 10.34 | None |
| | 2IPPDPP-ipPPP | 0.22 | 0.20 | 0.13 | FR, Plastics, UV Absorber, Textiles/ Foams | 368.4 | 2.28E-6 | 5.18 | 9.54 | Wristband & Hand wipe |
| | 3IPPDPP-ipPPP | **0.27*** | **--** | **--** | FR, Plastics, UV Absorber, Textiles/Foams | 368.4 | 8.86E-6 | 5.14 | 9.66 | Wristband |
| | 4IPPDPP-ipPPP | **0.31[#]** | 0.19[&] | **--** | FR, Plastics, UV Absorber, Textiles/ Foams | 368.4 | 1.49E-5 | 5.17 | 9.86 | Wristband |
| | 24DIPPDPP-ipPPP | 0.20 | -- | 0.12 | FR, Plastics, Textiles/ Foams, Resin/Lubricants | 410.5 | 1.60E-6 | 5.62 | 10.51 | Wristband |
| | B2IPPPP-ipPPP | 0.22 | **--** | **--** | FR, Plastics, UV Absorber, Textiles/ Foams, Resins | 410.5 | 1.93E-6 | 5.94 | 10.80 | Wristband |
| | B3IPPPP-ipPPP | **0.25*** | **--** | **--** | FR, Plastics, UV Absorber, Textiles/ Foams, Resins | 410.5 | 2.06E-8 | 7.61 | 12.82 | Wristband |
| | 4tBPDPP-tbPPP | **0.35[#]** | 0.16 | 0.05 | FR, Plastics, UV Absorber, Textiles/Foams, Resins/Lubricants | 382.4 | 1.28E-5 | 5.44 | 10.23 | Wristband |

| | | WB Corr | HW Corr | Dust Corr | Parent Compound Use[%] | MW | VP | Log Kow | Log Koa | Best Media? |
|---|---|---|---|---|---|---|---|---|---|---|
| | B4tBPPP-tbPPP | **0.35**[#] | **0.28*** | 0.11 | FR, Plastics, UV Absorber, Textiles/Foams, Resins/Lubricants | 438.5 | 2.19E-6 | 6.52 | 12.16 | Wristband |
| **Phthalates (n=74)** | DEP-MEP | **0.53**[†] | -- | 0.17 | Personal Care Products, Fragrance, Cleaning Supplies, Paints, Pesticides | 222.2 | 2.10E-3 | 2.42 | 10.04 | Wristband |
| | DiBP-MolSum | **0.32**[#] | **0.27*** | **0.27*** | Plastics, Adhesives, Building Materials, Automobiles, Product Manufacture | 278.4 | 4.06E-4 | 4.11 | 10.61 | Any but wristband may be best |
| | DBP-MolSum | 0.04 | -- | **0.28*** | Plastics, Adhesives, Nail products, Building Materials, Surface/Flooring Treatment, Cleaning, Fragrance | 278.4 | 2.01E-5 | 4.50 | 10.24 | Dust |
| | BBP-MBzP | **0.56**[†] | **0.56**[†] | **0.23*** | Arts/Crafts, Adhesives, Paints, Building Materials, Automobiles, Sealants, Upholstery (Vinyl) | 312.4 | 8.25E-6 | 4.73 | 12.28 | Wristband & Hand wipe |
| | DEHP-MolSum | 0.22 | 0.14 | 0.16 | Adhesives, Plastics, Paints, Building Materials, Material Manufacture, Upholstery (Fabric/Vinyl) | 390.6 | 1.42E-7 | 7.60 | 14.19 | Wristband |
| | DiNP^-MolSum | **0.24*** | 0.22 | 0.20 | Adhesives/Sealants, Plastics, Paints, Automobiles, Building Materials, Electronics, Fabrics/Textiles, Personal Care Products | 418.6 | 5.40E-7 | 8.80 | 14.62 | Wristband |
| | DEHTP-MolSum | 0.15 | 0.06 | **0.35**[#] | Cleaning, Personal Care Products, Nail Products, Fragrances, Plastics, Adhesives | 390.6 | 3.53E-7 | 8.45 | 15.24 | Dust |

| | | WB Corr | HW Corr | Dust Corr | Parent Compound Use% | MW | VP | Log Kow | Log Koa | Best Media? |
|---|---|---|---|---|---|---|---|---|---|---|
| **PBDEs (n=15)** | BDE-47 | **0.73#** | **0.61*** | **0.65#** | FR, antimicrobial | 485.8 | 7.00E-8 | 6.81 | 11.80 | Wristband & Dust |
| | BDE-99 | **0.63*** | -- | **0.75#** | FR, antimicrobial | 564.7 | 3.10E-8 | 7.32 | 12.28 | Dust & Wristband |
| | BDE-100 | **0.54*** | 0.37 | 0.47 | FR | 564.7 | 2.62E-7 | 7.24 | 12.11 | Wristband |
| | BDE-153 | 0.39 | 0.20 | **0.76#** | FR | 643.6 | 1.46E-8 | 7.90 | 12.86 | Dust |

& Significant relationship observed between 4IPPDPP and DPHP ($r_s$=0.23*)

*p<0.05, #p<0.01, †p<0.001

% based on top 10 Product or Use Categories in EPA Chemistry Dashboard or PubChem Patents

MW of parent- g/mol; EPA Chemistry Dashboard

VP- mmHg at 25°C; Average predicted or experimental value from EPA Chemistry Dashboard

Log Kow at 25°C; Average predicted value from EPA Chemistry Dashboard

Log Koa at 25°C; Based on WORM II Paper (Avg of log10(Kow/KH))

^Physical-chemical properties from PubChem

Regression models were utilized to evaluate the associations of each matrix on the urinary biomarkers for 3 OPE compounds (TCIPP, TDCIPP, and 4tBPDPP). The results of the models demonstrated similar results to the univariate correlation analyses (Table 34). When assessing the relationship between TCIPP and BCIPP, hand wipes were generally an equivalent measure of exposure compared to wristbands, both individually and when dust was included in the model. Hand wipes and wristbands appeared to be roughly similar for TDCIPP, and wristbands were observed to be an improved measure over hand wipes for 4tBPDPP. Because the results of the regression models were very similar to those observed in the correlation analyses, these are not extensively interpreted here. Among the 12 OPE compounds evaluated here for children's exposure, hand wipes and wristbands were roughly equal measures of exposure, although wristbands may be a slightly improved measure overall. When compared to adults, the results here suggest that hand wipes may have increased utility for evaluating children's exposure, since children have more hand-to-mouth contacts than adults and this pathway would be directly captured by hand wipes.

**Table 34: Regression models for predicting urinary metabolite levels based on exposure assessment tools for selected organophosphate esters and phthalates. All variables were $log_{10}$-transformed within the models.**

| Model | Variable | Urinary Metabolite – Parent | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BCIPP – TCIPP | | BDCIPP – TDCIPP | | tb-PPP – 4tBPDPP | | Σ*DiBP* – DiBP | | MBzP – BBP | |
| | | β estimate<br>*p-Value* | Model $R^2$ | β estimate<br>*p-Value* | Model $R^2$ | β estimate<br>*p-Value* | Model $R^2$ | β estimate<br>*p-Value* | Model $R^2$ | β estimate<br>*p-Value* | Model $R^2$ |
| **Urine = Dust + Hand Wipe** | Dust | -0.08<br>*0.38* | 0.06 | 0.13<br>*0.09* | 0.26 | 0.019<br>*0.82* | 0.02 | 0.13<br>*0.1* | 0.11 | 0.16<br>*0.11* | 0.36 |
| | Hand Wipe | **0.20**<br>*0.04* | | **0.39**<br>*<0.0001* | | 0.09<br>*0.24* | | **0.15**<br>*0.05* | | **0.59**<br>*<0.0001* | |
| **Urine = Dust + Wristband** | Dust | -0.05<br>*0.59* | 0.07 | 0.10<br>*0.19* | 0.22 | -0.03<br>*0.69* | 0.11 | 0.15<br>*0.06* | 0.09 | 0.18<br>*0.09* | 0.26 |
| | Wristband | **0.22**<br>*0.02* | | **0.36**<br>*<0.0001* | | **0.29**<br>*0.005* | | 0.10<br>*0.13* | | **0.45**<br>*<0.0001* | |
| **Urine = Dust** | Dust | -0.04<br>*0.64* | 0.003 | 0.12<br>*0.15* | 0.03 | 0.03<br>0.67 | 0.002 | **0.16**<br>*0.03* | 0.06 | **0.30**<br>*0.009* | 0.09 |
| **Urine = Hand Wipe** | Hand Wipe | **0.19**<br>*0.05* | 0.05 | **0.39**<br>*<0.0001* | 0.23 | 0.09<br>0.21 | 0.02 | **0.18**<br>*0.02* | 0.07 | **0.64**<br>*<0.0001* | 0.33 |
| **Urine = Wristband** | Wristband | **0.22**<br>*0.02* | 0.07 | **0.37**<br>*<0.0001* | 0.20 | **0.28**<br>*0.004* | 0.11 | 0.11<br>*0.09* | 0.04 | **0.50**<br>*<0.0001* | 0.23 |

#### 7.3.8.2 Phthalates

For the plasticizer compounds, wristbands were positively correlated with their urinary metabolites for 5 of the 7 compounds in which paired data (i.e., known parents and metabolites) was available (Table 26, 33). As such, these data suggest that wristbands are the best media available for estimating exposure to a number of these compounds, particularly the lower molecular weight phthalates. In the case of a few phthalates and DEHTP, house dust concentrations were positively correlated with the corresponding urinary metabolites (Table 33). This is particularly relevant for DBP and DEHTP, where neither hand wipes nor wristbands were significantly correlated with their urinary metabolites and suggesting that house dust may be the best measure of exposure for these compounds. The three assessment tools appeared to be roughly equivalent for DiBP, and hand wipes and wristbands could be interchangeable for evaluating BBP exposure. Again, when two of the compounds were assessed using regression models, the results reflected the correlation analyses; hence, the correlation analyses are used for interpretation here (Table 34). Overall, wristbands appeared to be consistently effective for evaluating children's exposure across the phthalate compounds, with house dust being a better measure for DBP and DEHTP.

### 7.3.9 Limitations and strengths

The results of this study should be interpreted and considered in the context of several potential limitations. First, we only collected one wristband from each

participant during the week following the home visit, and the other samples (hand wipes and dust) were collected at a single time point; as such, we could not account for individual variability with the wristbands and hand wipes nor determine how exposure may fluctuate from week to week. Second, we did not assess potential exposures to the compounds via diet, which could limit our ability to comment on total exposure to each chemical. Third, we were unable to collect detailed data regarding compliance of the wristband being worn during the sampling period and how the children's behaviors may have influenced the measurements (e.g., swimming, bathing). Therefore, we assumed that the wristbands were worn for at least 5 of the 7 days, despite asking the children not to remove them throughout the study period. Future studies will include improved logs of compliance. For comparisons to the various external exposure matrices, a pooled sample of three urine samples per child was collected over a 48-h period; however, many of these biomarkers for OPEs and phthalates have short half-lives in the body and may not adequately capture daily exposure variability. In this regard, the wristbands may provide an improved measure of exposure, as they could serve as an aggregate measure over the course of a week, in addition to sampling various microenvironments. In addition, we were limited by the lack of certain standards and high-resolution instrumentation to measure all of the ITPs and TBPPs in the hand wipes and dust, compared to when the wristbands were analyzed. While this could have impacted some of our ability to interpret results due to sensitivity and thus

decreased detection frequency, we do not expect that it impacted our analysis in evaluating the exposure matrices. While our study population was diverse and fairly representative of central North Carolina, participants were selected as a convenience sample from an established pregnancy cohort from Duke University Medical Center. This may limit the generalizability of our results to the broader population, but the sampling methodology should not impact the internal validity of this study.

Despite these limitations, our study had several important strengths, including the collection of multiple samples (wristband, hand wipe, house dust, urine, serum) from each child and the use of a pooled urine sample for the child versus a single spot urine sample. Within this study, 65 consumer product chemicals which span a wide range of physicochemical properties were quantified on the wristbands. This is the first study evaluate the measurements of these chemicals for such a wide range of compounds in the context of concurrently collected external exposure measures and biomarkers.

## *7.4 Conclusion*

Taken together, the results of this study suggest that wristbands are an effective and quantitative exposure assessment tool for evaluating children's exposure to organophosphate esters, phthalate/non-phthalate plasticizers, and brominated flame retardants. When evaluated in the context of contemporarily accepted exposure measures (i.e., hand wipes and house dust), wristbands were observed to be roughly

equivalent to hand wipes for OPEs and an improved measure for several of the phthalate compounds. While generalized here, the wristbands may be effective for assessing exposure to specific compounds or chemicals in specific consumer products, which could not be evaluated here within the context of this study. Still, they may be advantageous over hand wipes and dust due to their ease of sample collection and potential for supporting large-scale biomonitoring studies. Although the evaluation of specific exposure pathways measured by the wristbands was outside of the scope of this study, the wristbands are hypothesized to capture both inhalation and dermal absorption, both of which are difficult to measure accurately over time. The wristbands also likely measure the integrated, average exposure over time across multiple microenvironments, while both hand wipes and dust are cross-sectional samples which largely sample from a single microenvironment. This study supports the use of wristbands as a quantitative measure of exposure, as significant and positive associations were observed for over half of the compounds with biomarkers assessed here. While shown to be effective here, continued work to understand which pathways of exposure are captured by the wristbands will be essential for further validating their use in exposure assessment and epidemiological studies.

# 8. Conclusions

The overarching objectives of this research were to critically assess how humans are exposed to chemicals applied to consumer products and to evaluate the utility of silicone wristbands for measuring individual exposures to semi-volatile organic compounds (SVOCs). Presented here were several approaches to evaluating personal exposure to flame retardants and plasticizers across three classes of compounds-organophosphate esters (OPEs), phthalates, and brominated flame retardants (BFRs). First, we quantified specific flame retardant (FR) applications in furniture foam and examined associations with chemical concentrations in paired house dust and resident's serum. This was the first study to date to connect a verified exposure source (foam in upholstered furniture) to an environmental sample matrix (house dust) and a known biomarker of exposure in humans. Through this project, we examined how FR applications in polyurethane foam present in sofas relate to personal exposure to several BFR compounds. Second, we evaluated the utility of silicone wristbands for measuring adult exposure to OPEs and BFRs in two pilot studies, comparing levels on the wristbands to known biomarkers of exposure. Despite the wristbands' growing popularity in use for exposure assessment, these studies represent two of only four published manuscripts evaluating wristbands in the context of biomarkers of exposure. They provided evidence to support the claim that chemicals measured on the wristbands are representative of internal dose as measured as markers in two different

biological samples, urine and serum. Third, we assessed the use of silicone wristbands for examining children's exposures to OPEs, phthalates, and BFRs and compared their utility to existing exposure assessment tools that are currently employed in exposure science, specifically hand wipes, house dust, and biomarkers. This analysis is the most comprehensive wristband study to date, quantifying three classes of compounds on the wristbands and examining their associations with corresponding biomarkers. Overall, these results demonstrate that wristbands served as an equivalent or improved measure of exposure compared to existing tools. Taken together, this dissertation research highlighted an array of exposure assessment tools (product testing, hand wipes, house dust, silicone wristbands) for consumer product chemicals and evaluated them using urinary and serum biomarkers as the gold standards of exposure. Further, it provided some of the first insights on the use of silicone wristbands for evaluating exposure among both children and adults for sixty-five chemicals across three classes of compounds.

## *8.1 Why wristbands over other tools?*

Since the first paper using silicone wristbands as passive samplers was published in 2014 by O'Connell et al., wristbands have been deployed for the purpose of exposure assessment of a wide range of chemicals across numerous circumstances. In a small number of studies, wristbands have been shown to be positively and significantly correlated with exposure biomarkers in addition to being better than contemporary

exposure assessment tools.[249,250,252,262] In Chapter 3, we demonstrated that the wristbands may be an improved measure for adult OPE exposure compared to hand wipes. When we examined children's exposures in Chapter 7, we generally observed that wristbands were either equivalent or improved quantitative tools for OPEs and phthalates compared to hand wipes and house dust. So the question remains- if there were limited resources to evaluate average personal exposures over time to a wide array of chemical classes, why would we suggest wristbands over the contemporarily accepted exposure assessment tools?

Wristbands can provide a non-invasive and inexpensive method of quantitatively measuring personal exposure. As more research is conducted to evaluate chemicals on the wristbands in the context of their biomarkers of exposure, and therefore validating that the wristbands are predictive of internal dose, we can reduce the reliance on biomarkers. Biological samples (e.g., serum) for the purpose of biomarker analysis can be difficult to collect and invasive, particularly among small children. The wristbands can support large-scale biomonitoring studies to inform population-level exposure assessments and epidemiological studies because of their ease of collection and transport. Anderson et al. 2017 verified that the SVOCs on wristbands are stable in transport up to 30°C for a month and in storage at -20°C up to 6 months.[164] This would allow for pre-cleaned wristbands to be mailed to and from participants nationally or even globally for analysis of personal exposures. This ease of collection allows for

increased flexibility, especially when compared to biospecimens which typically need to be placed on ice or frozen soon after collection to maintain the stability of the sample. Further, wristbands remove the need for research personnel to be present for collection, as in collection of house dust, hand wipes or biological samples (e.g., serum), and therefore reduce the time and resources required to conduct the studies.

The wristbands also hold the potential for advances in exposure assessment of mixtures. The silicone material binds chemicals across a wide range of physicochemical properties, which allows for an integrated measure of exposure in a single sample. As epidemiology and toxicology begin evaluating exposure in the context of mixtures, and not on the basis of single chemicals, the wristbands may provide insights on relative levels of chemicals to which individuals may be exposed on average across a specified period of time. Currently, we assume that wristbands are an average measure over time. An ongoing research study in our laboratory is evaluating this claim through a study where participants wear five wristbands and remove one daily over a five-day period while performing a total urine collection. This will allow for intra-individual variability to be evaluated for each participant throughout a workweek and provide some insights on how the wristbands cumulatively capture chemicals on a day-to-day basis. If this study demonstrates that the wristbands are an average measure of exposure over time, they could be an improved measure of exposure over biomarkers. This is particularly the case with spot urine samples, which are typically cross-sectional measures of

exposure since many compounds with urinary metabolite biomarkers have short half-lives in the body. Oftentimes, due to lack of resources to collect and analyze more samples, spot urine samples are analyzed as being representative of total exposure based on the assumption that exposure to these chemicals is constant and chronic. As such, an abnormally high exposure event or the time of day for sampling (i.e., morning void versus daytime spot sample) could easily lead to exposure misclassification. The concentrations of SVOCs on the wristbands tend to be high, and often larger in magnitude than hand wipes (Chapters 3 and 7), thereby allowing for increased analytical sensitivity for evaluating personal exposure to consumer product chemicals. The range of analytical sensitivity is large even for a 1 g piece of a wristband, which allows for other pieces of each wristband sample to be reserved for future analyses (e.g., non-targeted work). Further, this could lead to the development of individual quantitative exposure profiles, which could be extremely helpful in defining the personal exposome and providing greater insight for evaluation of health outcomes. More specifically, we could determine what chemicals or chemical combinations could be harmful for human health on a population level and among marginalized groups and then seek ways to reduce these exposures. For instance, we would be able to target critical windows of development by having pregnant women wear wristbands during various trimesters or weeks within trimesters. Currently, exposures during pregnancy are often evaluated based on single spot urine samples whenever available from office

visits, and in many instances, the availability of urine data from multiple trimesters is not plausible. The use of wristbands here could easily allow for sampling at multiple time points in different trimesters to provide additional sensitivity for evaluating exposure across the pregnancy. This would be further validated by the current work in our laboratory (described above) that is evaluating whether wristbands are indeed a measure of average exposure over time in addition to studies involving the same participants wearing wristbands at multiple time points (e.g., once a month over the course of a year) to evaluate the intra-individual variability in exposure as measured by the wristbands. Based on these future studies, the wristbands could allow for more sensitive measures of their average exposures, and by extension *in utero* exposures, throughout gestation for evaluating pregnancy outcomes and neonatal and early children's health. As such, the wristbands provide a series of advantages over other more commonly used exposure assessment tools for more widespread and increasingly sensitive measures of individual exposures.

## *8.2 How should we be using the wristbands?*

Given the constraints of current exposure studies (e.g., limited resources), we suggest that the wristbands may be a more ideal measure of personal exposure compared to the available assessment tools. While this may be true for a variety of circumstances, this is not the case for every study examining exposure. In the research presented here, we did not evaluate the relationships between biomarkers of exposure

and wristband concentrations for volatile compounds. The most volatile compounds for which we had paired parent and urinary metabolites were TCIPP for the OPEs and DEP for the phthalates. We observed a positive and significant association between TCIPP and its urinary biomarker in adults and not in children, but we did observe a significant correlation for DEP and its corresponding metabolite in children (Chapters 3 and 7). However, volatile organic compounds (VOCs), which are defined having a boiling point less than or equal to 250°C at standard atmospheric pressure, may not be effectively captured by the wristbands, which was shown by Anderson et al. 2017, as they may volatilize more easily and lack stability on the wristbands at higher temperatures.[1]

When examining the three classes of compounds evaluated here (OPEs, phthalates, BFRs), several of the compounds in each class exceed a log Koa value of 13. Studies performed by other groups suggest that the wristbands captured compounds in the log Koa range of 2 to 13, which is likely due to their use of different methodologies which would remove particles prior to extraction.[164,263] In both of these studies, preparation of the wristband samples included washing the wristbands with water and isopropanol which could have removed particles bound to the bands and thus compounds with higher log Koa values. All of our analyses of the wristbands presented in this dissertation research did not include a rinsing step prior to extraction of wristband samples, thereby suggesting that the particles would have remained in our sample extracts. Throughout this dissertation research, we sought to evaluate whether

these compounds with higher log Koa values, and thus likely particle-bound, measured on the wristbands represented meaningful exposure. In Chapter 7, we observed several compounds with log Koa values between 12 and 13 to be significantly and positively correlated with their biomarkers in serum and urine. With a log Koa of 14.6, DiNP on the wristbands was also significantly correlated with the molar sum of its urinary metabolites. The relationship between wristband DEHP (log Koa = 14.2) and its urinary metabolite molar sum was suggestive of a positive relationship ($r_s = 0.22$, $p = 0.06$). Although biomarkers were unavailable for comparison, several of the BFR compounds (e.g., BEH-TEBP, DBDPE, and TBBPA-DBPE) all of which have log Koa values that exceed 14, were highly detected in both adult and children's wristbands (Chapters 4 and 7). As discussed briefly in Chapter 4, an important question remains whether the wristbands can effectively capture compounds regardless of whether they are in the gas phase or bound to aerosols. Harner and Shoeib reported that 80% of BDE-153 would be bound to aerosols whereas only 17% of BDE-47 would be particle-bound at room temperature.[163] Their work indicates that BDE-209 would be entirely particle-bound at room temperature; nearly every wristband analyzed in this dissertation research had measurable concentrations of BDE-209, which provides additional evidence that the wristbands capture aerosols. Based on the particle-gas partitioning coefficients ($K_P$) calculated by Weschler et al., 2008 using saturation vapor pressures, about 86% of DEHP would be bound to aerosols compared to 15% of BBP, again at room temperature.[161]

Since DiNP is less volatile than DEHP, it is likely that >86% would be bound to particles at room temperature. Taken together, these results indicate that the wristbands capture meaningful exposure to compounds which are largely aerosols at room temperature, and thus, the particles present on the wristbands are important to include in a thorough examination of personal exposure. As such, we recommend that wristbands are not rinsed with water and isopropanol prior to extraction processes.

Further, we posit that the wristbands capture exposures that occur both from inhalation and dermal absorption and would obviously have limited utility for detecting chemicals for which individual exposure primarily occurs via diet. Still, we have shown here that the wristbands may capture some secondary pathways of exposure, despite diet representing the lion share of personal exposure (e.g., DEHP). This, of course, relies on the prevalence of the chemical's use in consumer products and the continued use of these products in everyday microenvironments (e.g., homes, offices, schools). Regardless, it is imperative that researchers utilize the wristbands and interpret their results in the context of assumptions we currently make and have not yet verified (i.e., average exposure over time, external exposure pathways) and that researchers recognize the wristbands' limitations given the paucity of literature currently available on their associations with verified SVOC biomarkers.

## *8.3 Data gaps and future research*

Because the first wristband paper was published a mere five years ago, future research to address data gaps with regard to the use of wristbands as a quantitative exposure assessment tool is crucial and necessary. There is a myriad of questions about the wristbands still waiting to be answered, which emphasizes the need for collaborative efforts to encourage more researchers to utilize the wristbands to tackle the gaps in literature concurrently and in parallel. Three major data gaps in the wristband literature are (a) the relative contributions of various exposure pathways (i.e., inhalation versus dermal absorption versus inadvertent dust ingestion) to the concentrations measured on the wristbands, (b) the associations with biomarkers in validating their use for measuring personal exposures to chemicals other than OPEs, PBDEs, and phthalates, and (c) the evaluation of whether wristbands worn over a weeklong period are representative of average exposure.

Determining which exposure routes are captured by the wristbands and what are their relative contributions would be particularly insightful for interpreting the chemical levels measured on the wristbands. This will also provide additional information regarding the primary pathways of exposure for a number of SVOCs, specifically those that display significant correlations between wristbands and biomarkers. Determining the ways by which people are exposed to consumer product chemicals will allow for future work to be conducted to reduce these exposures, if

necessary. In addition to examining how inhalation and dermal pathways of exposure are captured by the wristbands, identifying how sweat, skin oils, and the use of personal care products like lotion affects the wristband measurements and mediates exposures, particularly in dermal absorption, would be important to determine.

Further studies examining the wristbands in the context of verified, known biomarkers of exposure for more classes of compounds, such as pesticides, are essential. As the wristbands are deployed all over the world and with the intent of evaluating exposure to various classes of SVOCs, it is critical that we are continually comparing the wristbands to accepted, contemporary measures of exposure that have been previously validated in addition to biomarkers. This will provide insights on what the wristbands mean for internal dose of individual chemicals as well as chemical mixtures. Previously, we discussed that biomarker measurements can be cross-sectional due to the short half-life of urinary metabolites, and thus, the use of single spot urine samples to characterize personal exposure could lead to exposure misclassification. Therefore, the positive, significant associations we observed between wristband concentrations and urinary metabolites from pooled urine samples does suggest that wristbands can reflect exposure over the sampling period. However, we only evaluated the wristbands in depth for three classes of compounds; this needs to be expanded in future research to a wider range of consumer chemicals (e.g., pesticides, phenols, precursors of PFASs measured in serum).

We have claimed here that the concentrations measured on the wristbands are representative of average exposure over time; however, this is a point that needs to be verified. Throughout this research, we utilized pooled urine samples from multiple time points within the sampling period for measurements of urinary metabolites, which we then compared to the wristband concentrations. While this suggests that the wristbands could represent average exposure, this is not a verification of this point. As mentioned earlier in this discussion, an ongoing study in our laboratory involves participants wearing five wristbands and removing one wristband each day over the five-day sampling period. Throughout this time, they are also conducting a total urine collection. This will allow for intra-individual variability to be evaluated for the wristbands as well as determine how the accumulation on each wristband changes day by day. Additionally, this study will provide insights on a mass-balance to evaluate the wristband concentrations in the context of total exposure to each compound by all pathways via urinary biomarkers. With the results of this study, we will be able to determine how well the wristbands measure average exposure over a five-day period and whether this is a valid claim. Further, a study which includes multiple participants wearing a single wristband at various time points throughout a year can improve understanding of how exposures change within an individual and provide intraclass correlation coefficients (ICCs) for a wide array of compounds, again to evaluate in the context of biomarkers.

Understanding the optimum conditions for wristband sampling will also improve future studies utilizing these personal samplers for exposure assessment. In particular, determining a general optimal sampling period for examining average exposure using the wristbands would be insightful. This could be performed by collecting multiple wristbands with total urine collections over a weeklong period to determine how the wristbands directly relate to internal dose and provide a proxy mass balance between the wristbands and biomarkers. This study may also provide direct evidence for how the wristbands could be an improved measure over biomarkers, especially through comparisons with spot urine samples. Previous work evaluating nicotine levels on the wristbands demonstrated that sampling periods of two and seven days yielded similar associations with the cotinine biomarker, with the concentrations of nicotine being slightly yet significantly higher when worn for seven days compared to two.[249] This suggests that exposure may fluctuate day by day, and therefore, chemical accumulation rates may change across a sampling period. Similar analyses should be conducted over multiple sampling periods and for a wider range of compounds. Studies examining optimum conditions should also include the deployment of multiple wristbands over time to evaluate the intra-individual variability for average exposures. ICCs have been used to evaluate the consistency of urinary metabolites of OPEs and phthalates. In general, metabolite ICCs for spot and morning void urine samples across a week to several months have been demonstrated to be fairly low for high molecular

weight phthalates (ICC = 0.1 – 0.3) and moderate to high for low molecular weight phthalates and some OPEs (ICC = 0.3 – 0.8).[86,264] Evaluating the wristband levels across multiple, separate sampling periods would allow for conclusions to be made regarding the change in individual average exposure over time.

With the increase in researchers utilizing wristbands for exposure assessments and the current lack of a standard reference material for comparative quality assurance and quality control, an inter-lab comparison of the wristbands will be vital to the field moving forward. As demonstrated by the published literature, nearly every lab utilizes a slightly different extraction and clean-up methodology for quantifying chemicals on the wristbands. Further, analytical GC/MS methods are also dissimilar (i.e., use of EI vs. ECNI for quantification of BFRs, low vs. high resolution analysis, scan vs. select ion monitoring for chemical detections). In many cases, the units in which the wristband concentrations are reported are different as well (e.g., ng/wristband, ng/g wristband, ng/g wristband/day). A large-scale collaboration to establish how the methods may be affecting the different concentrations measured on the wristbands will provide insights into which methodologies should be utilized moving forward and allow for more accurate comparisons to be made across the board.

## *8.4 Final insights*

The overall hypothesis of this dissertation was that silicone wristbands are effective exposure assessment tools for evaluating personal exposure to SVOCs. Based

on the range of physicochemical properties, exposure to OPEs, phthalates, and BFRs were specifically analyzed as representative chemical classes. In general, the wristbands provided an improved or equivalent measure of exposure compared to hand wipes for both adults and children, both of which were typically better measures than house dust. Product testing, while useful for evaluating sources of exposure, was less useful quantifying personal exposure to SVOCs. As the wristbands grow in popularity for use in exposure science, it is imperative to recognize under what conditions the wristbands are better mediums for evaluating personal exposure compared to the existing paradigms in exposure assessment as well as where they are limited and what data gaps still exist. Representing an integrated measure of inhalation and dermal exposure pathways, the wristbands may quantify individual exposure via two pathways that have been largely underestimated. As non-invasive and inexpensive personal samplers, the wristbands hold the potential for large-scale biomonitoring and the development of individual exposure profiles, both of which are currently lacking. Given the prevalence of SVOCs in our everyday environment, greater knowledge of exposure to chemical mixtures and body burdens is essential to characterizing health risks among the general population and in vulnerable groups. This dissertation research provided some of the first insights into utilizing silicone wristbands as novel exposure tools for this ultimate purpose. As a whole, it hopefully contributes to the foundational groundwork for future

studies to characterize specific exposure pathways captured by the wristbands and provide further validation for their continued use in exposure science.

# Appendix A

Appendix A contains the supporting information for Chapter 2, published online from Hammel, S. C.; Hoffman, K.; Lorenzo, A. M.; Chen, A.; Phillips, A. L.; Butt, C. M.; Sosa, J. A.; Webster, T. F.; Stapleton, H. M. Associations between flame retardant applications in furniture foam, house dust levels, and residents' serum levels. *Environ. Int.* 2017, *107*, 181–189 (Publisher: Elsevier).

**Contents**

**Table A1: Structures and CAS numbers for chemicals assessed in this study.**

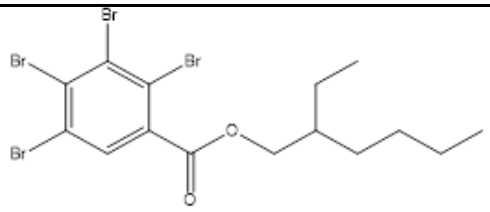
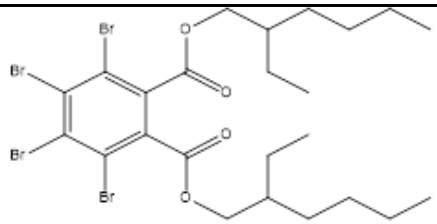
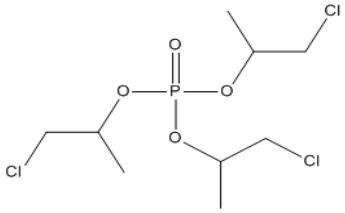
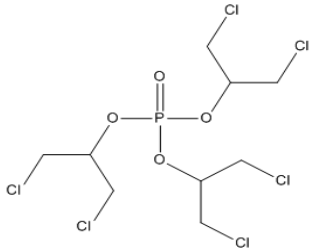
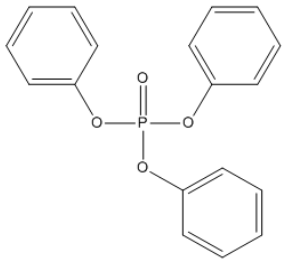
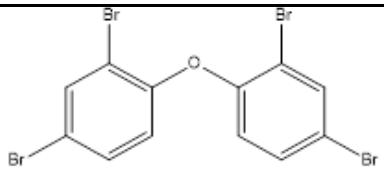
| Chemical | CAS Number | Structure |
|---|---|---|
| 2-ethylhexyl-2,3,4,5-tetrabromobenzoate<br><br>(EH-TBB) | 183658-27-7 |  |
| bis (2-ethylhexyl)-2,3,4,5-tetrabromophthalate<br><br>(BEH-TEBP) | 26040-51-7 |  |
| tris(1-chloro-2-isopropyl) phosphate<br><br>(TCIPP) | 13674-84-5 |  |
| tris(1,3-dichloroisopropyl) phosphate<br><br>(TDCIPP) | 13674-87-8 |  |
| triphenyl phosphate<br><br>(TPHP) | 115-86-6 |  |
| 2,2',4,4'-tetrabromodiphenyl ether<br><br>(BDE-47, Component of PentaBDE) | 5436-43-1 |  |

**Table A2: Abbreviations and names of components for mixtures examined in this study.**

| Abbreviation | Compound Name and Components |
|---|---|
| **ITPs** | Isopropylated triaryl phosphate mixture (also contains TPHP) |
| **FM550** | Firemaster® 550 (TPHP, ITPs, EH-TBB, BEH-TEBP) |
| **TBPP** | Tert-butylated phenyl phosphate esters mixture (also contains TPHP) |
| **MPP** | Methyl phenyl phosphate esters mixture |
| **PentaBDE** | BDE-17, 28, 47, 49, 66, 85, 99, 100, 153, 154, and 155. |

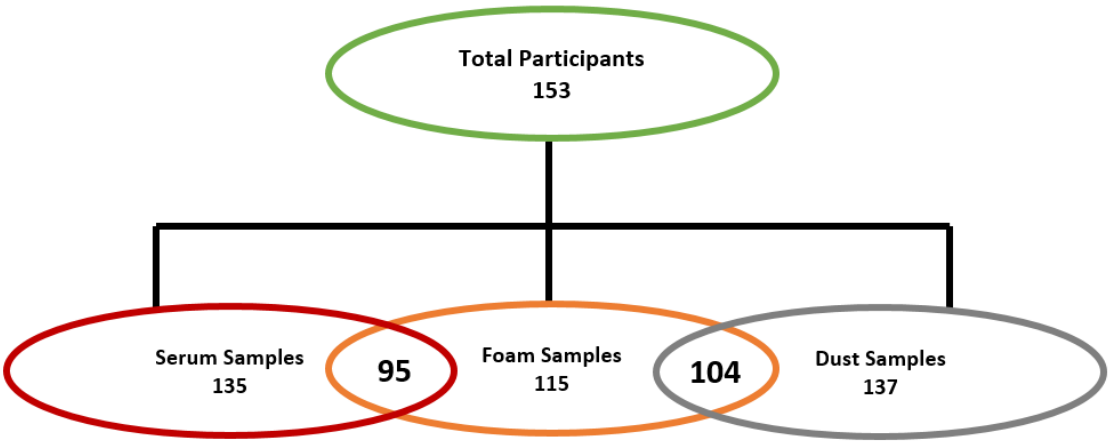



**Figure A1: Diagram of samples collected within this cohort study.**

# Appendix B

Appendix B contains the correction and supporting information for Chapter 3, published online from Hammel, S. C.; Hoffman, K.; Webster, T. F.; Anderson, K. A.; Stapleton, H. M. Measuring Personal Exposure to Organophosphate Flame Retardants Using Silicone Wristbands and Hand Wipes. *Environ. Sci. Technol.* 2016, *50* (8), 4483–4491. Copyright 2016 American Chemical Society.

**Contents**

**Correction to Measuring Personal Exposure to Organophosphate Flame Retardants using Silicone Wristbands and Hand Wipes**



The urine concentrations reported in the original paper were raw values but mistakenly reported as specific gravity-corrected. These do not change the overall results of the paper as the associations among specific gravity-corrected urine concentrations are very similar to those among the raw values.

Section, Statistical Analysis. The last sentence should read, "Analysis results using each set of urine concentrations were essentially not differentiable, and the associations and graphs with raw urine concentrations are presented here."

Section, Specific-Gravity Corrected Urine. This section heading should be labeled, "Urine."

Table 4. The values in this table are correct; however, the section heading under "matrix and compound" should be "Raw Urine" rather than "SG-Corrected Urine."

Table 5 caption. The values in this table are correct, but the caption should read "Spearman Correlation Coefficients for PFR and PFR Metabolite Levels Measured in Paired Wristbands ($n$ = 40), Hand Wipes ($n$ = 38), and Urine ($n$ = 40)."

Figure 6. The values within this figure are correct, but the headings should exclude "sg" prior to BDCIPP and BCIPHIPP.

Section, Comparing Wristbands and Hand Wipes to Urine. In the first paragraph, it should read, "TPHP and mono-ITP concentrations on the wristbands were not correlated with DPHP, but TPHP concentrations on the wristbands were correlated to specific-gravity-corrected DPHP concentrations."

Table 6 caption and headings. Again, the values in this table are correct for the raw urine concentrations. Therefore, the caption should read, "Results of Regression Analyses for Associations with Raw Urinary Metabolites Based on Parent Compounds on Wristbands and Hand Wipes Categorized as Tertiles." The headings within the table should exclude "SG-corrected" before each of the PFR metabolites- BDCIPP, BCIPHIPP, and DPHP.

Table 7 headings. The regression analyses utilized raw urine concentrations as the outcome; therefore, the headings should exclude "SG-corrected" before each of the metabolites.

**Table B1: Average PFR and PFR metabolite levels in field blanks for wristbands ($n$ = 8), hand wipes ($n$ = 4), and specific gravity-corrected urine ($n$ = 8).**

| Matrix and Compound | $n$ | Average Blank |
|---|---|---|
| **Wristbands (ng/band)** | | |
| **TDCIPP** | 8 | 6.31 |
| **TCIPP** | 8 | 46.1 |
| **TPHP** | 8 | 3.92 |
| **Mono-ITP** | 8 | 16.0 |
| **Hand wipes (ng/wipe)** | | |
| **TDCIPP** | 4 | 3.98 |
| **TCIPP** | 4 | 0.988 |
| **TPHP** | 4 | 0.998 |
| **Mono-ITP** | 4 | 2.50 |
| **SG-corrected urine (ng/mL)** | | |
| **BDCIPP** | 4 | 0.100 |
| **BCIPHIPP** | 4 | 0.473 |
| **BCIPP** | 4 | 0.176 |
| **DPHP** | 4 | 0.202 |
| **ip-PPP** | 4 | 0.0200 |

**Table B2: Expanded Spearman correlation matrix for PFR and PFR metabolites in paired wristbands (*n* = 40), hand wipes (*n* = 38) and specific gravity-corrected urine (*n* = 40).**

| | | Wristbands | | | | Hand wipes | | | | Urine | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TDCIPP | TCIPP | TPHP | Mono-ITP | TDCIPP | TCIPP | TPHP | Mono-ITP | BDCIPP | BCIPHIPP | DPHP | ip-PPP |
| **Wrist bands** | TDCIPP | 1.00 | | | | | | | | | | | |
| | TCIPP | -0.13 | 1.00 | | | | | | | | | | |
| | TPHP | 0.09 | 0.002 | 1.00 | | | | | | | | | |
| | Mono-ITP | 0.29 | -0.11 | 0.77† | 1.00 | | | | | | | | |
| **Hand wipes** | TDCIPP | 0.39* | 0.04 | -0.12 | -0.09 | 1.00 | | | | | | | |
| | TCIPP | 0.11 | 0.69† | -0.15 | -0.20 | 0.49# | 1.00 | | | | | | |
| | TPHP | 0.13 | 0.09 | 0.23 | 0.23 | 0.48# | 0.23 | 1.00 | | | | | |
| | Mono-ITP | 0.02 | 0.15 | 0.32* | 0.31 | 0.47# | 0.30 | 0.71† | 1.00 | | | | |
| **Urine** | BDCIPP | 0.59† | -0.01 | 0.24 | 0.33* | 0.37* | 0.05 | 0.19 | 0.04 | 1.00 | | | |
| | BCIPHIPP | -0.17 | 0.62† | -0.04 | -0.06 | -0.01 | 0.46# | 0.16 | 0.06 | 0.11 | 1.00 | | |
| | DPHP | -0.10 | 0.06 | 0.27 | 0.09 | 0.09 | -0.02 | 0.29 | 0.14 | 0.27 | 0.34* | 1.00 | |
| | ip-PPP | 0.09 | -0.01 | -0.23 | -0.25 | 0.18 | 0.09 | -0.23 | -0.24 | 0.15 | -0.18 | 0.26 | 1.00 |

*p<0.05, #p<0.01, †p<0.0001

**Table B3: Spearman correlation coefficients for parent and metabolite PFR compounds based on low time spent in home (*n*=22) and high time spent in home (*n*=18).**

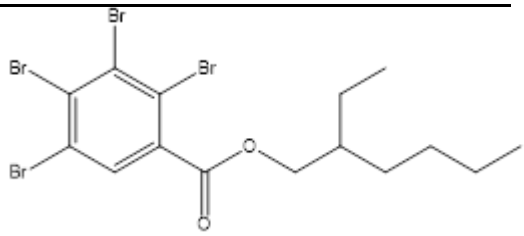
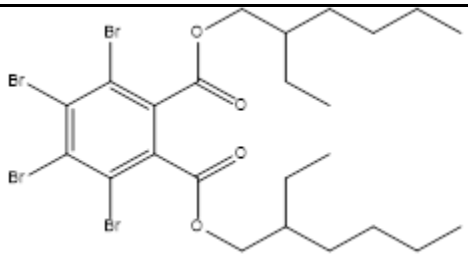
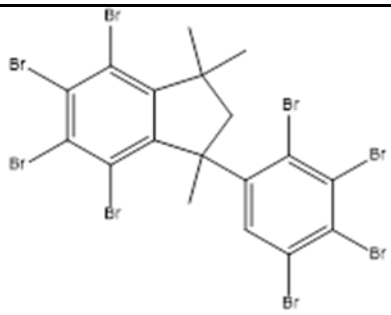
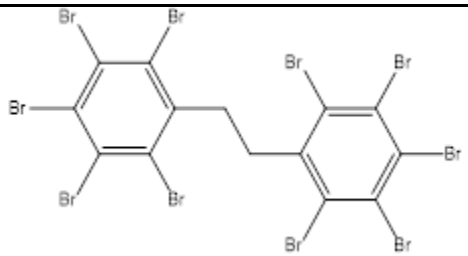
| Time spent in Home | TDCIPP - BDCIPP | | TCIPP - BCIPHIPP | | TPHP - DPHP | |
|---|---|---|---|---|---|---|
| | Hand wipe | Wristband | Hand wipe | Wristband | Hand wipe | Wristband |
| **Low (<15 hrs/day)** | -0.002 | 0.40 | 0.20 | 0.62# | 0.33 | 0.20 |
| **High (≥ 15 hrs/day)** | 0.72# | 0.84† | 0.67# | 0.58# | 0.21 | 0.30 |

# Appendix C

Appendix C contains supporting information for Chapter 4, published online from Hammel, S.C.; Phillips, A.L.; Hoffman, K.; Stapleton, H.M. Evaluating the Use of Silicone Wristbands to Measure Personal Exposure to Brominated Flame Retardants. *Environ. Sci. Technol.* 2018, *52* (20), 11875-11885. 

**Contents**

## Table C1: Structures and properties of novel BFRs in this study.

| Chemical | CAS RN | Int. Std. | m/z quant (qual) | log Koa (from EPA Dashboard) | RT rel. to $^{13}$C BDE-209 | Structure |
|---|---|---|---|---|---|---|
| **2-ethylhexyl-2,3,4,5-tetrabromo benzoate (EH-TBB)** | 18365 8-27-7 | $^{13}$C-EH-TBB | 357 (471) | 11.8 | n/a |  |
| **bis (2-ethylhexyl) -2,3,4,5-tetrabromo phthalate (BEH-TEBP)** | 26040 -51-7 | $^{13}$C-BEH-TEBP | 463.7 (79, 81) | 15.7 | n/a |  |
| **octabromo trimethyl phenyl indane (OBIND)** | 10848 89-51-9 | $^{13}$C-BDE-209 | 79 (81) | 19.9 | -1.60 |  |
| **decabromo diphenyl ethane (DBDPE)** | 84852 -53-9 | $^{13}$C-BDE-209 | 79 (81) | 14.5 | +2.80 |  |

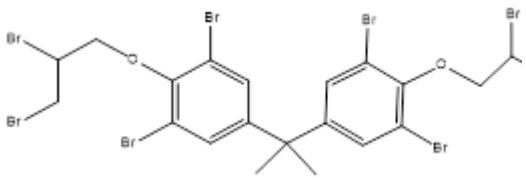
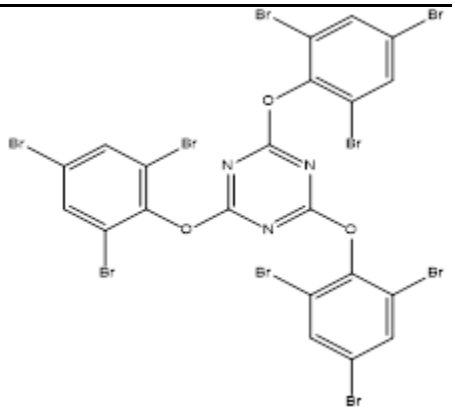
| Chemical | CAS RN | Int. Std. | m/z quant (qual) | log Koa (from EPA Dashboard) | RT rel. to $^{13}$C BDE-209 | Structure |
|---|---|---|---|---|---|---|
| **tetrabromo bisphenol A bis(2,3-dibromo propyl ether)** **(TBBPA-DBPE)** | 21850-44-2 | $^{13}$C-BDE-209 | 79 (81) | 14.9 | +6.15 |  |
| **2,4,6-tris(2,4,6-tribromo phenoxy)-1,3,5-triazine** **(TTBP-TAZ)** | 25713-60-4 | $^{13}$C-BDE-209 | 79 (81) | 15.9 | +8.71 |  |

**Table C2: Results of bivariate regression analyses for predicting wristband concentrations of BFRs without serum biomarkers**

| Predictor | BDE 209 [$10^{\beta}$ (95% CI) *p-Value*] | EH-TBB [$10^{\beta}$ (95% CI) *p-Value*] | BEH-TEBP [$10^{\beta}$ (95% CI) *p-Value*] | TTBP-TAZ [$10^{\beta}$ (95% CI) *p-Value*] | DBDPE [$10^{\beta}$ (95% CI) *p-Value*] | TBBPA-DBPE [$10^{\beta}$ (95% CI) *p-Value*] |
|---|---|---|---|---|---|---|
| **Sex** | | | | | | |
| **Female** | Reference | Reference | Reference | Reference | Reference | Reference |
| **Male** | 1.60 (0.95, 2.70) *0.08* | 1.71 (0.72, 4.06) *0.22* | 0.57 (0.07, 4.58) *0.59* | 2.03 (0.61, 6.79) *0.24* | 1.44 (0.59, 3.56) *0.41* | 2.43 (1.06, 5.56) *0.04* |
| **Age (yr)** | 1.01 (0.99, 1.04) *0.26* | 0.97 (0.93, 1.01) *0.12* | 0.99 (0.89, 1.09) *0.77* | 1.00 (0.94, 1.06) *0.96* | 1.03 (0.99, 1.07) *0.18* | 1.00 (0.95, 1.04) *0.87* |
| **Avg times hands washed/day** | | | | | | |
| **≤ 6** | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 6** | 0.87 (0.51, 1.49) *0.60* | 0.77 (0.33, 1.84) *0.55* | 3.99 (0.55, 28.8) *0.16* | 1.67 (0.51, 5.55) *0.39* | 1.09 (0.45, 2.67) *0.84* | 0.76 (0.32, 1.82) *0.52* |
| **Avg hours of day spent in home** | | | | | | |
| **≤ 15** | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 15** | 1.48 (0.88, 2.49) *0.13* | 1.29 (0.54, 3.08) *0.55* | 0.40 (0.05, 3.01) *0.36* | 1.95 (0.59, 6.37) *0.26* | 1.47 (0.61, 3.56) *0.38* | 1.78 (0.76, 4.16) *0.18* |
| **Avg hours of day spent at work/school** | | | | | | |
| **≤ 5.5** | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 5.5** | 0.70 (0.42, 1.19) *0.18* | 1.25 (0.52, 2.97) *0.61* | 1.34 (0.67, 5.87) *0.78* | 0.54 (0.17, 1.79) *0.30* | 0.67 (0.28, 1.61) *0.36* | 0.52 (0.22, 1.20) *0.12* |
| **Avg hours of day spent in car** | | | | | | |
| **≤ 1** | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 1** | 1.20 (0.69, 2.07) *0.50* | 0.61 (0.25, 1.45) *0.25* | 1.09 (0.13, 8.89) *0.93* | 1.16 (0.34, 4.01) *0.80* | 1.11 (0.45, 2.75) *0.82* | 0.49 (0.21, 1.15) *0.10* |

**Table C3: Results of bivariate regression analyses for predicting wristband and serum concentrations of selected BDEs.**

| Predictor | BDE 28,33 [$10^{\beta}$ (95% CI) *p-Value*] | | BDE 47 [$10^{\beta}$ (95% CI) *p-Value*] | | BDE 99 [$10^{\beta}$ (95% CI) *p-Value*] | | BDE 100 [$10^{\beta}$ (95% CI) *p-Value*] | | BDE 153 [$10^{\beta}$ (95% CI) *p-Value*] | | BDE 154 [$10^{\beta}$ (95% CI) *p-Value*] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Band | Serum | Band | Serum | Band | Serum | Band | Serum | Band | Serum | Band | Serum |
| **Sex** | | | | | | | | | | | | |
| **Female** | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| **Male** | 1.1 (0.5, 2.3) *0.87* | 1.1 (0.6, 2.2) *0.69* | 1.2 (0.5, 3.0) *0.63* | 0.8 (0.4, 1.9) *0.66* | 1.1 (0.4, 3.0) *0.84* | 0.8 (0.3, 1.8) *0.55* | 1.0 (0.4, 2.7) *0.99* | 1.0 (0.4, 2.5) *0.99* | 1.4 (0.6, 3.4) *0.45* | 1.9 (0.7, 5.1) *0.17* | 1.1 (0.4, 3.0) *0.77* | 0.9 (0.4, 2.2) *0.87* |
| **Age (yr)** | 1.0 (1.0, 1.1) *0.12* | 1.0 (1.0, 1.0) *0.79* | 1.0 (1.0, 1.1) *0.27* | 1.0 (1.0, 1.1) *0.41* | 1.0 (1.0, 1.1) *0.49* | 1.0 (1.0, 1.1) *0.35* | 1.0 (1.0, 1.1) *0.33* | 1.0 (1.0, 1.1) *0.05* | 1.0 (1.0, 1.1) *0.25* | 1.0 (0.9, 1.0) *0.56* | 1.0 (1.0, 1.1) *0.20* | 1.1 (1.0, 1.1) *0.006* |
| **Avg times hands washed/day** | | | | | | | | | | | | |
| **≤ 6** | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 6** | 0.8 (0.4, 1.8) *0.59* | 1.6 (0.9, 3.1) *0.12* | 0.7 (0.3, 1.7) *0.44* | 0.9 (0.4, 2.1) *0.81* | 1.4 (0.5, 3.6) *0.53* | 1.0 (0.4, 2.3) *0.94* | 0.8 (0.3, 2.2) *0.72* | 0.9 (0.4, 2.3) *0.84* | 1.0 (0.4, 2.4) *0.98* | 0.9 (0.3, 2.3) *0.78* | 1.1 (0.4, 2.9) *0.79* | 0.6 (0.3, 1.3) *0.17* |
| **Avg hrs of day spent in home** | | | | | | | | | | | | |
| **≤ 15** | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 15** | 1.4 (0.6, 2.9) *0.40* | 1.5 (0.8, 2.9) *0.20* | 1.6 (0.7, 3.7) *0.29* | 1.5 (0.7, 3.3) *0.33* | 1.9 (0.8, 5.0) *0.16* | 1.3 (0.5, 3.0) *0.57* | 2.1 (0.8, 5.3) *0.12* | 1.5 (0.6, 3.7) *0.37* | 2.0 (0.9, 4.7) *0.10* | 1.6 (0.6, 4.2) *0.34* | 2.5 (1.0, 5.9) *0.05* | 0.8 (0.4, 1.9) *0.63* |
| **Avg hrs of day spent at work/school** | | | | | | | | | | | | |
| **≤ 5.5** | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 5.5** | 1.2 (0.6, 2.6) *0.59* | 1.0 (0.5, 2.0) *0.90* | 1.3 (0.6, 3.2) *0.51* | 1.3 (0.6, 2.8) *0.57* | 1.7 (0.6, 4.3) *0.29* | 1.3 (0.6, 3.1) *0.53* | 1.2 (0.5, 3.2) *0.67* | 1.0 (0.4, 2.4) *0.91* | 0.8 (0.3, 1.8) *0.52* | 0.9 (0.3, 2.4) *0.85* | 0.9 (0.4, 2.4) *0.91* | 1.4 (0.6, 3.1) *0.43* |
| **Avg hrs of day spent in car** | | | | | | | | | | | | |
| **≤ 1** | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference | Reference |
| **> 1** | 1.3 (0.6, 2.9) *0.44* | 2.4 (1.3, 4.3) *0.005* | 1.5 (0.6, 3.6) *0.37* | 2.1 (1.0, 4.7) *0.06* | 2.3 (0.9, 6.1) *0.08* | 2.1 (0.9, 4.9) *0.07* | 1.5 (0.6, 4.1) *0.37* | 1.4 (0.5, 3.5) *0.48* | 1.2 (0.5, 2.9) *0.73* | 1.2 (0.4, 3.2) *0.76* | 1.4 (0.6, 3.7) *0.44* | 1.6 (0.7, 3.6) *0.29* |

**Table C4: Pearson correlation coefficients for $log_{10}$-transformed BFRs measured on wristbands.**

| | BDE-28,33 | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-154 | BDE-209 | EH-TBB | BEH-TEBP | DBDPE | TBBPA-DBPE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **BDE-47** | **0.91**# | | | | | | | | | | |
| **BDE-99** | **0.59**# | **0.66**# | | | | | | | | | |
| **BDE-100** | **0.81**# | **0.92**# | **0.78**# | | | | | | | | |
| **BDE-153** | **0.74**# | **0.84**# | **0.56**# | **0.85**# | | | | | | | |
| **BDE-154** | **0.74**# | **0.86**# | **0.75**# | **0.94**# | **0.94**# | | | | | | |
| **BDE-209** | 0.08 | 0.19 | 0.03 | 0.24 | 0.32 | 0.25 | | | | | |
| **EH-TBB** | 0.12 | 0.21 | -0.07 | -0.01 | 0.06 | -0.01 | 0.07 | | | | |
| **BEH-TEBP** | -0.25 | -0.25 | -0.36 | -0.33 | -0.21 | -0.29 | -0.18 | **0.04** | | | |
| **DBDPE** | 0.22 | 0.20 | -0.08 | 0.12 | 0.27 | 0.14 | **0.56**# | 0.32 | 0.04 | | |
| **TBBPA-DBPE** | -0.20 | -0.29 | **-0.38*** | -0.31 | -0.20 | -0.24 | 0.20 | 0.17 | 0.07 | 0.06 | |
| **TTBP-TAZ** | 0.02 | 0.02 | 0.03 | 0.01 | 0.09 | 0.08 | 0.31 | 0.36 | 0.20 | 0.35 | 0.30 |

*p<0.05, #p<0.01

**Table C5: Pearson correlation coefficients for $log_{10}$-transformed PBDEs measured in paired wristbands and serum.**

| | | Serum | | | | | |
|---|---|---|---|---|---|---|---|
| | | BDE-28,33 | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-154 |
| **Wristbands** | BDE-28,33 | 0.30 | **0.52**# | **0.41*** | **0.47*** | 0.30 | **0.40*** |
| | BDE-47 | **0.38*** | **0.64**# | **0.52*** | **0.49**# | **0.48**# | 0.34 |
| | BDE-99 | **0.58**# | **0.56**# | **0.64**# | **0.46*** | 0.22 | 0.16 |
| | BDE-100 | 0.36 | **0.69**# | **0.57**# | **0.47*** | **0.38*** | 0.21 |
| | BDE-153 | 0.25 | **0.59**# | **0.52**# | **0.51**# | **0.40*** | 0.21 |
| | BDE-154 | **0.37*** | **0.69**# | **0.61**# | **0.58**# | **0.37*** | 0.21 |
| | BDE-209 | -0.09 | 0.13 | 0.07 | 0.01 | 0.14 | -0.01 |

*p<0.05, #p<0.01

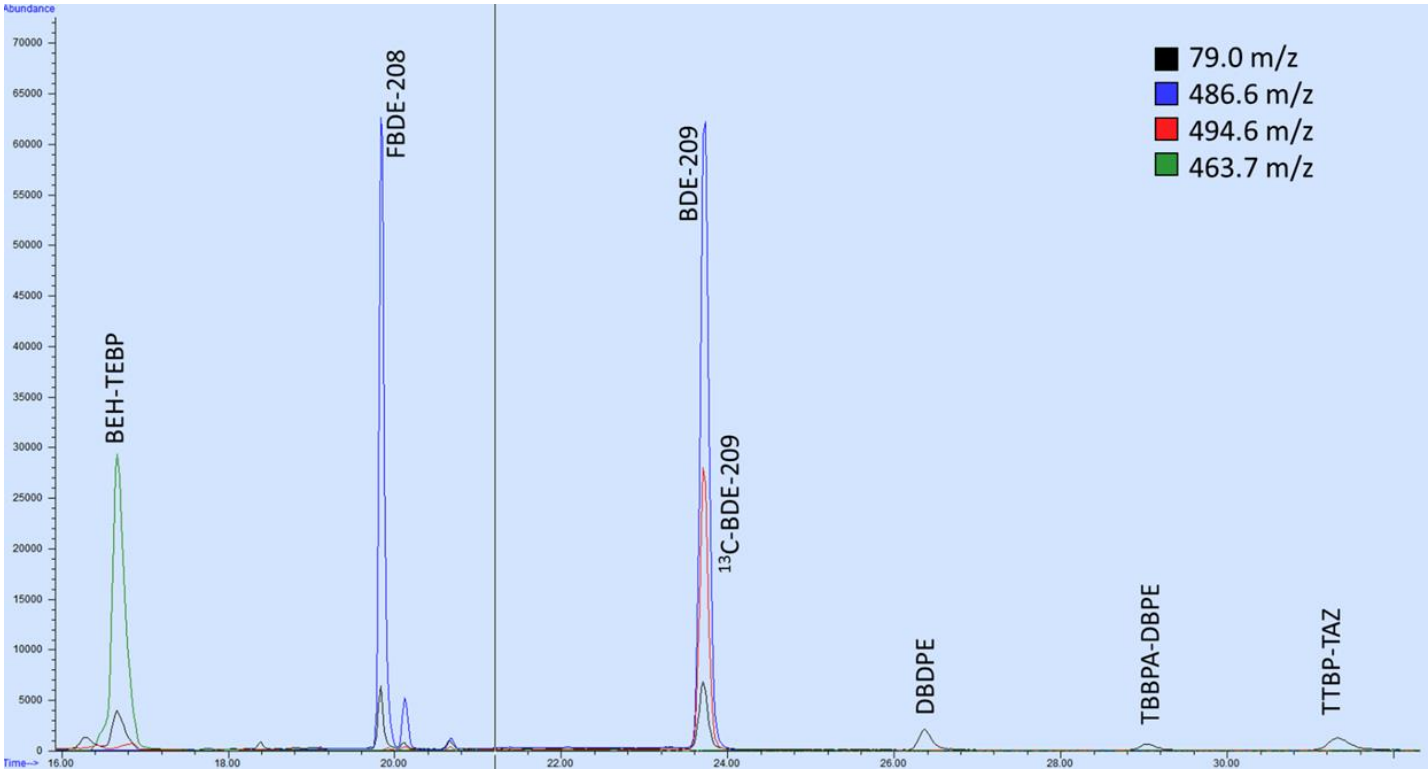



**Figure C1: Merged extracted ion chromatogram for a wristband sample run in GC/ECNI-MS shows peaks identified as novel BFRs which were quantified in all of the wristband samples. Specific m/z values and retention times relative to $^{13}$C-BDE-209 are included in Table C1.**

# Appendix D

Appendix D contains supporting information for Chapter 5, published online from Phillips, A.L. and Hammel, S. C.; Hoffman, K.; Lorenzo, A. M.; Chen, A.; Webster, T. F.; Stapleton, H. M. Children's residential exposure to organophosphate ester flame retardants and plasticizers: Investigating exposure pathways in the TESIE study. *Environ. Int.* 2018, *116*, 176–185 (Publisher: Elsevier).

**Contents**

**Table D1: Demographics of the TESIE study population (n = 203).**

| Characteristic | | N | % |
|---|---|---|---|
| **Child sex** | Male | 113 | 55.7 |
| | Female | 90 | 44.3 |
| **Child age** | 38-47 months | 34 | 16.7 |
| | 48-59 months | 130 | 64.0 |
| | 60-73 months | 39 | 19.2 |
| **Maternal race/ethnicity** | Non-Hispanic white | 84 | 41.4 |
| | Non-Hispanic black | 75 | 36.9 |
| | Hispanic | 41 | 20.2 |
| | Other | 3 | 1.5 |
| **Maternal education** | Less than college graduate | 113 | 55.7 |
| | College graduate or more | 90 | 44.3 |
| **Month of sample collection** | Winter | 53 | 26.1 |
| | Spring | 45 | 22.2 |
| | Summer | 34 | 16.7 |
| | Fall | 71 | 35.0 |

**Table D2: Average OPE levels in field blanks for hand wipes and laboratory blanks for dust, and average OPE metabolite levels in laboratory blanks for specific gravity-corrected urine.**

| Matrix and Compound | *n* | Average Blank |
|---|---|---|
| **Hand Wipe (ng/wipe)** | 14 | |
| **TCEP** | | 17.5 |
| **TCIPP** | | 5.80 |
| **TDCIPP** | | 0.70 |
| **TBOEP** | | 92.7 |
| **EHDPHP** | | 0.30 |
| **TPHP** | | 0.60 |
| **2IPPDPP** | | 0.12 |
| **4IPPDPP** | | 0.12 |
| **4tBPDPP** | | 0.04 |
| **B4tBPPP** | | 0.18 |
| **T4tBPP** | | 0.38 |
| **Dust (ng/g)** | 6 | |
| **TCEP** | | 0.93 |
| **TCIPP** | | 1.63 |
| **TDCIPP** | | 0.45 |
| **TBOEP** | | 2.57 |
| **EHDPHP** | | 0.09 |
| **TPHP** | | 0.92 |
| **2IPPDPP** | | 0.26 |
| **4IPPDPP** | | 0.19 |
| **24DIPPDPP** | | 0.20 |
| **B2IPPPP** | | 0.16 |
| **B4IPPPP** | | 0.14 |
| **B24DIPPPP** | | 0.11 |
| **4tBPDPP** | | 0.11 |
| **B4tBPPP** | | 0.10 |
| **T4tBPP** | | 0.16 |
| **SG-corrected urine (ng/mL)** | 11 | |
| **BCIPP** | | 0.38 |
| **BCIPHIPP** | | 0.71 |
| **BDCIPP** | | 0.15 |
| **DPHP** | | 0.30 |
| **ip-PPP** | | 0.10 |
| **tb-PPP** | | 0.14 |

**Table D3: Expanded correlation tables for compounds within individual matrices**

a. Urinary metabolites

| | BCIPP | BCIPHIPP | BDCIPP | DPHP | ip-PPP |
|---|---|---|---|---|---|
| **BCIPHIPP** | 0.14 | | | | |
| **BDCIPP** | **0.32†** | 0.02 | | | |
| **DPHP** | 0.00 | 0.12 | 0.14 | | |
| **ip-PPP** | -0.11 | **0.27†** | 0.06 | **0.30†** | |
| **tb-PPP** | **-0.17*** | 0.07 | 0.01 | **0.49†** | **0.26†** |

*p<0.05, #p<0.01, †p<0.001

b. Hand wipes

| | TCEP | TCIPP | TDCIPP | EHDPHP | TBOEP | TPHP | 2IPPDPP | 4IPPDPP | 4TBPDPP |
|---|---|---|---|---|---|---|---|---|---|
| **TCIPP** | **0.46†** | | | | | | | | |
| **TDCIPP** | **0.33†** | **0.55†** | | | | | | | |
| **EHDPHP** | **0.20#** | **0.21#** | **0.35†** | | | | | | |
| **TBOEP** | **0.41†** | **0.28†** | **0.41†** | **0.25†** | | | | | |
| **TPHP** | 0.10 | **0.18*** | **0.38†** | **0.35†** | **0.20#** | | | | |
| **2IPPDPP** | 0.13 | **0.18#** | **0.44†** | **0.46†** | **0.30†** | **0.70†** | | | |
| **4IPPDPP** | **0.20#** | **0.20#** | **0.42†** | **0.36†** | **0.34†** | **0.53†** | **0.78†** | | |
| **4TBPDPP** | 0.00 | 0.04 | **0.20#** | **0.20#** | 0.10 | **0.46†** | **0.48†** | **0.37†** | |
| **B4TBPPP** | 0.05 | 0.01 | **0.24†** | **0.26†** | 0.11 | **0.39†** | **0.43†** | **0.31†** | **0.78†** |

*p<0.05, #p<0.01, †p<0.001

c. Dust

| | TCEP | TCIPP | TDCIPP | EHDPHP | TBOEP | TPHP | 2IPP DPP | 24DIPP DPP | 4TBP DPP |
|---|---|---|---|---|---|---|---|---|---|
| **TCIPP** | **0.52†** | | | | | | | | |
| **TDCIPP** | **0.39†** | **0.36†** | | | | | | | |
| **EHDPHP** | **0.35†** | **0.32†** | **0.39†** | | | | | | |
| **TBOEP** | **0.25†** | **0.17*** | 0.13 | **0.24†** | | | | | |
| **TPHP** | **0.21#** | **0.25†** | **0.16*** | **0.17*** | **0.25†** | | | | |
| **2IPPDPP** | **0.25†** | **0.25†** | **0.14*** | **0.21†** | **0.33†** | **0.57†** | | | |
| **24DIPPDPP** | 0.01 | 0.02 | 0.06 | 0.14 | -0.01 | **0.28†** | **0.47†** | | |
| **4TBPDPP** | -0.11 | 0.08 | 0.09 | 0.07 | 0.05 | **0.22#** | **0.18#** | **0.26†** | |
| **B4TBPPP** | 0.00 | 0.11 | 0.13 | **0.17*** | **0.16*** | 0.12 | **0.17*** | **0.19#** | **0.83†** |

*p<0.05, #p<0.01, †p<0.001

**Table D4: Results of regression analyses for predicting urinary metabolites based on parent compounds on hand wipes, child's sex and age, mother's race/ethnicity and education, and average outdoor temperature. Shading indicates known parent-metabolite pairs.**

| Level of Parent Compound on Hand Wipe | | SG-Corrected BCIPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected BCIPHIPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected BDCIPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected DPHP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected ip-PPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected tb-PPP [$10^{\beta}$ (95% CI)- *p*-Val] |
|---|---|---|---|---|---|---|---|
| **TCEP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 0.91 (0.60, 1.37) – 0.65 | **1.51 (1.05, 2.18) – 0.025** | 0.95 (0.62, 1.47) – 0.83 | 1.29 (0.88, 1.88) – 0.19 | **1.53 (1.15, 2.15) – 0.003** | 1.05 (0.65, 1.69) – .85 |
| | Quartile 3 | 0.80 (0.50, 1.30) – 0.37 | **1.68 (1.15, 2.46) – 0.007** | 1.05 (0.67, 1.65) – 0.83 | 1.28 (0.83, 1.98) – 0.26 | 1.39 (0.98, 1.96) – 0.061 | 1.05 (0.63, 1.76) – 0.85 |
| | Quartile 4 | 1.07 (0.64, 1.79) – 0.80 | 1.36 (0.89, 2.08) – 0.16 | 0.94 (0.61, 1.45) – 0.78 | 1.00 (0.66, 1.53) – 0.98 | **1.55 (1.12, 2.03) – 0.009** | 1.18 (0.72, 1.93) – 0.52 |
| **TCIPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.09 (0.69, 1.72) – 0.71 | 1.09 (0.75, 1.58) – 0.67 | 1.26 (0.80, 1.98) – 0.32 | 0.79 (0.53, 1.19) – 0.26 | 1.15 (0.83, 1.58) – 0.40 | 0.92 (0.59, 1.45) – 0.73 |
| | Quartile 3 | 1.19 (0.79, 1.80) – 0.41 | 1.24 (0.85, 1.81) – 0.26 | 1.58 (0.99, 2.51) – 0.056 | 0.97 (0.63, 1.47) – 0.87 | 1.20 (0.88, 1.65) – 0.25 | 1.02 (0.60, 1.73) – 0.94 |
| | Quartile 4 | **1.84 (1.19, 2.84) – 0.006** | 1.40 (0.91, 2.15) – 0.12 | 1.59 (0.99, 2.55) – 0.056 | 1.07 (0.73, 1.58) – 0.72 | 1.17 (0.80, 1.69) – 0.42 | 1.10 (0.62, 1.96) – 0.75 |
| **TDCIPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.33 (0.83, 2.11) – 0.23 | 1.06 (0.71, 1.58) – 0.78 | **1.52 (1.04, 2.23) – 0.032** | 1.25 (0.81, 1.91) – 0.31 | 1.11 (0.81, 1.53) – 0.50 | 0.80 (0.49, 1.31) – 0.38 |
| | Quartile 3 | 1.07 (0.70, 1.63) – 0.76 | 0.74 (0.51, 1.08) – 0.12 | **2.56 (1.72, 3.82) – <0.001** | 1.35 (0.92, 1.99) – 0.13 | 1.36 (0.99, 1.85) – 0.054 | 1.39 (0.79, 2.45) – 0.25 |
| | Quartile 4 | 1.20 (0.75, 1.91) – 0.44 | 1.21 (0.76, 1.90) – 0.42 | **2.73 (1.67, 4.48) – <0.001** | 1.19 (0.79, 1.80) – 0.41 | 1.42 (0.98, 2.07) – 0.067 | 1.11 (0.68, 1.82) – 0.67 |
| **TBOEP** | Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Tertile 2 | 0.92 (0.59, 1.45) – 0.73 | 1.28 (0.89, 1.85) – 0.19 | 0.87 (0.62, 1.23) – 0.43 | 0.98 (0.68, 1.39) – 0.89 | 1.07 (0.79, 1.44) – 0.67 | 1.04 (0.68, 1.61) – 0.85 |
| | Tertile 3 | 0.83 (0.56, 1.21) – 0.32 | 1.11 (0.82, 1.51) – 0.49 | 1.20 (0.81, 1.76) – 0.36 | 1.37 (0.96, 1.95) – 0.081 | 1.25 (0.94, 1.67) – 0.12 | 1.28 (0.85, 1.93) – 0.23 |
| **EHDPHP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.34 (0.86, 2.10) – 0.20 | **2.00 (1.39, 2.87) – 0.0002** | 0.91 (0.57, 1.44) – 0.69 | 1.12 (0.78, 1.66) – 0.57 | 1.01 (0.73, 1.41) – 0.95 | 0.87 (0.55, 1.38) – 0.55 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Quartile 3 | 1.39 (0.88, 2.20) – 0.16 | **1.71 (1.19, 2.45) – 0.004** | 1.37 (0.91, 2.07) – 0.13 | **1.69 (1.09, 2.60) – 0.018** | 1.27 (0.90, 1.79) – 0.18 | 1.17 (0.75, 1.82) – 0.49 |
| | Quartile 4 | 1.35 (0.84, 2.18) – 0.22 | **1.55 (1.09, 2.22) – 0.015** | 1.28 (0.79, 2.08) – 0.32 | **1.58 (1.03, 2.43) – 0.038** | 1.13 (0.79, 1.62) – 0.49 | 1.02 (0.61, 1.72) – 0.94 |
| **TPHP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 0.78 (0.49, 1.23) – 0.28 | **0.58 (0.38, 0.88) – 0.010** | 1.45 (0.94, 1.51) – 0.095 | 1.10 (0.76, 1.60) – 0.63 | 1.11 (0.78, 1.58) – 0.57 | **1.77 (1.11, 2.82) – 0.016** |
| | Quartile 3 | 1.15 (0.71, 1.84) – 0.57 | 0.85 (0.58, 1.25) – 0.41 | 1.03 (0.61, 1.74) – 0.90 | 1.02 (0.67, 1.55) – 0.92 | 0.90 (0.67, 1.22) – 0.50 | 1.16 (0.70, 1.93) – 0.56 |
| | Quartile 4 | 1.12 (0.68, 1.84) – 0.66 | 0.88 (0.59, 1.31) – 0.52 | 0.95 (0.60, 1.51) – 0.84 | **1.78 (1.13, 2.80) – 0.012** | 0.92 (0.65, 1.28) – 0.61 | **2.33 (1.32, 4.11) – 0.004** |
| **2IPPDPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 0.88 (0.54, 1.41) – 0.59 | 0.93 (0.61, 1.40) – 0.71 | 1.36 (0.90, 2.07) – 0.15 | 1.11 (0.76, 1.60) – 0.59 | 1.31 (0.94, 1.83) – 0.11 | 1.31 (0.84, 2.05) – 0.23 |
| | Quartile 3 | 1.12 (0.71, 1.75) – 0.63 | 1.19 (0.83, 1.71) – 0.34 | 1.23 (0.75, 2.01) – 0.41 | 1.12 (0.75, 1.67) – 0.57 | **1.51 (1.08, 2.12) – 0.016** | 1.29 (0.78, 2.14) – 0.32 |
| | Quartile 4 | 1.19 (0.76, 1.87) – 0.46 | 0.75 (0.49, 1.14) – 0.17 | 1.05 (0.63, 1.74) – 0.86 | **2.11 (1.31, 3.40) – 0.002** | 1.34 (0.95, 1.90) – 0.091 | **2.42 (1.31, 4.48) – 0.005** |
| **4IPPDPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.18 (0.77, 1.81) – 0.44 | 1.31 (0.90, 1.91) – 0.15 | 1.28 (0.82, 1.98) – 0.28 | 0.97 (0.69, 1.37) – 0.87 | 1.22 (0.87, 1.70) – 0.24 | 0.95 (0.64, 1.43) – 0.82 |
| | Quartile 3 | 1.19 (0.79, 1.81) – 0.41 | 1.19 (0.80, 1.78) – 0.39 | 1.41 (0.89, 2.24) – 0.15 | 1.21 (0.81, 1.82) – 0.35 | 1.19 (0.86, 1.64) – 0.29 | 1.32 (0.82, 2.13) – 0.25 |
| | Quartile 4 | 0.94 (0.56, 1.59) – 0.82 | 1.00 (0.69, 1.45) – 0.99 | 0.95 (0.60, 1.50) – 0.83 | **1.70 (1.12, 2.59) – 0.013** | 1.22 (0.87, 1.71) – 0.24 | **1.78 (1.07, 2.97) – 0.026** |
| **4tBPDPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | **1.60 (1.04, 2.45) – 0.033** | **1.56 (1.05, 2.32) – 0.027** | 1.03 (0.65, 1.63) – 0.90 | 1.11 (0.75, 1.64) – 0.60 | 1.29 (0.92, 1.80) – 0.14 | **1.51 (1.04, 2.19) – 0.032** |
| | Quartile 3 | 1.34 (0.79, 2.28) – 0.28 | 0.87(0.57, 1.34) – 0.53 | 0.78 (0.49, 1.24) – 0.29 | 0.99 (0.65, 1.49) – 0.95 | 0.84 (0.60, 1.18) – 0.32 | 1.19 (0.74, 1.90) – 0.48 |
| | Quartile 4 | 1.65 (0.99, 2.77) – 0.056 | 0.95 (0.62, 1.46) – 0.82 | 1.15 (0.72, 1.82) – 0.56 | 1.49 (0.97, 2.29) – 0.066 | 1.03 (0.70, 1.52) – 0.86 | **2.65 (1.56, 4.49) – 0.0003** |
| **B4tBPPP** | Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Tertile 2 | **1.66 (1.12, 2.48) – 0.012** | 1.00 (0.69, 1.45) – 0.99 | 1.08 (0.67, 1.58) – 0.69 | 1.05 (0.75, 1.48) – 0.76 | 1.07 (0.77, 1.49) – 0.68 | 1.25 (0.84, 1.85) – 0.28 |
| | Tertile 3 | 1.12 (0.50, 1.03) – 0.65 | 0.72 (0.50, 1.03) – 0.073 | 1.03 (0.74, 1.58) – 0.90 | 1.17 (0.77, 1.78) – 0.45 | 1.00 (0.72, 1.41) – 0.98 | **2.48 (1.45, 4.23) – 0.001** |

**Table D5: Results of regression analyses for predicting urinary metabolites based on parent compounds in house dust, adjusted for child's sex and age, mother's race/ethnicity and education, and average outdoor temperature. Shading indicates known parent-metabolite pairs.**

| Level of Parent Compound in Dust | | SG-Corrected BCIPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected BCIPHIPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected BDCIPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected DPHP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected ip-PPP [$10^{\beta}$ (95% CI)- *p*-Val] | SG-Corrected tb-PPP [$10^{\beta}$ (95% CI)- *p*-Val] |
|---|---|---|---|---|---|---|---|
| **TCEP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.11 (0.74, 1.68) – 0.61 | **0.57 (0.39, 0.85) – 0.006** | 1.43 (0.90, 2.26) – 0.13 | 1.09 (0.74, 1.61) – 0.67 | 0.85 (0.60, 1.21) – 0.36 | 1.31 (0.80, 2.15) – 0.29 |
| | Quartile 3 | 1.03 (0.63, 1.68) – 0.92 | **0.63 (0.45, 0.90) – 0.012** | 1.17 (0.72, 1.91) – 0.53 | 1.01 (0.63, 1.63) – 0.97 | 0.90 (0.61, 1.33) – 0.61 | 1.20 (0.68, 2.12) – 0.52 |
| | Quartile 4 | 1.08 (0.68, 1.69) – 0.75 | 0.91 (0.62, 1.32) – 0.61 | 1.21 (0.74, 1.98) – 0.46 | 1.12 (0.77, 1.63) – 0.56 | 0.94 (0.68, 1.31) – 0.72 | 0.71 (0.43, 1.17) – 0.18 |
| **TCIPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | **2.04 (1.31, 3.17) – 0.002** | 0.86 (0.58, 1.30) – 0.48 | 1.31 (0.83, 2.08) – 0.24 | 1.39 (0.94, 2.04) – 0.10 | 0.92 (0.64, 1.32) – 0.64 | 1.03 (0.61, 1.71) – 0.92 |
| | Quartile 3 | **1.67 (1.12, 2.50) – 0.012** | 0.89 (0.62, 1.27) – 0.51 | 1.05 (0.65, 1.70) – 0.85 | **1.48 (1.03, 2.13) – 0.036** | 1.06 (0.74, 1.51) – 0.75 | 1.08 (0.62, 1.89) – 0.78 |
| | Quartile 4 | **1.80 (1.14, 2.83) – 0.011** | 0.84 (0.58, 1.23) – 0.37 | 0.99 (0.59, 1.68) – 0.98 | 1.06 (0.73, 1.55) – 0.75 | 1.04 (0.73, 1.48) – 0.81 | 0.98 (0.58, 1.67) – 0.95 |
| **TDCIPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 0.78 (0.49, 1.23) – 0.28 | 0.82 (0.57, 1.18) – 0.29 | 1.19(0.79, 1.80) – 0.40 | 1.15 (0.77, 1.72) – 0.50 | 1.23 (0.86, 1.78) – 0.26 | 0.92 (0.53, 1.61) – 0.78 |
| | Quartile 3 | 1.07 (0.68, 1.70) – 0.77 | 0.79 (0.53, 1.16) – 0.23 | 1.43(0.93, 2.18) – 0.10 | 0.83 (0.55, 1.25) – 0.37 | 1.03 (0.73, 1.46) – 0.86 | **0.61 (0.39, 0.96) – 0.031** |
| | Quartile 4 | 0.86 (0.53, 1.39) – 0.54 | **0.63 (0.42, 0.96) – 0.030** | 1.54 (0.91, 2.61) – 0.11 | 0.87 (0.60, 1.27) – 0.48 | 0.99 (0.69, 1.41) – 0.95 | 0.79 (0.46, 1.35) – 0.39 |
| **TBOEP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 0.94 (0.54, 1.62) – 0.81 | 0.99 (0.62, 1.59) – 0.96 | 0.80 (0.51, 1.24) – 0.31 | 0.88 (0.58, 1.34) – 0.54 | 1.07 (0.72, 1.59) – 0.75 | 0.89 (0.52, 1.55) – 0.69 |
| | Quartile 3 | 0.87 (0.53, 1.45) – 0.60 | 1.21 (0.78, 1.88) – 0.40 | 0.96 (0.57, 1.62) – 0.87 | 1.11 (0.70, 1.78) – 0.65 | 1.16 (0.76, 1.78) – 0.49 | 0.98 (0.56, 1.72) – 0.95 |
| | Quartile 4 | 1.08 (0.67, 1.76) – 0.74 | 1.15 (0.73, 1.79) – 0.55 | 1.27 (0.80, 2.01) – 0.31 | 0.97 (0.62, 1.50) – 0.88 | 0.96 (0.65, 1.42) – 0.83 | 0.92 (0.53, 1.60) – 0.78 |
| **EHDPHP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Quartile 2 | 1.21 (0.77, 1.89) – 0.40 | **0.60 (0.40, 0.90) – 0.013** | 1.51 (0.97, 2.37) – 0.071 | 1.12 (0.75, 1.67) – 0.58 | 0.77 (0.52, 1.13) – 0.18 | 1.68 (0.96, 2.92) – 0.068 |
| | Quartile 3 | 1.20 (0.72, 2.01) – 0.48 | **0.64 (0.45, 0.91) – 0.014** | 1.48 (0.91, 2.40) – 0.11 | 1.05 (0.67, 1.66) – 0.82 | 0.89 (0.62, 1.28) – 0.53 | 0.98 (0.60, 1.61) – 0.94 |
| | Quartile 4 | 1.21 (0.77, 1.90) – 0.40 | 0.71 (0.48, 1.07) – 0.099 | 1.24 (0.78, 1.96) – 0.36 | 1.22 (0.86, 1.73) – 0.26 | 1.03 (0.74, 1.45) – 0.85 | 1.07 (0.71, 1.59) – 0.75 |
| **TPHP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.34 (0.83, 2.18) – 0.23 | 0.88 (0.57, 1.39) – 0.59 | 1.04 (0.69, 1.56) – 0.84 | 1.41 (0.94, 2.10) – 0.096 | 0.84 (0.57, 1.23) – 0.38 | 1.28 (0.82, 2.02) – 0.28 |
| | Quartile 3 | 1.61 (0.96, 2.68) – 0.069 | 0.91 (0.60, 1.38) – 0.66 | 1.47 (0.92, 2.34) – 0.11 | 1.14 (0.74, 1.75) – 0.55 | 0.76 (0.52, 1.09) – 0.14 | 0.68 (0.39, 1.16) – 0.16 |
| | Quartile 4 | 1.31 (0.81, 2.14) – 0.27 | 1.12 (0.73, 1.71) – 0.62 | 1.07 (0.63, 1.80) – 0.81 | 0.97 (0.66, 1.43) – 0.87 | **0.62 (0.44, 0.88) – 0.008** | 0.84 (0.51, 1.38) – 0.49 |
| **2IPPDPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 0.93 (0.55, 1.57) – 0.79 | 1.09 (0.70, 1.70) – 0.69 | 1.02 (0.65, 1.59) – 0.93 | 1.12 (0.74, 1.70) – 0.58 | 1.33 (0.89, 1.97) – 0.16 | 1.13 (0.69, 1.84) – 0.63 |
| | Quartile 3 | 0.88 (0.56, 1.40) – 0.59 | 1.04 (0.65, 1.66) – 0.87 | 1.51 (0.88, 2.57) – 0.13 | 0.95 (0.61, 1.49) – 0.83 | 1.21 (0.84, 1.74) – 0.31 | 0.75 (0.48, 1.16) – 0.19 |
| | Quartile 4 | 1.44 (0.89, 2.34) – 0.14 | 1.14 (0.75, 1.73) – 0.53 | 1.29 (0.80, 2.08) – 0.30 | 1.15 (0.72, 1.83) – 0.56 | 0.90 (0.61, 1.33) – 0.59 | 0.94 (0.56, 1.56) – 0.80 |
| **24DIPP DPP** | Tertile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Tertile 2 | 1.03 (0.66, 1.60) – 0.91 | 1.06 (0.74, 1.54) – 0.74 | 1.18 (0.76, 1.82) – 0.46 | 1.15 (0.82, 1.61) – 0.41 | 1.26 (0.87, 1.60) – 0.14 | 1.43 (0.92, 2.23) – 0.11 |
| | Tertile 3 | 1.22 (0.80, 1.86) – 0.37 | 1.28 (0.90, 1.83) – 0.17 | 1.15 (0.74, 1.79) – 0.53 | 1.11 (0.75, 1.63) – 0.61 | 1.04 (0.82, 1.49) – 0.78 | 0.86 (0.55, 1.33) – 0.49 |
| **4IPPDPP** | ND | Reference | Reference | Reference | Reference | Reference | Reference |
| | Detected | 1.16 (0.80, 1.69) – 0.44 | 1.12 (0.84, 1.49) – 0.45 | **1.60 (1.11, 2.29) – 0.011** | 1.08 (0.77, 1.50) – 0.66 | 1.08 (0.81, 1.45) – 0.60 | 0.93 (0.62, 1.40) – 0.73 |
| **4tBPDPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |
| | Quartile 2 | 1.00 (0.58, 1.71) – 0.99 | 1.21 (0.81, 1.83) – 0.35 | 0.81 (0.52, 1.25) – 0.34 | 1.05 (0.68, 1.61) – 0.83 | 0.79 (0.54, 1.14) – 0.20 | 1.29 (0.74, 2.25) – 0.36 |
| | Quartile 3 | 1.08 (0.66, 1.78) – 0.75 | 0.89 (0.60, 1.34) – 0.59 | 0.70 (0.45, 1.08) – 0.11 | 1.17 (0.81, 1.68) – 0.41 | 1.01 (0.70, 1.45) – 0.97 | 1.26 (0.80, 2.00) – 0.32 |
| | Quartile 4 | 0.81 (0.52, 1.26) – 0.34 | 0.97 (0.63, 1.48) – 0.87 | 0.86 (0.53, 1.39) – 0.53 | 1.04 (0.72, 1.49) – 0.84 | 1.13 (0.77, 1.66) – 0.53 | **1.72 (1.12, 2.66) – 0.014** |
| **B4tBPPP** | Quartile 1 | Reference | Reference | Reference | Reference | Reference | Reference |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Quartile 2 | 1.06 (0.62, 1.80) – 0.84 | 0.96 (0.64, 1.44) – 0.85 | 1.23 (0.82, 1.84) – 0.32 | 0.96 (0.68, 1.37) – 0.84 | 1.13 (0.77, 1.65) – 0.54 | 1.12 (0.70, 1.78) – 0.63 |
| | Quartile 3 | 1.07 (0.68, 1.69) – 0.76 | 0.76 (0.51, 1.15) – 0.19 | 1.14 (0.73, 1.77) – 0.57 | 1.37 (0.94, 1.99) – 0.098 | 0.98 (0.72, 1.33) – 0.89 | **1.70 (1.11, 2.59) – 0.014** |
| | Quartile 4 | 0.79 (0.49, 1.28) – 0.34 | 0.85 (0.56, 1.31) – 0.47 | 0.99 (0.60, 1.62) – 0.96 | 1.20 (0.81, 1.79) – 0.36 | 1.31 (0.91, 1.87) – 0.15 | **2.61 (1.60, 4.26) – 0.0001** |

# Appendix E

Appendix E contains an excerpt of the supporting information for Chapter 6, which was included in the submission from Hammel, S. C. and Levasseur, J. L.; Hoffman, K.; Phillips, A. L.; Lorenzo, A. M.; Calafat, A. M.; Webster, T. F.; Stapleton, H. M. Children's exposure to phthalates and non-phthalate plasticizers in the home: The TESIE study. *Environ. Int.* Accepted.

**Contents**

Table E7. Measurements of total children's dose of BBP and DEHTP as compared to reference doses (RfDs) (μg/$kg_{bw}$/day).

**Table E1: Compounds and metabolites for phthalate and non-phthalate plasticizers.**

| **Phthalates** | |
|---|---|
| *Parent compound* | *Metabolite(s)* |
| Dimethyl phthalate (DMP) | Mono-methyl phthalate (MMP) |
| Di-ethyl phthalate (DEP) | Monoethyl phthalate (MEP) |
| Di-isobutyl phthalate (DiBP) | Mono-2-hydroxy-isobutylphthalate (MHiBP) |
| | Mono-isobutyl phthalate (MiBP) |
| Dibutyl phthalate (DBP) | Mono-3-carboxypropyl phthalate (MCPP)* |
| | Monobutyl phthalate (MBP) |
| | Mono-3-hydroxybutyl phthalate (MHBP) |
| Benzylbutyl phthalate (BBP) | Monobenzyl phthalate (MBzP) |
| Bis(2-ethylhexyl) phthalate (DEHP) | Mono-2-ethyl-5-carboxypentyl phthalate (MECPP) |
| | Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) |
| | Mono-2-ethyl-5-oxohexyl phthalate (MEOHP) |
| | Mono-2-ethylhexyl phthalate (MEHP) |
| Di-isononylphthalate (DINP) | Mono carboxyisooctyl phthalate (MCOP) |
| | Mono-isononyl phthalate (MNP) |
| | Mono-oxo-isononyl phthalate (MONP) |
| Di-isodecyl phthalate (DDP) | Mono carboxyisononyl phthalate (MCNP) |
| Bis(2-ethylhexyl) terephthalate (DEHTP) | Mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP) |
| | Mono-2-ethyl-5-hydroxyhexyl terephthalate (MEHHTP) |
| **Non-Phthalate Plasticizers** | |
| *Parent compound* | *Metabolite(s)* |
| Bis(2-ethylhexyl)adipate (DEHA) | NA |
| Tris (2-Ethylhexyl) Trimellitate (TOTM) | NA |
| 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) | Cyclohexane-1 2-dicarboxylic acid monohydroxy isononyl ester (MHiNCH) |
| | Cyclohexane-1 2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH) |

*non-specific

**Item E1: GC/MS method for analyzing phthalate and non-phthalate plasticizers in hand wipes and dust samples.**

Phthalates and non-phthalate plasticizers in the hand wipe and dust samples using an Agilent gas chromatograph (model 7890A) mass spectrometer (model 5975C) in electron impact (EI) mode. Pressurized temperature vaporization (PTV) injection was employed in the inlet, and a 0.25 mm (I.D.) x 30 m fused silica capillary column coated with 5% phenyl methylpolysiloxane (J&W Scientific, 0.25 μm film thickness) was used in the GC for separation of the analytes. Helium was used as the carrier gas at a constant flow rate of 1.3 mL/min. The inlet was set to a temperature of 80°C for 0.3 min, and a 600°C/min ramp was employed to increase the inlet temperature to 300°C in order to efficiently transfer the samples to the head of the GC column. The GC oven was held at 80°C for 2 min followed by a temperature ramp of 20°C/min to 250°C, a ramp of 1.5°C/min to 260°C, and a ramp of 25°C/min to 300°C, at which the oven was held at 300°C for 20 min. The transfer line temperature was held at 300°C, and the ion source was held at 230°C. Table S2 describes the m/z ions and retention times used for quantifying the plasticizer parents on the hand wipe and in dust samples.

**Table E2: m/z and retention times for quantifying plasticizers in hand wipes and dust samples.**

| Compound | m/z quantifier | m/z qualifier | retention time (min)[a] |
|---|---|---|---|
| *Phthalates* | | | |
| **DMP** | 163 | 194 | 7.81 |
| **DEP** | 149 | 177 | 8.76 |
| **DiBP** | 149 | 104 | 10.44 |
| **DBP** | 149 | 223 | 10.99 |
| **BBP** | 149 | 91 | 14.02 |
| **DEHP** | 149 | 167 | 16.08 |
| **DEHTP** | 149 | 167 | 18.69 |
| **DINP** | 149 | 293 | 18.82 – 19.82 |
| *Non-phthalate plasticizers* | | | |
| **DEHA** | 147 | 241 | 14.28 |
| **TOTM** | 305 | 193 | 27.51 |

[a] Retention time reported as it was observed on a 30 m DB5-MS Agilent J&W Column.

**Table E3: Average hand wipe and dust blank levels.**

| Matrix and Compound | Average Blank |
|---|---|
| **Hand Wipe (ng/wipe) n = 14** | |
| ***Phthalates*** | |
| **DMP** | 2.13 |
| **DiBP** | 4.80 |
| **DBP** | 75.4 |
| **BBP** | 8.15 |
| **DEHP** | 147 |
| **DINP** | 27.5 |
| **DEHTP** | 101 |
| ***Non-phthalate plasticizers*** | |
| **DEHA** | 198 |
| **TOTM** | 0.71 |
| **Dust (ng/g) n = 6** | |
| ***Phthalates*** | |
| **DMP** | 1.28 |
| **DEP** | 25.4 |
| **DiBP** | 7.60 |
| **DBP** | 47.0 |
| **BBP** | 18.0 |
| **DEHP** | 160 |
| **DINP** | 138 |
| **DEHTP** | 8.46 |
| ***Non-phthalate plasticizers*** | |
| **DEHA** | 149 |
| **TOTM** | 58.7 |

**Table E4: Spearman correlation coefficients for parent compounds and metabolite concentrations measured in paired hand wipes (*n* = 179) and dust (*n* = 178) with ≥70% detection and specific gravity-corrected urine for compounds with multiple metabolites.**

| | | Urine | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MBP | MHBP | MHiBP | MiBP | MCPP | MEHP | MEOHP | MEHHP | MECPP | MCOP | MCNP | MONP | MHINCH | MCOCH | MECPTP | MEHHTP |
| **Hand Wipe** | DMP | 0.08 | 0.04 | 0.11 | 0.09 | 0.07 | -0.03 | 0.08 | 0.07 | 0.07 | -0.02 | 0.05 | -0.01 | 0.05 | 0.06 | 0.05 | 0.08 |
| | DiBP | 0.10 | 0.05 | **0.27†** | **0.34†** | 0.07 | 0.12 | 0.07 | 0.07 | 0.01 | 0.02 | 0.00 | 0.07 | 0.01 | -0.03 | 0.01 | 0.03 |
| | BBP | **0.36†** | **0.31†** | **0.22#** | **0.22#** | 0.08 | **0.18*** | 0.12 | **0.15*** | 0.05 | 0.02 | 0.00 | 0.07 | 0.02 | -0.03 | 0.03 | 0.06 |
| | DEHP | 0.11 | 0.03 | **0.15*** | 0.13 | **0.18*** | **0.23#** | **0.26†** | **0.26†** | **0.22#** | **0.18*** | 0.07 | **0.25†** | 0.01 | -0.02 | -0.03 | 0.06 |
| | DINP | **0.17*** | 0.04 | **0.16*** | **0.17*** | **0.25†** | **0.22#** | **0.19*** | **0.21#** | **0.18*** | **0.25†** | **0.17*** | **0.32†** | 0.04 | -0.03 | -0.04 | 0.01 |
| | DEHTP | 0.12 | 0.04 | 0.12 | **0.18*** | 0.01 | 0.10 | 0.04 | 0.06 | -0.02 | 0.05 | 0.04 | 0.07 | 0.13 | 0.13 | 0.12 | 0.14 |
| | TOTM | 0.01 | -0.07 | 0.11 | 0.08 | 0.09 | **0.17*** | 0.06 | 0.08 | 0.04 | **0.14*** | 0.09 | **0.20#** | 0.08 | 0.04 | -0.04 | 0.03 |
| **Dust** | DEP | 0.11 | -0.02 | -0.01 | 0.01 | **0.19*** | 0.10 | 0.05 | 0.07 | 0.04 | 0.11 | 0.07 | 0.13 | 0.04 | -0.01 | 0.07 | 0.12 |
| | DiBP | **0.30†** | **0.34†** | **0.41†** | **0.42†** | **0.31†** | **0.16*** | **0.18*** | **0.23#** | **0.25†** | **0.24†** | **0.21#** | **0.20#** | 0.10 | 0.06 | **0.18*** | **0.22#** |
| | DBP | **0.23#** | **0.26†** | **0.15*** | **0.20#** | 0.10 | 0.05 | 0.12 | 0.13 | 0.15 | 0.04 | 0.06 | 0.05 | 0.11 | 0.07 | **0.19*** | **0.19*** |
| | BBP | **0.28†** | **0.27†** | **0.16*** | **0.22#** | 0.06 | 0.13 | 0.03 | 0.07 | 0.04 | 0.05 | 0.05 | 0.00 | 0.10 | 0.06 | **0.27†** | **0.28†** |
| | DEHP | 0.11 | 0.10 | 0.11 | 0.13 | **0.22#** | **0.15*** | **0.14** | **0.16*** | **0.19*** | **0.15*** | **0.17*** | 0.13 | 0.04 | 0.01 | 0.08 | 0.10 |
| | DINP | 0.11 | 0.07 | 0.06 | 0.09 | **0.24#** | **0.18*** | **0.16*** | **0.16*** | **0.18*** | **0.19*** | 0.13 | **0.18*** | **0.16*** | 0.11 | **0.18*** | **0.18*** |
| | DEHTP | 0.06 | 0.09 | 0.04 | 0.12 | **0.17*** | 0.04 | -0.03 | -0.01 | 0.04 | 0.13 | 0.13 | 0.09 | 0.13 | 0.14 | **0.33†** | **0.29†** |
| | TOTM | -0.05 | -0.02 | 0.13 | 0.06 | 0.05 | **-0.15*** | -0.11 | -0.12 | -0.11 | -0.06 | -0.02 | -0.06 | -0.01 | -0.02 | 0.00 | 0.01 |

*p<0.05, #p<0.01, †p<0.001

**Table E5: Detailed results of regression analyses for hand wipe levels of phthalates plasticizers with their paired urinary metabolite or metabolite molar sum.**

| Parent Phthalate | Quartile | Estimate | 95% Confidence Limits | | Pr > \|Z\| |
|---|---|---|---|---|---|
| DEP (metabolite = MEP) | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 0.99 | 0.68 | 1.43 | 0.9563 |
| | Q3 | 1.03 | 0.68 | 1.57 | 0.8825 |
| | Q4 | 0.93 | 0.61 | 1.42 | 0.7315 |
| DiBP (metabolite = MHiBP and MiBP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.28 | 0.90 | 1.80 | 0.1655 |
| | Q3 | 1.44 | 1.07 | 1.94 | **0.0159** |
| | Q4 | 1.71 | 1.23 | 2.37 | **0.0013** |
| BBP (metabolite = MBzP) | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.33 | 0.93 | 1.89 | 0.1195 |
| | Q3 | 1.76 | 1.12 | 2.76 | **0.0148** |
| | Q4 | 6.29 | 3.98 | 9.96 | **<.0001** |
| DBP (metabolites = MCPP, MBP, MHBP)*† | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 0.91 | 0.69 | 1.21 | 0.5259 |
| | Q3 | 0.89 | 0.70 | 1.12 | 0.3121 |
| DEHP (metabolites = MECPP, MEHHP, MEOHP, MEHP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.05 | 0.79 | 1.40 | 0.7466 |
| | Q3 | 1.35 | 1.01 | 1.80 | **0.0447** |
| | Q4 | 1.67 | 1.24 | 2.24 | **0.0007** |
| DEHTP (metabolites = MECPTP, MEHHT)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.52 | 1.01 | 2.30 | **0.0453** |
| | Q3 | 1.12 | 0.76 | 1.64 | 0.5750 |
| | Q4 | 1.18 | 0.77 | 1.79 | 0.4449 |
| DINP (metabolites = MCOP, MONP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 0.74 | 0.47 | 1.16 | 0.1953 |
| | Q3 | 1.36 | 0.90 | 2.05 | 0.1494 |
| | Q4 | 1.45 | 0.91 | 2.31 | 0.1168 |

* reported as molar sums; † reported as tertiles due to detection frequency; All p values significant at $p < 0.05$ are bolded. Urinary metabolite levels were all SG-corrected. All values were $\log_{10}$ transformed.

**Table E6: Detailed results of regression analyses for dust concentrations of phthalates plasticizers with their paired urinary metabolite or metabolite molar sum. All p values significant at p < 0.05 are bolded. Urinary metabolite levels were all SG-corrected. All values were $log_{10}$ transformed.**

| Parent Phthalate | Quartile | Estimate | 95% Confidence Limits | | Pr > \|Z\| |
|---|---|---|---|---|---|
| DEP (metabolite = MEP) | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 0.99 | 0.67 | 1.47 | 0.9624 |
| | Q3 | 0.90 | 0.61 | 1.34 | 0.6145 |
| | Q4 | 1.17 | 0.77 | 1.76 | 0.4599 |
| DiBP (metabolite = MHiBP and MiBP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.31 | 0.93 | 1.84 | 0.127 |
| | Q3 | 1.64 | 1.23 | 2.19 | 0.0009 |
| | Q4 | 2.06 | 1.51 | 2.81 | **<.0001** |
| BBP (metabolite = MBzP) | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.14 | 0.74 | 1.75 | 0.5592 |
| | Q3 | 1.72 | 1.07 | 2.77 | **0.0256** |
| | Q4 | 4.72 | 2.57 | 8.67 | **<.0001** |
| DBP (metabolites = MCPP, MBP, MHBP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 0.88 | 0.62 | 1.25 | 0.4645 |
| | Q3 | 1.29 | 0.99 | 1.68 | 0.0635 |
| | Q4 | 1.19 | 0.89 | 1.59 | 0.2487 |
| DEHP (metabolites = MECPP, MEHHP, MEOHP, MEHP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.30 | 0.97 | 1.73 | 0.074 |
| | Q3 | 1.45 | 1.12 | 1.87 | **0.0045** |
| | Q4 | 1.42 | 1.09 | 1.87 | **0.0107** |
| DEHTP (metabolites = MECPTP, MEHHTP)* | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.05 | 0.70 | 1.56 | 0.8254 |
| | Q3 | 1.33 | 0.86 | 2.06 | 0.1962 |
| | Q4 | 1.67 | 1.09 | 2.57 | **0.0187** |
| DINP (metabolites = MCOP, MONP) | | | | | |
| | Q1 | 1.00 | 1.00 | 1.00 | . |
| | Q2 | 1.24 | 0.81 | 1.90 | 0.3251 |
| | Q3 | 1.41 | 0.95 | 2.09 | 0.0862 |
| | Q4 | 1.53 | 0.99 | 2.35 | 0.0542 |

* reported as molar sums

**Item E2. Calculation of metabolite measurements versus reference dose (RfD) for BBP and DEHTP**

Equations:

Calculation of Estimated DEHTP Reference Dose:

$$Reference\ Dose\ (RfD) = \frac{chronic\ NOAEL}{UF_{interspecies} \times\ UF_{intraspecies}}$$

Chronic NOAEL = 79 mg/$kg_{bw}$/day (European Chemicals Agency, 2019)

Uncertainty Factor (UF), interspecies = 10

Uncertainty Factor (UF), intraspecies = 10

Calculation of Children's Dose, Based on Measured Metabolite Level:

$$Children's\ Dose = \frac{(M_i \times UE\ \times 24h\ \times MR)}{\frac{BW}{1000}}$$

Children's dose = μg/$kg_{bw}$/day

$M_i$ = metabolite (ng/mL)

UE = Child urinary excretion (assumed 13 mL/hr)

BW = Child's body weight ($kg_{bw}$)

Molar Ratio = Parent Compound MW/Metabolite Compound MW(s)

BBP molecular weight = 312.365 g/mol

MBzP molecular weight = 256.257 g/mol

DEHTP molecular weight = 390.564 g/mol

MECPTP molecular weight = 308.33 g/mol

MEHHTP molecular weight = 294.34 g/mol

**Results:**

**Table E7: Measurements of total children's dose of BBP and DEHTP as compared to reference doses (RfDs) (μg/kg$_{bw}$/day).**

| | RfD | Median[α] | 95th Percentile[α] | Maximum[α] |
|---|---|---|---|---|
| BBP | 200 | 62.1 (31%) | 7.4 (4%) | 0.3 (0.1%) |
| DEHTP | 790 | 54.9 (7%) | 14.9 (2%) | 1.4 (0.2%) |

[α] percentage of RfD reported in parentheses

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# Biography

Stephanie Hammel received Bachelor's of Science degrees in Chemistry and Biological Sciences in 2012 and a Master's in Public Health in 2014 from the University of California, Irvine. Stephanie started her doctoral studies at Duke University in 2014 under the supervision of Heather Stapleton. Stephanie was the recipient of the International Society of Exposure Science IPA/DGUV Award for a Young Exposure Scientist in 2017 and the Duke Environmental Health Scholars Award in 2018. She was also recognized as an Outstanding Teaching Assistant for the Program in Public Health at UC Irvine in 2014. During her graduate studies, Stephanie has published six first-author manuscripts and contributed as an author to seven published research articles.

Publications (*authors contributed equally)

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